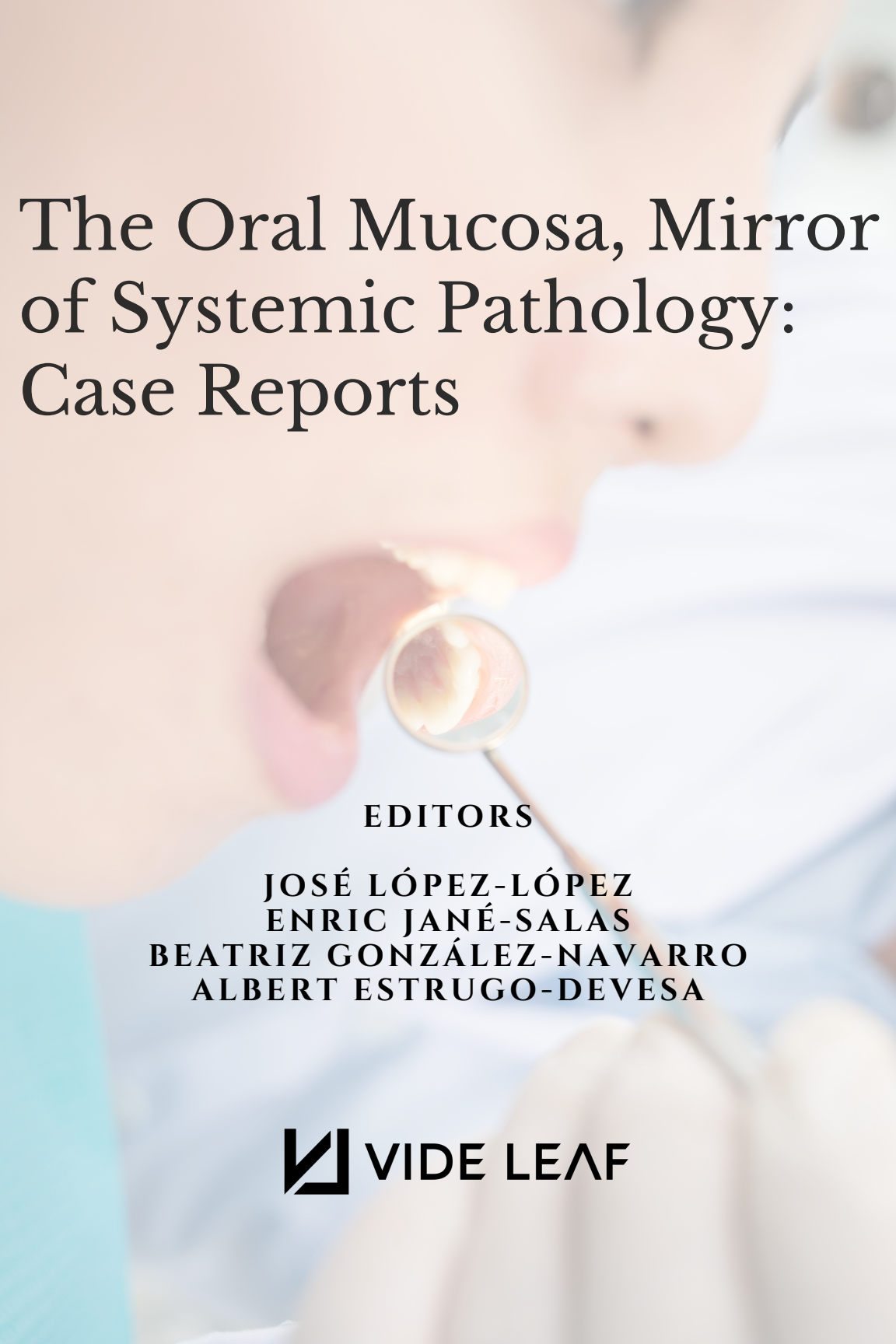

# The Oral Mucosa, Mirror of Systemic Pathology: Case Reports


EDITORS

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**Monograph**

# The Oral Mucosa, Mirror of Systemic Pathology: Case Reports

**Editors:** José López-López, Enric Jané-Salas, Beatriz González-Navarro and Albert Estrugo-Devesa

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# Presentation

The objective of the present manuscript is not to make a manual of medical pathology, an aspect that on the other hand is well registered in the current literature. If you wish to expand your knowledge, the reader may turn to: [Cawson E. Cawson. Fundamentals of medicine and oral pathology 9th edition. Barcelona: Elsevier, 2009]; [José Vicente Bagán Sebastián, Medicine and Oral Pathology. Valencia: Oral Medicine, 2013]; [Sapp JP, Eversole LR, Wysocki GP. Contemporary oral and maxillofacial pathology. Barcelona: Elsevier, 2004]; and [Camile S. Farah, Ramesh Balasubramaniam, Michael J. McCullough. Contemporary Oral Medicine. A Comprehensive Approach to Clinical Practice. London: Springer, 2019]

Our interest, is to draw the reader's attention to the importance of correct exploration of the oral cavity [based on representative clinical cases] to the possible diagnosis of diseases. Some of them local, but on other occasions, a showcase for systemic diseases of varying importance. Thus, you will observe that there is a first introductory chapter on oral pathology, reviewing the elemental lesions and the possible repercussions of systemic diseases in the oral cavity. Then we present, as case reports, some of these systemic diseases with greater or lesser local involvement. Below we collect some cases of immunological alterations that affect the oral cavity, highlighting lichen and its unlikely but possible malignancy. To continue with some frequent and infrequent infectious diseases and dedicate two cases to benign tumors of the mucosa, one frequent the other infrequent. Finally, we present a case of bone dysplasia, and we review the diagnosis of bone lesions in chapter 1 and given the growing interest in antiresorptive mediation, we dedicate the final chapter to reviewing these drugs and their management in dentistry.

We hope that the agile reading of this manuscript, which collects frequent and infrequent cases, will awaken interest in knowing more about oral pathology.

*The editors*

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## Case Report

# The Mouth and its Diagnostic Value

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## Abstract

In this first chapter, we present elementary lesions of the oral mucosa. We review oral pathology, present diagnostic tables, and review the Table most related to the cases we present later. At the end, we present some diagnostic tables of radiological bone lesions. Because it is a subject that we do not address in the following chapters, we believe that it could be of interest to the readers.

## Highlights

- The importance of differential diagnosis in dentistry.
- The value of oral mucosa as a site of systemic diseases

- The importance of becoming familiar with elementary lesions

## Introduction

The mouth, and therefore the oral mucosa, is the site of multiple pathologies. Some are of local origin and others are manifestations of systemic processes of lesser or greater importance. It is common for the dentist to focus on the teeth and how to replace them either using conventional prostheses or, in recent years, implant prostheses.

The area of Dentistry that addresses predominantly diseases of the mouth and the oral mucosa is called Oral Medicine. One of the current fathers of this discipline, Professor José Vicente Bagán Sebastián, professor at the University of Valencia (Spain), states in his book, a groundwork for many of his disciples: "Diseases of the oral mucosa are characterized by causing the appearance of various types of lesions in the mucosa that have different characteristics and morphology; they are called elementary lesions of the oral mucosa" [1]. The author indicates that such lesions can be primary [those that begin in an initially healthy mucosa or semi-mucosa] and that they may evolve to healing or transform into secondary elementary lesions. Giglio & Nicolosi [2], in their seminari work on semiology, refer to them as the evidential alphabet of pathological processes that affect the mouth and the skin. The authors classify them as primary and secondary. Although not all authors agree with their classification, their study allows us to infer on many occasions what disease we are addressing, and the handbook guides us to a specific group of diseases. A classification that we find useful, because it includes additional concepts for diagnosis, is that of García Pola Vallejo & García Martín [3] (Table 1, Figure 1-4).

**Table 1:** Elementary skin and mucosal lesions according to García Pola Vallejo & García Martín,[3] in italics and in square brackets. They are considered primary or secondary lesions, respectively, by Giglio & Nicolosi [3].

| Characteristic | **Primary** | **Secondary** |
|---|---|---|
| Color alteration | -Stain | -Macula |
| Liquid content | -Vesicle, -Vial, -Pustule | - [Scab], -Erosion or ulceration |
| Solid content | SINGLE<br>-Papule<br>-Tuber, -Nodule, -Plate<br>-Papilloma MULTIPLE<br>-Vegetation or wartiness GENERALIZED<br>-Hypertrophy OTHER<br>-Tumor | -Ulcer/ulceration, -Perforation, -[Scar], -[Scab], -[Lichenification] |
| Alteration of the corneal layer | -Scale / slough<br>-Keratosis | -[Atrophy, Sclerosis] |
| Loss of mucosa | CONSISTENCY<br>-Atrophy<br>CONTINUITY<br>SOLUTION<br>-Necrobiosis<br>-Necrosis | - [Ulceration], -[Erosion], -Excoriation<br>-Scale, - [Slough], -[Ulcer], -[Piercing] .- [Fissure / crack] |
| Inflammation | -Erythema, -Abscess, -phlegmon, -Cellulitis | -Fistula, - [Cavity] |

If we put aside elementary lesions, we can read about the oral pathology that occurs in the oral cavity by the work of the doctors Ibsen & Phelan, in their magnificent book of 2014. This book aims dental hygienists. It succinctly collects a well-argued summary of this pathology [4], and we can complement it with broad-scope texts [1,5-7].

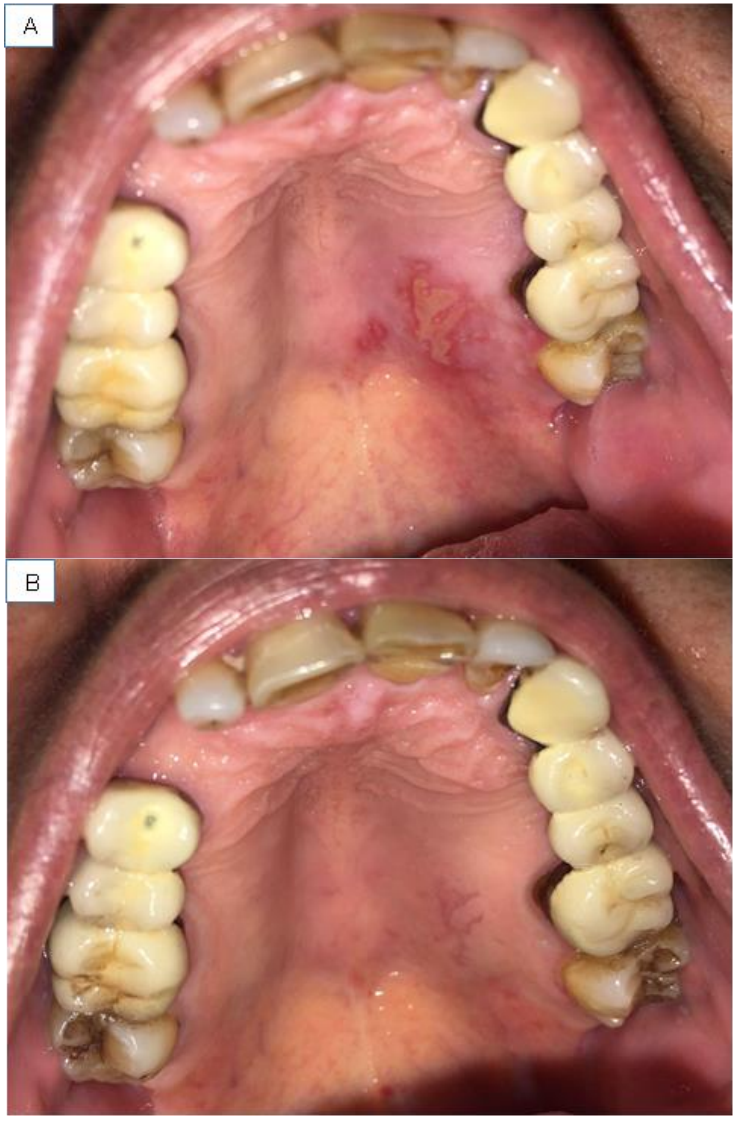


**Figure 1:** A) Elemental ulcer lesion corresponding to different vesicles that have joined each other after breaking. In Figure B), we observe how the lesion evolves.

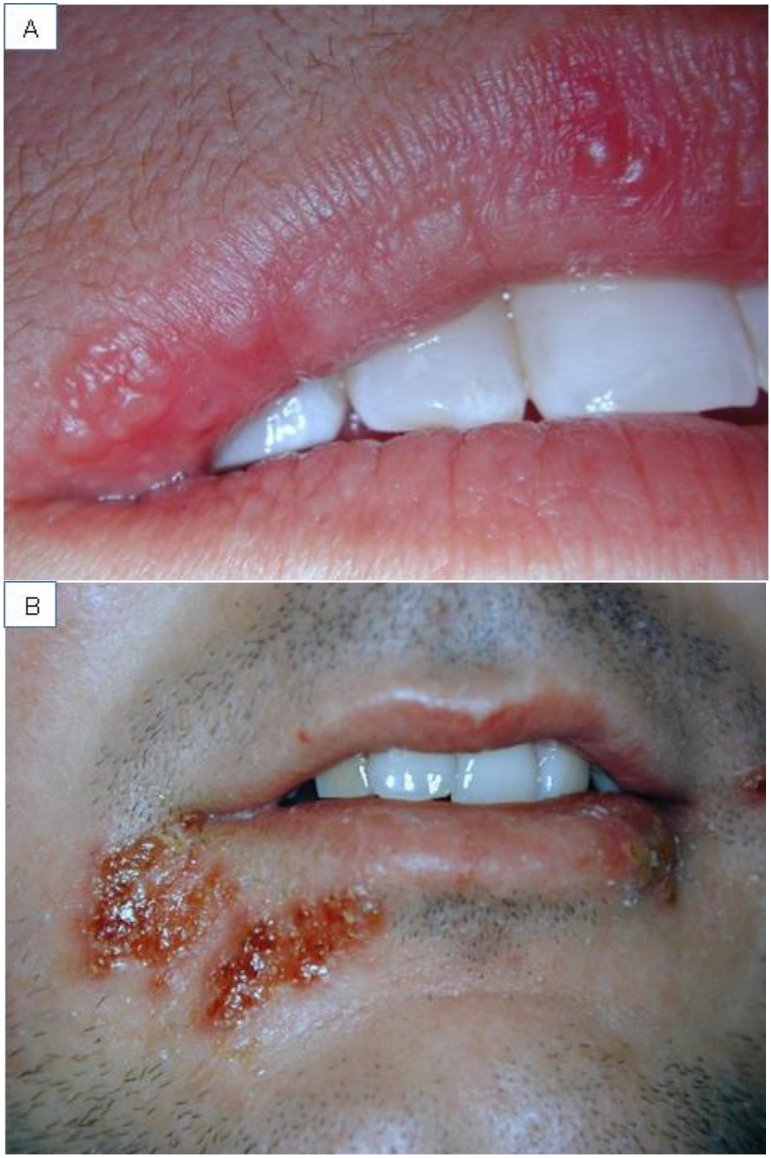


**Figure 2:** A) We observe another state of the previous disease (recurrent herpes). In this case, we see the patient at an initial stage of disease, and we can observe the vesicles attached to each other. B) Natural evolution, another patient, as meliceric scabs.

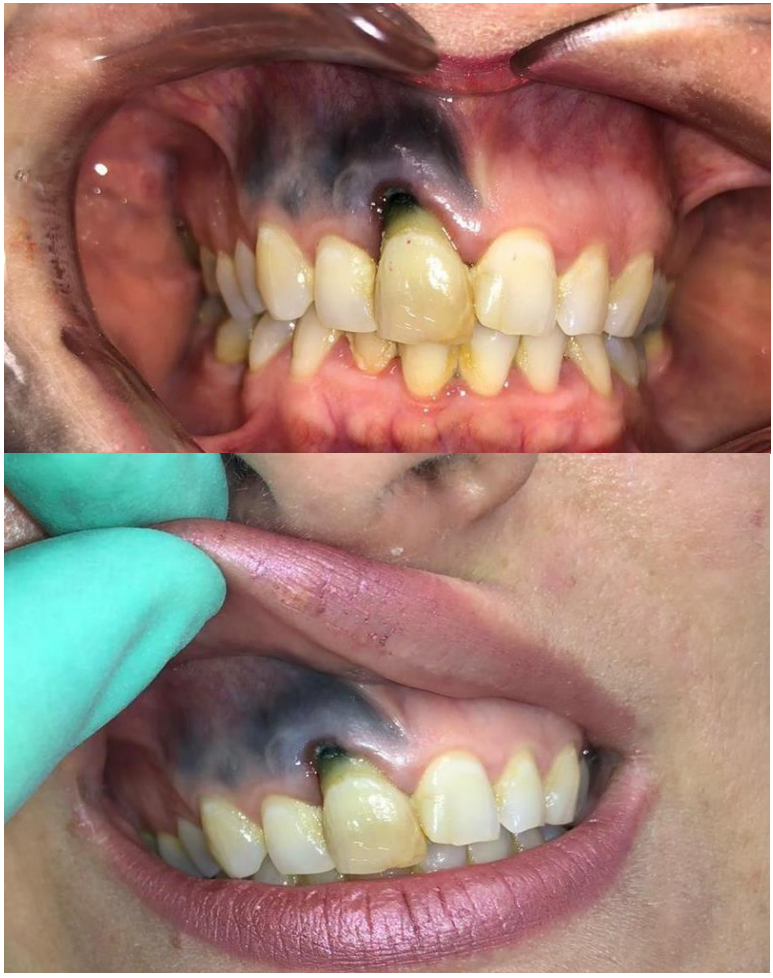

**Figure 3:** Clear example of a macula, a flat lesion with discoloration, in this case associated with a periapical surgery with retro filling with amalgam [original image by Dr.B. González Navarro].

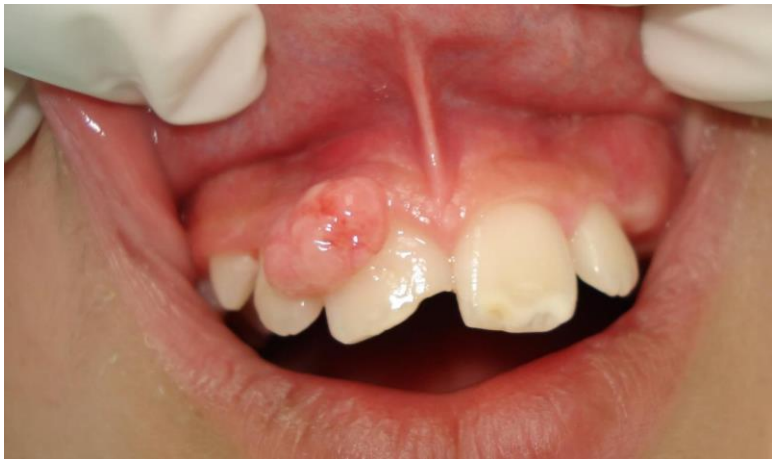

**Figure 4:** Another example of an elementary lesion, in this case corresponding to a tumor, whose underlying pathology is a pyogenic granuloma. [Image courtesy of Dr. MM. Sabater Recolons].

**Table 2:** Common causes of tumors in the jaw and/or maxilla. Cyst ratio. (some recognized percentages in parentheses).

| **Causes of tumor** |
|---|
| Cysts *Preferably odontogenic cysts* |
| Odontogenic tumors<br>*-Benign // -Malign* |
| Primary bone neoplasms (non-odontogenic)<br>*-Benign // -Malign* |
| Giant cell lesions |
| Fibro-bone injuries |
| Metastatic neoplasms |
| **Cysts of jaws, face and neck** |
| ***Odontogenic cysts*** |
| Cysts of inflammatory origin |
| -Root cyst [50-55%]<br>-Residual root cyst [7%]<br>-Inflammatory collateral cysts |
| Developmental cysts or of unknown origin |

| |
|---|
| -Dental cyst [10-20%] Rash cyst<br>-Odontogenic keratocyst [8-12%]*<br>-Lateral periodontal cyst: [<1%] Globulomaxillary cyst<br>-Botryoid odontogenic cyst<br>-Glandular odontogenic cyst<br>-Gingival cysts:<br>Gingival cysts of infants Gingival cysts of adults<br>-Ortokeratinized odontogenic cyst Calcifying odontogenic cyst |
| ***Non-odontogenic (developmental) cysts*** |
| -Incisive canal cyst (nasopalatine) [6-10%]<br>-Nasolabial cyst<br>-Sublingual dermoid cyst<br>-Thyroglossal duct cyst<br>-Branchial cyst Cysts of the foregut |
| ***Pseudocysts*** |
| -Lone bone cyst<br>-Aneurysmal bone cyst<br>-Stafne idiopathic cavity |

*It has a primordial origin in 60% of the cases and dental in 40%. The possibility of a Keratocystic Odontogenic Tumor (KOT) has been assessed.

**Table 3:** Odontogenic and non-odontogenic tumors in the mandible and/or maxilla.

| **Odontogenic tumors** |
|---|
| Benign epithelial neoplasms |
| Ameloblastoma and its variants Squamous odontogenic tumor Calcifying epithelial odontogenic tumor Adenomatoid odontogenic tumor<br>Calcifying cystic odontogenic tumor (calcifying odontogenic cyst) |
| Benign mixed epithelial and conjunctival neoplasms |
| Ameloblastic fibroma |
| Benign connective tissue neoplasms |
| Odontogenic fibroma Odontogenic myxoma<br>Cementoblastoma |
| Malignant epithelial neoplasms |
| Odontogenic carcinoma<br>Clear cell odontogenic carcinoma |
| Hamartomas |
| Simple and compound odontomas |
| Malignant connective tissue neoplasms |
| Odontogenic sarcomas |
| Dysplasias |
| Cement-bone dysplasia |

| **Non-odontogenic bone tumors** |
|---|
| Non-neoplastic: |
| Exostoses and gum pads* Osteochondroma |
| Central giant cell granuloma* |
| Histiocytosis: |
| Langerhans cell histiocytosis* |
| Primary (benign neoplasms): |
| Osteoma<br>Ossifying fibroma* Hemangioma<br>Melanotic neuroectodermal tumor* |
| Primary (malignant neoplasms): |
| Osteosarcoma Chondrosarcoma Ewing's sarcoma |
| Multifocal or potentially multifocal myeloma |
| Secondary (metastatic malignancies): |
| Carcinoma |

(*) More frequent in jaws than in other bones.

***Thus,*** localized diseases can occur in the mucosa associated ***to inflammation and repair***. We present here some cases. Generically, we can include physical or chemical aggressions to the mucosa and semi-mucosa (burns, traumatic ulcers, friction keratosis, solar cheilitis, melanosis, or necrotizing sialometaplasia, among others) (Figure 5) [8]. In this same group we find reactive hyperplasias of the connective tissue: pyogenic granuloma, peripheral giant cell granuloma, fibroma due to irritation, fibrous hyperplasia (of which we also report some cases here), papillary hyperplasia of the palate [not always associated with prostheses] [9], or gingival enlargement of an idiopathic or drug cause (Figure 6). In this same section, we include the local manifestations of pulpal disease and its evolution (Figure 7). Given the special relevance of this section, we present several clinical cases reported by different Spanish groups working in Spanish oral pathology. The final section addresses the management of patients with cardiovascular disease in the dental clinic.

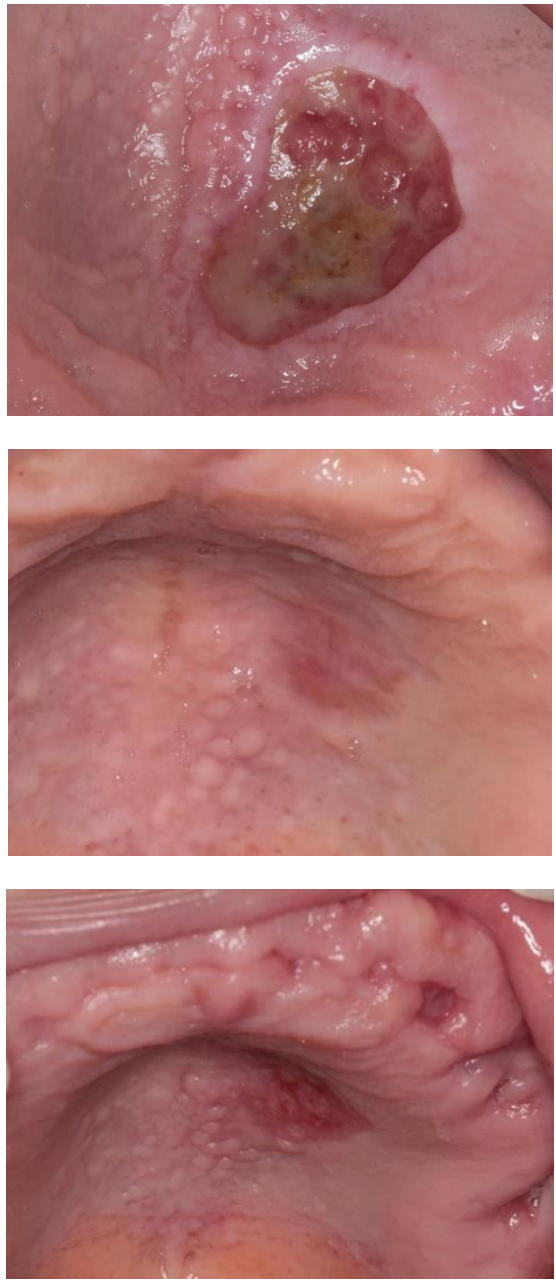

**Figure 5:** Traumatic ulcer after dental anesthesia and its evolution after two and four weeks. Image from Omaña Cepeda et al [8].

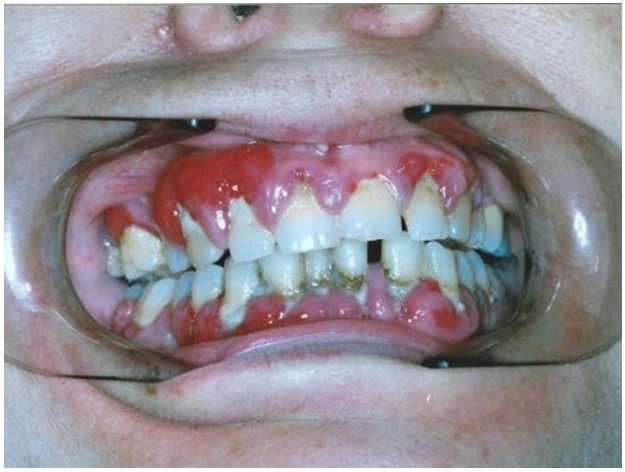

**Figure 6:** Gingival enlargement in a transplant patient receiving cyclosporine. An important local component is seen that aggravates the problem.

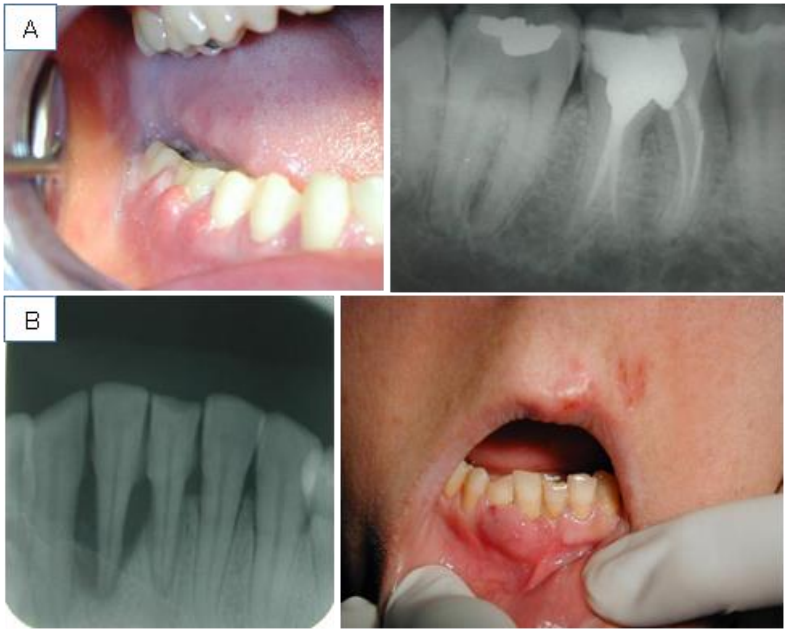


**Figure 7**: Abscess in a tooth with root canal treatment (A) and in a tooth with periodontal problems (B).

The next section presents pathologies associated with ***immunological lesions***. Here we have different options: very localized lesions and lesions associated with more relevant systemic diseases: aphthous ulcers, urticaria, angioedema, contact mucositis, contact dermatitis, fixed drug eruption, erythema multiforme [in its different varieties], Reiter's syndrome, histiocytosis [localized or generalized], eosinophilic granuloma, Sjogren's syndrome; or different mucocutaneous diseases with oral involvement, among which lichen [and its different varieties], pemphigoid, pemphigus, and to a lesser extent lupus erythematosus or Bechet's syndrome (Figure 8). Thus, it is a very broad section. We therefore present a review on blistering diseases and two cases of lichen, one of them malignant.

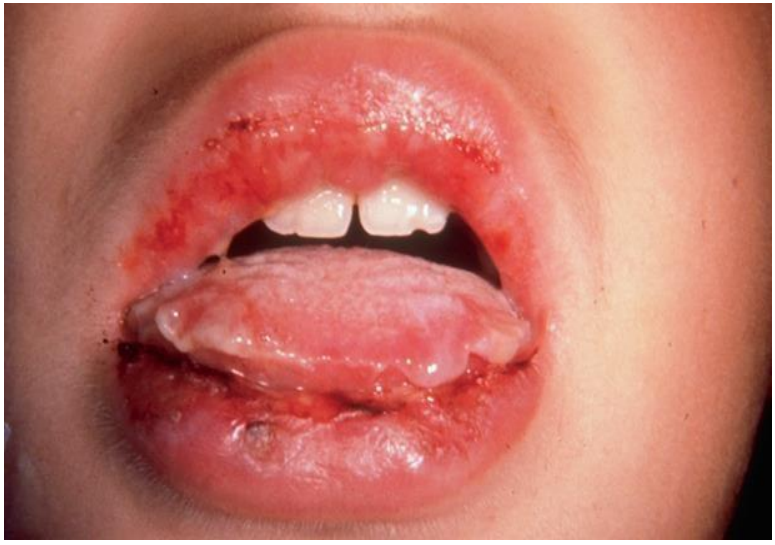

**Figure 8:** Young patient with an acute condition associated with intensive chemotherapy treatment indistinguishable from a herpetic condition or erythema multiforme if we do not consider the clinical history. UB Oral Medicine Master Fund.

The next chapter addresses ***infectious diseases*** and all of its possibilities, specific or polymicrobial, and of viral, bacterial, or fungal origin. Among polymicrobial diseases, we highlight impetigo and diseases derived from the dental organ

(periodontitis, pericoronitis, and osteomyelitis, generally associated with dental processes). Among specific ones, tuberculosis, actinomycosis, and syphilis, among bacterial ones, deserve special attention. Among fungal infections and infections of viral origin, candidiasis deserves special attention, in addition to those associated with the papilloma virus, the herpes virus, and, due to their special relevance, those associated with the HIV virus. Some cases of injuries associated with COVID-19 have also begun to be recorded [10-11]. Here we present from an oral candidiasis to a leishmaniasis, and we review HIV and syphilis, in this case presenting several cases recorded in southern Spain.

In the section on ***developmental disorders***, we include ankyloglossia and enamel pearls, as well as all other lesions that tend to have little diagnostic clinical implications in terms of mucosal involvement. They include different cysts, dental affectations, and some types of dysplasias. It is thus a broad chapter. It is not the objective of this book to classify them. We have included only one case of dysplasia. We present in final part of this chapter several diagrams that allow a differential diagnosis of bone pathology from a radiographic point of view. Genetic disorders, such as trisomy 21 and 32, and different syndromes with oral involvement, such as Turner syndrome, Papillon-Lefevre syndrome, Gardner syndrome, nevoid basal cell carcinoma, von Recklinghausen neurofibromatosis, or that of Peutz-Jeghers, among others, are part of this section.

***Neoplasms***, both benign and malignant, specifically oral squamous cell carcinoma (OSCC) [widely reported in the literature], should always be considered in oral pathology (Figure 9). In this handbook, we present a case of benign mass and a case of malignant lichen planus. If we want to classify them in a simple way and have a clear idea from a clinical point of view, we can resort to Tables 2 and 3.

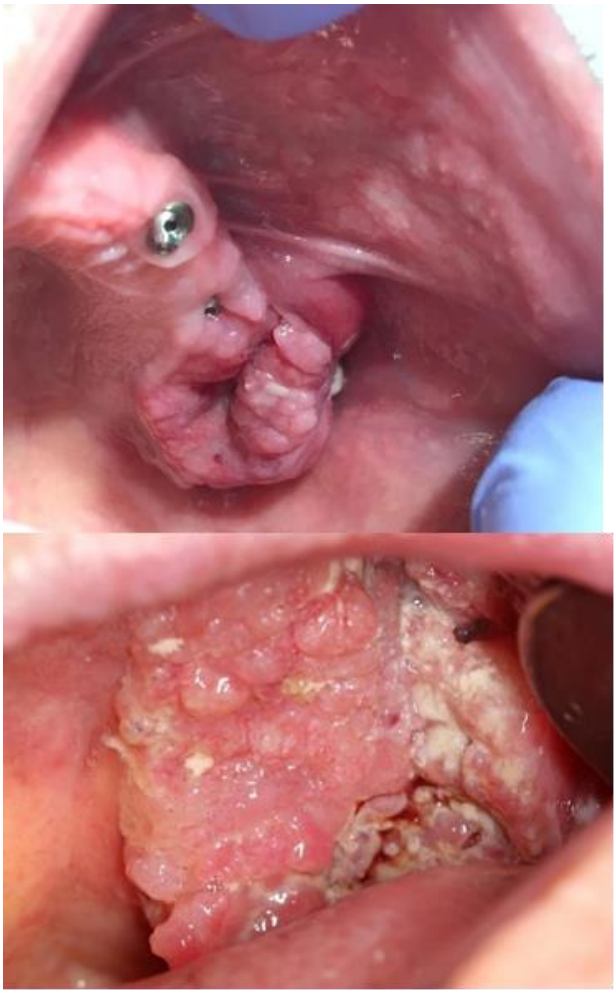

**Figure 9:** Two recent cases of evolved OSCC, one in a patient with a removable prosthesis and the other with a prosthesis on implants. Something must have gone wrong for these patients with treatments in the mouth to come so late for review.

A separate section encompasses the ***non-neoplastic bone pathology***. Here, we include benign fibrous lesions [periapical cementum dysplasia, florid cementum dysplasia, focal bone cementum dysplasia, fibrous dysplasia], Paget's disease, central giant cell granuloma, aneurysmal bone cyst, and osteomalacia.

As we have mentioned, we present a simple case of localized bone dysplasia.

On ***bone pathology***, which is not the main objective of this handbook, the decision Tables Sapp et al. [6] presented are relevant. They are reproduced here in modified versions (Figures 10-13).

Finally, we review ***oral manifestations of systemic diseases*** following the scheme Ibsen & Phelan [4] presented combined with the topics Cawson E [5] highlighted. We summarize them in Table 4 and complement them in Tables 5-7.

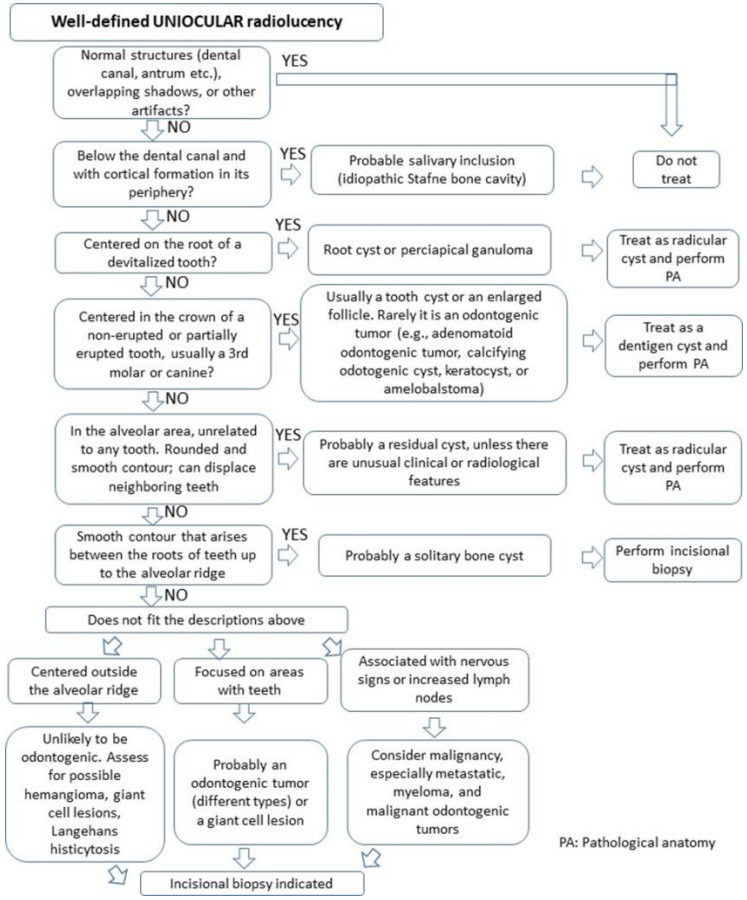


**Figure 10:** - Differential diagnosis of a well-defined radiolucent bone image. Modified from Cawson E [5].

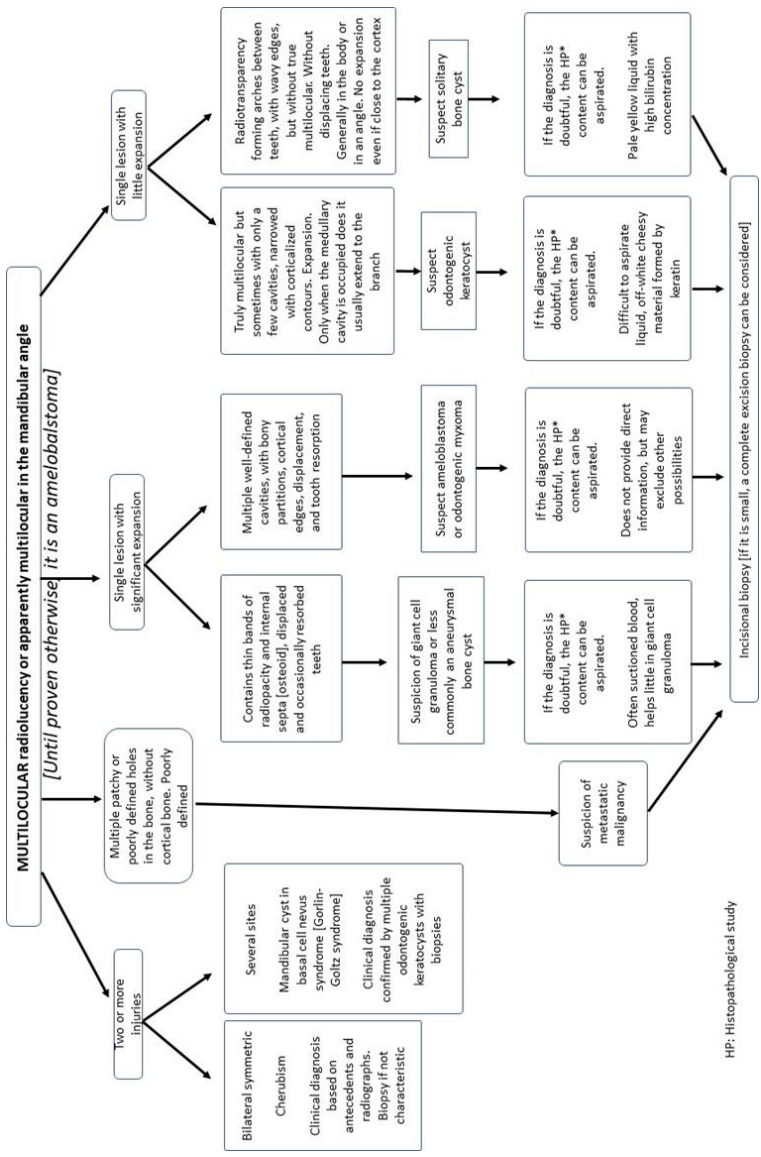


**Figure 11:** - Differential diagnosis of a multilocular bone image at the angle of the mandible. [until proven otherwise, it is an ameloblastoma]. Modified from Cawson E [5].

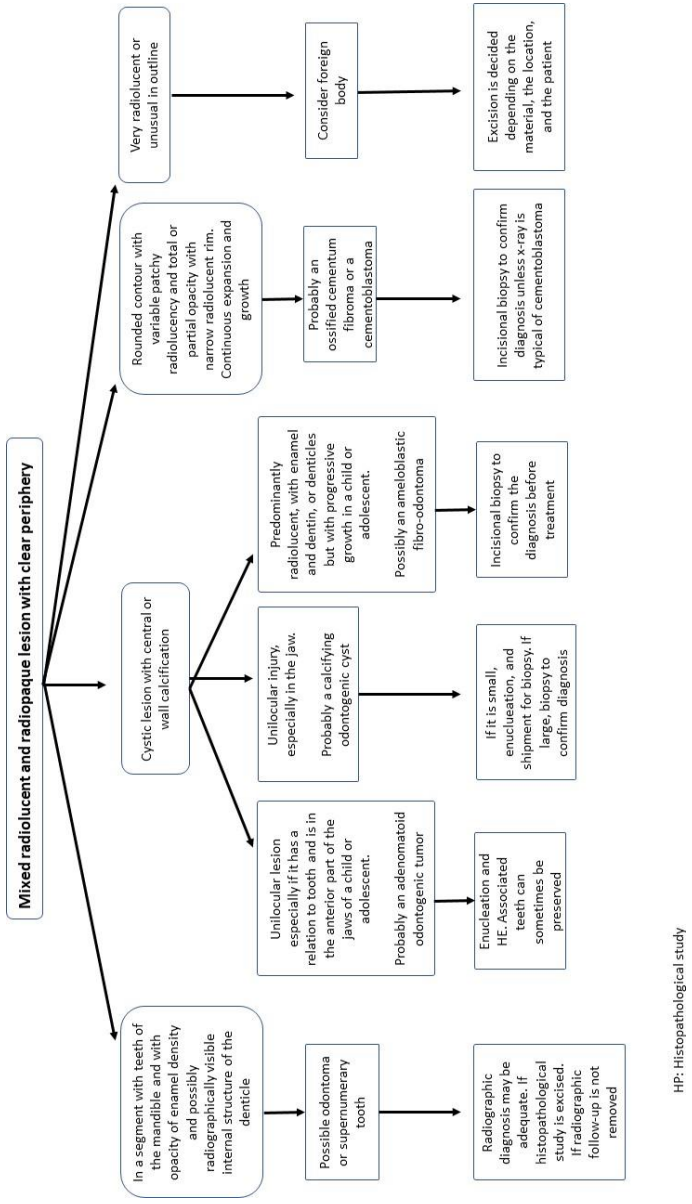


**Figure 12:** - Differential diagnosis of a radiolucent bone image and a mixed radiopaque lesion with a sharp periphery. Modified from Cawson E [5].

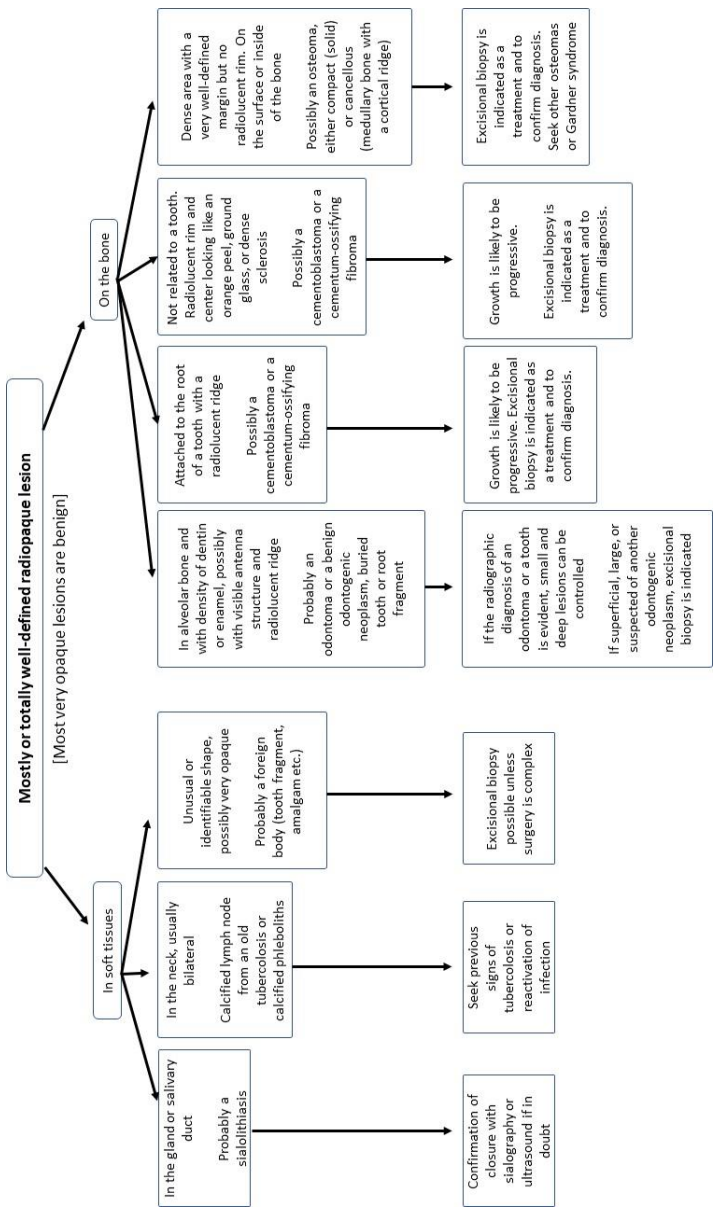


**Figure 13:** - Differential diagnosis of a radiopaque lesion image well-defined in its majority or in its entirety. Modified from Cawson E [5].

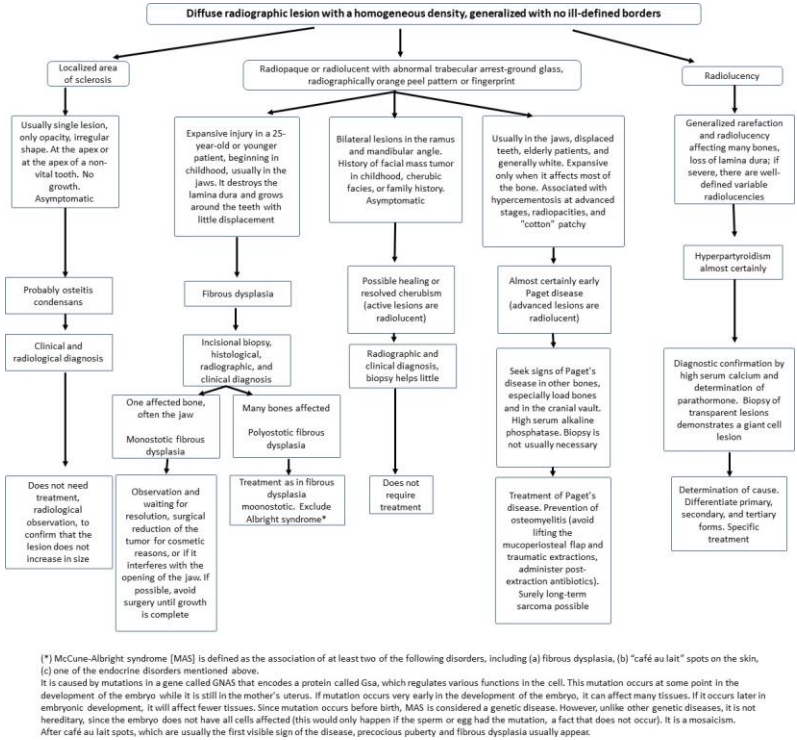


**Figure 14**: Diffuse radiographic lesion with a homogeneous density, generalized with no ill-defined borders. Modified from Cawson E [5].

**Table 4:** Summary of oral implications of systemic diseases. Adapted from Ibsen & Phelan[4] and Cawson E [5].

| *Disease* | *Data of interest* | *Remarkable clinic development* | *Dentistry* |
|---|---|---|---|
| **Anemias** (See Table 5) | Secondary anemias to the deficiency of iron or vitamin B12 and folic acid are the most frequent. | Paleness, fatigue and lassitude, panting, tachycardia and palpitations, glossitis and other mucosal lesions. | Mucosal disorders: Glossitis, angular cheilitis, recurrent canker sores, infections [especially by candida], tongue depapillation. |
| **Leukemia** | It is due to the overproduction of white blood cells and suppress of other cell lines. The different types of acute leukemias are not clinically different. Conics are slow and usually occur in adults. | Anemia due to bone marrow suppression.<br>Increased infections due to neutrophil involvement.<br>Tendency to bleeding (purpura) due to suppression of platelets. | Gingival inflammation. Ulcers of the mucosa. Leukemic deposits.<br>Purples, Anemia.<br>Cervical lymphadenopathy. *Chronicle:* [infrequent] Pale mucous membranes.<br>Inflammation of the gums and palate.<br>Purple.<br>Oral ulcers (due to the disease or drugs used). |
| **Lymphomas** | They are solid tumors; lymphocytic lymphomas can present lymphocytic leukemia.<br>They can frequently involve cervical lymph nodes.<br>In HIV, they can be more frequent in the mouth.<br>They are:<br>-Non-Hodgkin lymphomas.<br>-Hodgkin lymphoma.<br>-Burkitt lymphoma.<br>-MALT lymphoma [mucosa-associated lymphoid tissue].<br>-Nasopharyngeal lymphomas. | It usually presents ganglion tumors and a greater or lesser degree of decay. | If we focus on the nasopharyngeal T-cell:<br>-In the beginning, it could resemble a Wegener granulomatous.<br>-A central ulceration or necrosis of the palate may appear. |
| **Leukopenia and agranulocytosis** | It is a deficiency of granulocytes [below 5,000/µl] due to:<br>-Leukemia<br>-Aplastic anemia.<br>-Drugs [especially phenylbutazone, chloramphenicol, and occasionally cotrimoxazole, phenothiazine, thiouracil, and cytotoxic drugs].<br>-Autoimmune.<br>-HIV. | It can manifest without symptoms at the beginning of the disease.<br>Agranulocytosis: these are the clinical effects of severe neutropenia with fever, general malaise, and ulcerations of the mucosa, especially in the gums and pharynx. | Regardless of possible ulcers, special care should be taken in improving oral hygiene, controlling infections, avoiding extractions, and evaluating the use of antibiotics. |
| **Hemorrhagic diseases** | Platelet alterations [Purple]. Clotting time is usually normal and there is an increase in bleeding time [except for the Von Willebrand disease].<br>Thrombocytopenia: platelets < 100,000 platelets/$mm^3$.<br>Bleeding or spontaneous < 50,000 platelets/$mm^3$.<br>If we list them:<br>-Idiopathic thrombocytopenic purpura.<br>-Purple associated with AIDS.<br>-Purple is associated with drugs: chloramphenicol, phenylbutazone, indomethacin, thiazide diuretics, quinine, and quinidine.<br>-Antiplatelet treatment.<br>-Associated with infections: viral hemorrhagic | They occur with purples (bleeding in the skin or mucous membranes, which causes petechiae or ecchymoses or spontaneous bruises). They are usually associated with trauma and are self-limited. | There may be spontaneous bleeding in the gum, especially in Idiopathic Thrombocytopenic Purpura [ITP], [presence of IgG autoantibodies against platelets].<br>Sometimes hemorrhagic blisters. |

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| | fevers.<br>-Nutritional alterations: Scurvy, only historical value.<br>-Hereditary hemorrhagic telangiectasia.<br>-Localized oral purpura.<br>-Von Willebrand's disease.<br>-Disseminated intravascular coagulation. | | |
| | Hereditary clotting diseases:<br>-Hemophilia A, Hemophilia B, Von Willebrand's disease with low factor VIII. | There is a positive family history [but in 30% of hemophiliacs it is negative], however one's own is always positive.<br>In hemophilia, there is usually spontaneous bleeding into the skin and joints. | In cases with factor VIII < 25%, minimal dental treatments can trigger severe bruising.<br>The suture and/or pressure does not contain the bleeding. Treatment with hospital admission and replacement treatment. |
| | Acquired coagulation diseases:<br>-Acquired deficits: Vitamin K deficiency, liver disease, anticoagulant treatment. | They are relatively frequent<br>-Vitamin K deficiency. It is usually caused by obstructive jaundice or malabsorption.<br>-ACO and NACA. | The patient should be treated by stabilizing the problem. Give vitamin K orally. Fresh plasma, tranexamic acid. |
| **Immunodeficiencies and HIV (*)** | They can be primary or acquired and can affect antibody production and/or cell-mediated immunity. There are two large groups:<br>*Primary (congenital)*<br>-TO B lymphocyte defects (Swiss type, agammaglobulinemia, Di George syndrome etc.).<br>-Immunoglobulin A deficiency.<br>-Deficiencies in the components of the complement.<br>-Down syndrome (multiple defects).<br>*Secondary (Acquired)*<br>-Infections (HIV, other serious viral or bacterial infections, malaria etc.).<br>-Induced by drugs (immunosuppressive and oncological treatment).<br>-Malnutrition (it is a leading cause worldwide).<br>-Cancer (particularly lymphoma and leukemia).<br>-Mellitus diabetes.<br>-Aging. | Recurrent infections, especially from unusual germs.<br>Those of the associated pathology.<br>Sometimes atopic and connective tissue disease (lupus) [especially selective IgA deficits]. | They can cause infections: Herpes I and II, Human herpes 8, Epstein Bar, Cytomegalovirus, Candida, Bacterial infections<br>Neoplasia: Kaposi's sarcoma, Lymphomas.<br>Other: lymphadenopathy, hairy leukoplakia, mucositis, ulcers, bleeding, silky mouth, mumps, graft versus host reaction. |
| **Allergies** | They are entities mediated by immune complexes and a response to external allergens. They can affect 10% of the population and are mediated by IgE. | Respiratory issues due to asthma. Contact dermatitis, allergy to latex, mercury, and other metals. | There are no specific oral affectations, and oral eczema has not been described.<br>Acute angioedema** [sometimes as a reaction to a drug] can manifest in the oral cavity as swelling and lip edema.<br>The drugs used can cause oral involvement. Thus, antihistamines can cause drowsiness and dry |

| | | | |
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| | | | mouth; inhaled corticosteroids, canker sores, erythema, and candidiasis; and systemic corticosteroids superinfection. |
| **Autoimmune diseases** | They are diseases caused by an inadequate response of immune activity. They all have several characteristic signs (Table 6). | They affect different organs and systems with varying degrees of severity. | Among them, we mention here systemic lupus erythematosus and scleroderma.<br>In the former, the secondary effects of its treatment, oral lesions, association with Sjogren's syndrome, tendency to bleeding [antibodies against platelets], anemia, and heart disease must be considered.<br>Scleroderma is associated with Sjogren's syndrome, limited opening, periodontal widening etc. |
| **Cardiovascular diseases** | At present, the possible bi- directionality among oral patients is analyzed, especially periodontal disease and cardiovascular events. | They are frequent diseases with different degrees of impairment of functional capacity, especially when related to physical activity. | Special care depending on the degree of affectation (***)<br>Perhaps it is worth reviewing the dental implication of different drugs in its treatment (Table 7). |
| **Respiratory diseases** | Acute and chronic sinusitis have a special implication in their relationship with the oral cavity.<br>Pulmonary tuberculosis is rare, but it must be considered.<br>Sarcoidosis, as an example of granulomatous disease, is an entity of unknown origin with multisystemic symptoms.<br>Chronic obstructive pulmonary disease and asthma are common diseases.<br>Sleep apnea syndrome can affect 2-4% of the population. | Sinusitis has its own signs: runny nose, fever, headache, earache etc., and sometimes associated dental pain.<br>In sarcoidosis, the respiratory symptoms and chest X-ray are highly indicative. | Tooth pain can be confused with sinus pain.<br>There may be lymphadenopathy of tuberculosis origin.<br>Sarcoidosis can present non-painful inflammatory reactions, especially in the gums. There may also be involvement of salivary glands.<br>COPD and asthma medication can have dental implications |
| **Gastrointestinal diseases** | We can consider:<br>-Gastroesophageal reflux.<br>-Celiac disease.<br>-Inflammatory bowel disease: Chron and ulcerative colitis: Malabsorption syndrome (****).<br>-Pseudomembranous colitis [*Clostriodium difficile* infection, associated with treatment with clindamycin or lincomycin]<br>-Familial polyposis, autosomal dominant disease.<br>-Peutz-Jeghers syndrome. | -The clinic manifestation varies greatly from asymptomatic to weight loss or growth retardation in celiac disease.<br>-Inflammatory bowel disease occurs with diarrhea/constipation, abdominal pain, malabsorption, and in the case of ulcerative colitis joint alterations are more frequent.<br>-Familial polyposis is associated with osteomas in jaws and sometimes dental defects or epidermoid cysts. It has a high percentage of malignancy.<br>-In Peutz-Jeghers disease, intestinal polyps are associated with perioral pigmented macules. | Direct oral involvement is rare.<br>-Vomiting, if continuous, can cause dental and mucosa problems.<br>-Up to 5% of celiac patients have thrush, and/or recurrent glossitis even without anemia.<br>-Inflammation and ulceration sometimes as cobblestones in inflammatory bowel disease. There may also be a diffuse and soft inflammation of the lips, gingival erythema, thrush, malabsorption glossitis. In colitis, a chronic ulcer (pyoestomatitis vegetans) is described. |
| **Liver disease** | Among the most notable liver diseases, there are:<br>-Viral infections.<br>-Obstructive jaundice.<br>-Frequently alcoholic cirrhosis. | Apart from the clinical manifestations, we must remember that most drugs are metabolized in the liver.<br>The symptoms are usually variable, | In the case of viral hepatitis, it is especially involved as a vehicle for transmission.<br>From the dental point of view, we must consider: |

| | | | |
|---|---|---|---|
| | -Tumors.<br>-Drug poisoning. | but generally there is weakness and decay. | -Tenancy to bleeding.<br>-Alteration of drug metabolism.<br>-Skin manifestations: purpura, telangiectasias, acrocyanosis).<br>-Sjogren's syndrome in primary biliary cirrhosis. |
| **Endocrine diseases** | Hyperpituitarism:<br>Excess growth hormone is manufactured in the pituitary gland. There is usually a pituitary adenoma. | The skeleton grows excessively, especially hands and feet.<br>. | Hypertrophy of the maxilla, the mandible, and the maxillary sinus.<br>Separation of teeth with malocclusion.<br>Frontal bulging of hypertrophy of<br>the nasal bones. |
| | Hyperthyroidism (Graves disease): Excess thyroid hormone is produced. | Rosy appearance, palmar erythema, excessive sweating, exophthalmos, soft hair and nails<br>Anxiety, weakness, restlessness, heart problems. | Children: Premature exfoliation of temporary teeth and early eruption of permanent ones.<br>Adults: osteoporosis, tooth decay, periodontal disease [apparently rapidly progressing]. |
| | Hypothyroidism:<br>Low production of thyroid hormone. | Hypodynamia, bradycardia, asthenia. | Children: thickened lips, macroglossia, delayed tooth eruption.<br>Adults: macroglossia. |
| | Hyperthyroidism<br>Excessive secretion of parathyroid hormone. It may be due to a parathyroid tumor [primary], kidney disease, or vitamin D deficiency, among others [secondary]. | Joint pain and stiffness, drowsiness. | Periodontal widening with "tooth loosening." |
| | Diabetes mellitus [12]<br>Insulin deficiency and/or resistance. Type 2 frequently associated with metabolic syndrome. | More atherosclerosis.<br>-More ulcers and gangrene in distal areas.<br>Polyneuropathy Eye injuries. | Less resistance to infections, including candidiasis.<br>Delayed healing.<br>Salivary gland hypertrophy. Xerostomia.<br>Pigmentation and some degree of<br>oral melanosis. |
| | Addison's disease:<br>Insufficient adrenal steroid production: Adrenal tumor, Infections such as TB, autoimmune causes etc. | Brown pigmentation of the skin. | Oral melanocytic spots. |
| **Kidney diseases** (see Table 8) | We have to consider patients with chronic renal failure [CRF] and those with CRF who are controlled by dialysis or kidney transplantation. | | Dialysis patients usually have hemostasis alterations for six-12 hours due to heparin.<br>Arteriovenous fistulas can become superinfected and antibiotic prophylaxis should be considered. Transplant patients are immunosuppressed.<br>Children with CKD may have enamel hypoplasia and delayed eruption. |

(*) It is reviewed in depth in a case; (**) The hereditary version is due to the deficiency of the C1 esterase inhibitor, which alters the complement pathway and causes severe reactions to minor stimuli; (***) This issue is insisted on in a case report; (****) Other causes of malabsorption are intestinal or gastric resection, pancreatic insufficiency, chronic intestinal infections; (*****) Very dependent on the degree of control of dia.

**Table 5:** Types and characteristics of the main anemias. Adapted from Cawson E [5].

| **Type of anemia** | **Causes or effects** |
|---|---|
| Iron deficiency (hypochromic microcytic anemia)* | Usually due to chronic blood loss |
| Folate deficiency (macrocytic) | Pregnancy, malabsorption, alcoholism**, induced by phenytoin etc. |
| Vitamin B12 deficiency (macrocytic anemia) | Usually due to anemia Pernicious and occasionally malabsorptive |
| Leukemia and aplastic anemia (normochromic normocytic) | Reduced red cell synthesis, and associated susceptibility to infection and bleeding tendency |
| Sickle cell anemia (normocytic anemia) | Genetics. Hemolytic anemia. Sickle cells are seen on special histopathology slides |
| ß-thalassemia (hypochromic microcytic) | Genetics. Hemolytic anemia. Many red blood cells are poorly formed |
| Chronic inflammatory disease (normochromic, normocytic) | Rheumatoid arthritis is a common cause |
| Liver disease (usually normocytic) | May be associated with increased bleeding |

*There is a rare variant that is associated with chronic iron deficiency and that causes dysphagia, glossitis, angular cheilitis, atrophy of the lingual papillae, atrophy of the proximal digestive tract, and predisposition to develop esophageal cancer. It is the Plummer Vinson syndrome; **Alcoholism should always be ruled out when macrocytosis is found in the absence of anemia, since it is a characteristic sign of alcoholism.

**Table 6:** Autoimmune diseases and their common signs. Adapted from Cawson E [5].

| **Typical characteristics of autoimmune diseases** |
|---|
| Significantly more common in women |
| Appearance in middle-aged patients |
| Generally high immunoglobulin levels |
| Frequent family history |
| Circulating auto-antibodies are usually detected in unaffected relatives |
| Multiple circulating auto-antibodies against distinct and possibly unrelated antigens |
| There is usually a higher risk of developing a second autoimmune disease |
| Immunoglobulin and/or complement are usually detected in areas of tissue damage (e.g., pemphigus vulgaris) |
| It is usually associated with human leukocyte antigens B8 and DR3 |
| Immunosuppressive or anti-inflammatory treatment usually limits tissue damage |
| **Types and examples of autoimmune diseases** |
| *Specific antibodies against an organ or tissue:*<br>-Hashimoto's thyroiditis<br>-Chronic atrophic gastritis (pernicious anemia)<br>-Addison's disease<br>-Idiopathic hypothyroidism<br>-Pemphigus<br>-Pemphigoid<br>-Idiopathic thrombocytopenic purpura.<br>-Autoimmune hemolytic anemia<br>-Myasthenia *gravis* |
| *Non-organ specific autoantibodies (connective tissue diseases):*<br>-Lupus erythematosus<br>-Rheumatoid arthritis<br>-Sjogren syndrome<br>-Systemic sclerosis<br>-Primary biliary cirrhosis<br>-Dermatomyositis<br>-Mixed connective tissue disease |

**Table 7:** - Drugs used in cardiovascular disease treatment and their dental implication. Adapted from Cawson E [5].

| ***Drugs*** | ***Implications in dental treatment*** |
|---|---|
| Diuretics | Sometimes oral dryness |
| Angiotensin converting enzyme (ACE) inhibitors, captopril, enalapril etc. | Oral burning symptoms, lichenoid reactions, Angioedema |
| Angiotensin-II receptor blockers, losartan, disopyramide etc. | Taste disturbance, oral dryness |
| Calcium channel blockers, amlodipine, diltiazem etc. | Gingival hypertrophy (especially with diltiazem and nifedipine) |
| P-adrenergic blockers, labetalol, propranolol etc. | Oral dryness, lichenoid reactions, theoretical interaction with adrenaline |
| Antihypertensives (as the above) | Potentized by general anesthetics |
| Anticoagulants, Warfarin | Risk of prolonged postoperative bleeding |
| Antianginal drugs: Nicorandil, Digoxin | Oral ulcers |

**Table 8:** Other aspects of interest in kidney diseases. Adapted from Cawson E [5].

| ***Aspects of interest associated with kidney disease*** |
|---|
| -Administration of heparin before dialysis<br>-Possibility of being a carrier of hepatitis B or C after chronic dialysis<br>-Permanent venous fistulas susceptible to infection<br>-Increased risk of endocarditis<br>-Secondary hyperparathyroidism<br>-Immunosuppressive treatment for nephrotic syndrome or in transplant patients<br>-Oral lesions due to drugs, particularly immunosuppressants<br>-Reduced excretion of some drugs<br>-Oral lesions of chronic kidney failure:<br>..Mucous paleness (anemia)<br>..Xerostomia<br>..Purpura<br>..Mucous ulcers<br>..Muguet<br>..Oral keratosis [whitish epithelial plaques]<br>..Mandibular brown tumors (secondary hyperparathyroidism) |
| ***Considerations in dental treatment*** |

| |
|---|
| -Corticosteroids and other immunosuppressive treatments<br>-Hemorrhagic tendency<br>-Anemia<br>-Alteration of drug excretion<br>-Hypertension<br>-Patient with hepatitis B or C<br>-Underlying causes (e.g., diabetes mellitus, hypertension, or connective tissue diseases) |

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## Case Report

# Oral Manifestations of Acute Myeloid Leukemia

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## Abstract

Leukemia is a cancerous disease that affects the production of blood cells, resulting in an uncontrolled increase in these same cells, a delay in diagnosis could be fatal. In many cases, this pathology is manifested by oral lesions. We present the case of a male who referred pain in the lower molars where there were ulcerated lesions. Fifteen days later and after removing all possible causes, there was no improvement and, furthermore, he indicated discomfort, fatigue and fever. An underlying disease was suspected, so he was asked for a blood test and referred to

the haematologist. He was diagnosed with myeloid leukemia. It is very important for the dentist to recognize the oral lesions in order to obtain an early diagnosis and thus achieve an early diagnosis of the disease.

## Keywords

Leukemia; Oral Manifestations; Ulcer; Aphtous Lesions; Oral Mucosa; Systemic Disease

## Key Points

Gingival ulcer as oral manifestation of leukemia

## Introduction

Leukemia is a cancerous process of hematopoietic origin which affects the production of blood cells. This pathology causes large amounts of abnormal blood cells that later will enter into the bloodstream. Depending on the speed with which it develops, it can be acute or chronic, in the case of acute leukemias blood cells are not well differentiated, while in chronic leukemias there is good cell maturation and differentiation [1-3].

Two types of leukemia are known according to the affected primary hematopoietic line (Figure 1), the most frequent types are: myeloid (monocyte involvement) and lymphocytic (lymphocytes involvement). Acute lymphocytic leukemia (ALL) is the most frequent pediatric cancer, although adults of all ages can be involved too, in this entity progenitor hematopoietic cells undergo a malignant transformation and uncontrolled proliferation with abnormal differentiation, they have a long survival which determines a high number of circulating blastocytes, the regular bone marrow is replaced by malignant cells and there may be a leukemic infiltration in the central nervous system (CNS) and abdominals organs. Acute myeloid leukemia (AML) is more common in adults, under normal circumstances the bone marrow is the natural responsible for myeloblasts production which matures and give rise the granulocytes, therefore, in the case of AML, these myeloblasts

proliferate in an abnormal way and progressively invade the bone marrow, interfering with the normal production of blood cells and provoke a decrease of red blood cells and platelets [4].

At the systemic level, leukemia can manifest with fatigue, anemia, lymphadenopathy, recurrent infections, fever, bone and abdominal pain, bleeding and purpura [5]. In the oral cavity can also appear signs which may mean an underlying hematopoietic disease. Oral manifestations, as detail below, have been widely described and related to leukemia over the years and, sometimes can even be considered primary signs of the appearance of this pathology. Among these manifestations we can find petechiae on the tongue, lips, hard and soft palate, gingival enlargement as well as spontaneous gingival bleeding, nonspecific ulcerations, infections, sore throat or pharyngitis [6-8]. These symptoms may be isolated or in combination with each other and can be present in any type of leukemia, although oral manifestations are more frequent in acute leukemias and in myeloid type [9,10].

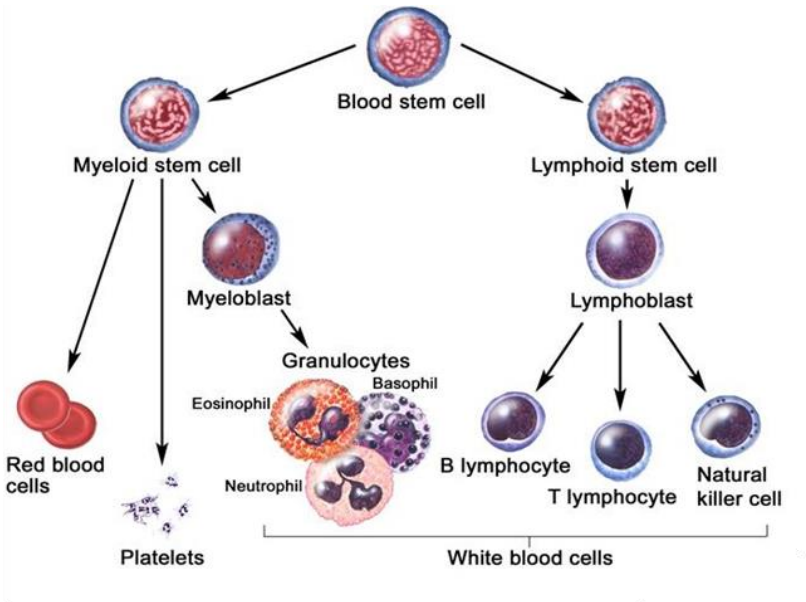



**Figure 1:** Blood cell development. A blood stem cell goes through several steps to become a red blood cell, platelet, or white blood cell. Adapted of USA National Cancer Institute [3].

## Case Report

A 63-years-old male patient came to the dental clinic in early June 2019 referred by another dentist to assess periodontal disease and its treatment, since he presented 6mm of probing depth in areas of lower molars. The patient reported a lot of pain at lingual face of these molars that interfered with swallowing and speaking, a few days before the dentist had prescribed him dexketoprofen 25mg every 8 hours and amoxicillin 750mg every 8 hours per 7 days.

Regarding his medical general history there was not any relevant data of interest, no drugs allergies, neither pathology nor being under any pharmacological treatment.

In relation to his dental history, he was bruxist and did not have a nightguard. A year and a half before, an implant was placed on 36 position, which molar had been removed previously due to a fracture. In the middle 2018 this implant failed so it was removed and at the beginning of 2019 it was replaced in the same position and it was rehabilitated with an implant supported crown on April 2019.

To clinical examination a pseudopocket was observed in distal of both 37 and 47, even so, periodontal general health was good. In 37 lingual there was an ulcer (Figure 2) it was rounded, 5mm diameter approximately, well defined, regular edges, erythematous and tough base at touch, there was no affectation of the gingival margin which showed erythematous and swollen because of plaque accumulation since he referred a lot of pain at brushing teeth. In lingual face of 47 (Figure 3) it was observed an ulcer that reached the gingival margin, 3-4mm diameter approximately, irregular shape and well defined edges. He also complained of discomfort on his tongue, where he had an aphtous lesion in the middle third of the lingual dorsum, 2mm diameter approximately, rounded and well defined (Figure 4). It was suspected the existence of a possible sequestrum in 37 so a X- ray was taken and asked for a CT (Figure 5), no data of interest was observed, however, a bone remodeling of the base of the ulcer was made and we had an expectation attitude[11]. After ten

days, the patient came back to the dental clinic for review, the 37's ulcer had got worst (Figure 6) meanwhile 47's ulcer had remained equal (Figure 7) and the aphtous lesion on the lingual dorsum had disappeared. Additionally, the patient reported fatigue, malaise, febricula and the pain of the ulcer had not decreased, for all these reasons it was recommended to do a blood test (Table 1). It was suspected a possible underlying hematopoietic disease so he was referred to the Hematology Department of his hospital where, after relevant exams, the patient was diagnosed with Acute Myeloid Leukemia. In spite of being under chemotherapy treatment and evolve properly, the patient phoned us and returned two months later for review because the discomfort in 37 had lightly decreased but it was unsolved and still remained. He had been recommended to carry periodontal therapy out to improve his situation but after evaluate the molar, a bigger bone exposition was noticed (Figure 8) and finally 37 was extracted. Otherwise, ulcer in 47 was full recovered (Figure 9).

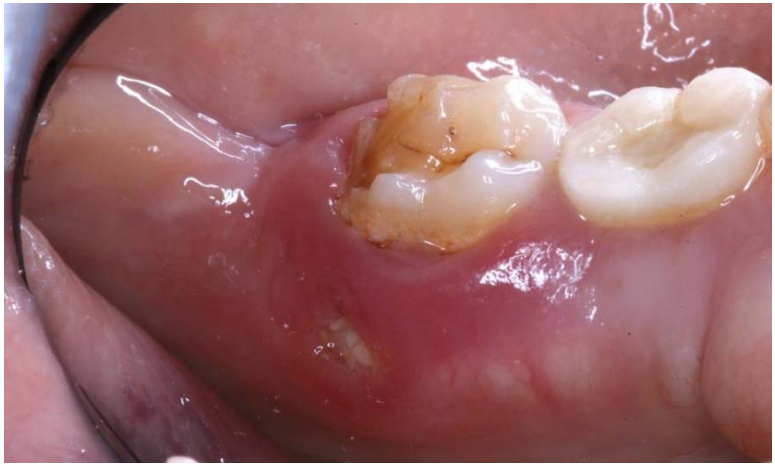


**Figure 2:** Ulcer in lingual of 37.

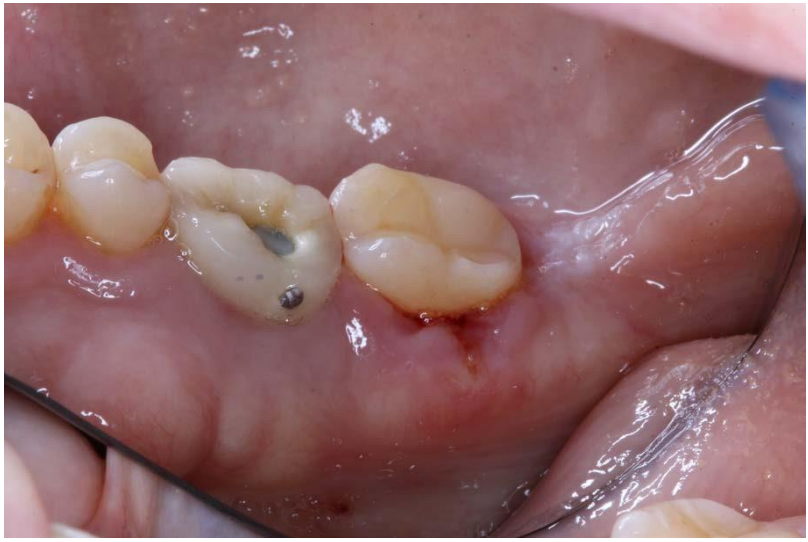


**Figure 3:** Ulcer in lingual of 47.

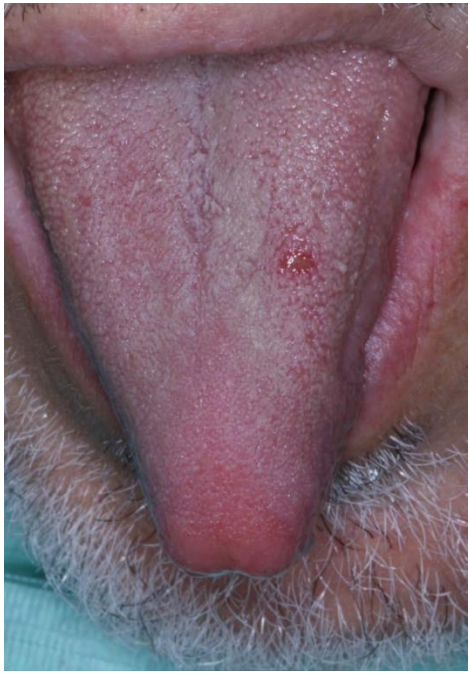


**Figure 4:** Aphtous lesion in dorsum tongue.

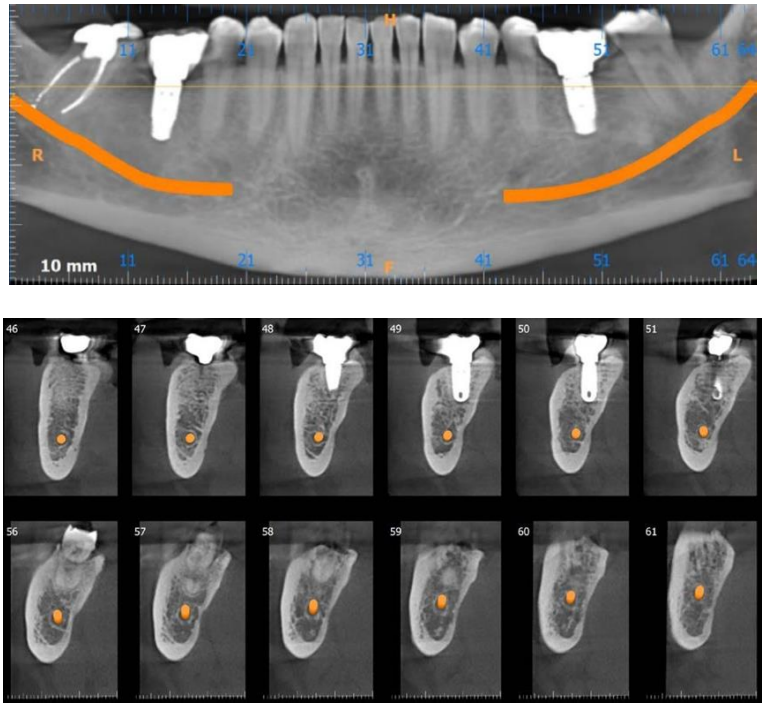



**Figure 5:** CBTC correlated to 37 where there is no presence of sequestrum.

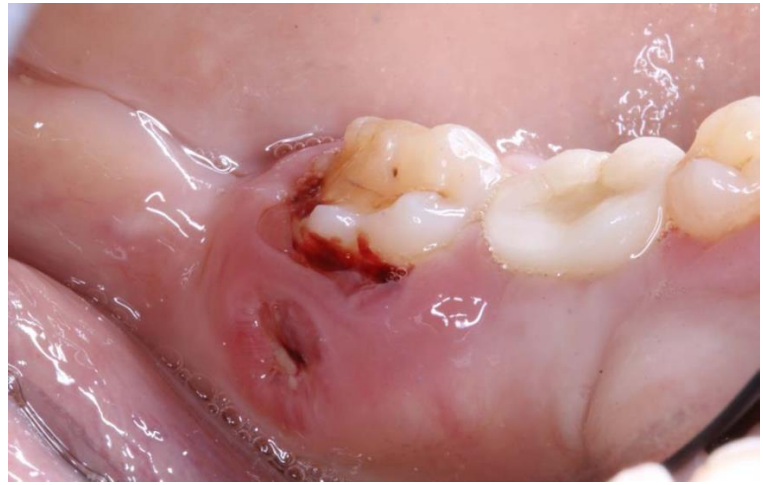
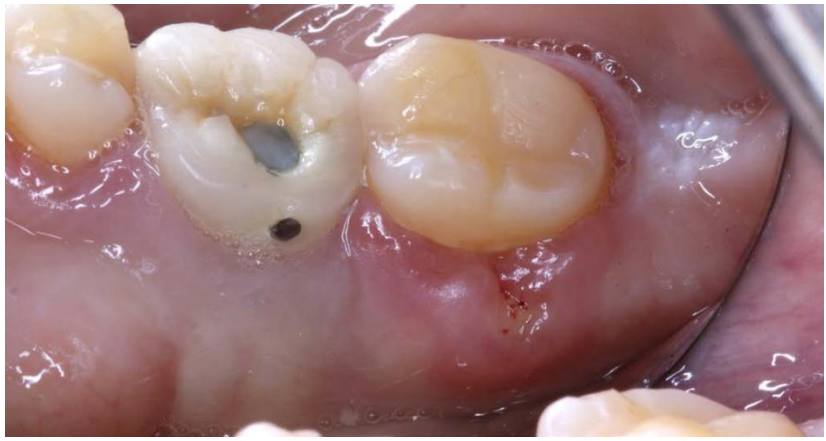


**Figure 6:** Ulcer in 37 after 10 days.



**Figuere 7:** Ulcer in 47 after 10 days.

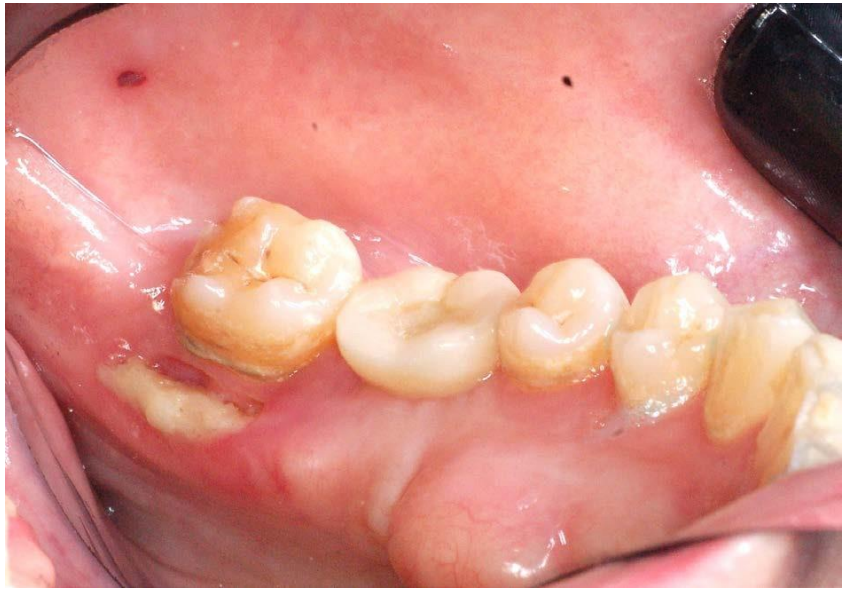


**Figure 8:** Ulcer in lingual of 37 after two months.

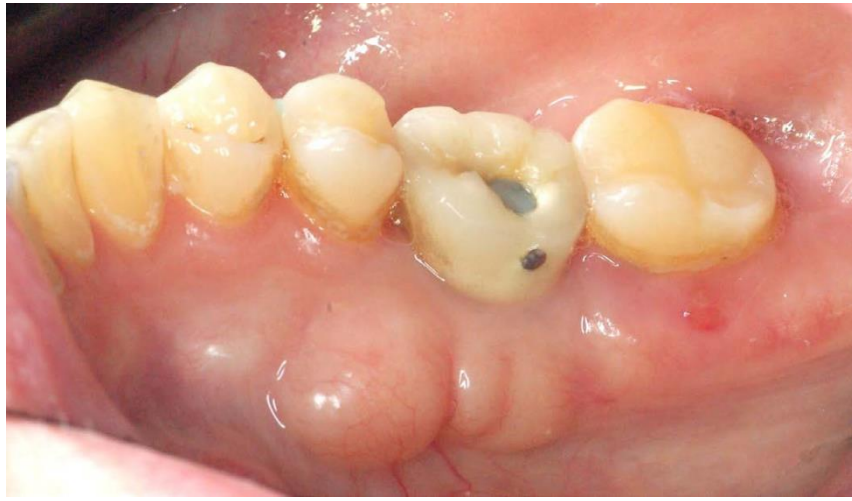


**Figure 9:** Lingual face of 47 after two months.

The patient was successfully treated, he responded favorably to the therapy so it was not needed to execute a bone marrow transplantation. Nowadays, he is stable, has got over the disease and keep the review appointments according to the medical protocol.

**Table 1:** Altered blood test results of the patient are shown.

| ANALYTICAL DETERMINATION | RESULT | UNITS | REFERENCE RANK |
|---|---|---|---|
| Erythrocytes | 2,72 | $x10^6/mm^3$ | 4,1-5,75 |
| Hemoglobin | 9,0 | g/dl | 12,5-17,2 |
| Hematocrit | 27,2 | % | 36,5-50,5 |
| Average Corpuscular Volume (ACV) | 100 | fL | 78-99 |
| Neutrophils | 33,3 | % | 42-77 |
| Lymphocytes | 50,8 | % | 20-44 |
| Monocytes | 14,4 | % | 1,5-9,5 |
| Eosinophils | 0,3 | % | 0,5-5,5 |
| Monocytes | 1,1 | $x10^3/mm^3$ | 0,1-0,95 |
| Eosinophils | 0,0 | $x10^3/mm^3$ | 0,02-0,5 |
| Platelets | 52 | $x10^3/mm^3$ | 150-370 |

## Discussion

Cancer is one of the main morbi-mortality causes around the world, in 2018 about 18 million of new cases were diagnosed and the experts' forecast is that in 2040 it will increase until 30 million cases approximately. In Spain, cancer is also an important cause of morbi-mortality among the population, by 2020 it's expected about 280.000 new cases will be diagnosed, this number will keep on increasing due to different factors risk as the aging of the population, pollution, obesity, tobacco or alcohol among others [11,12]. In this sense, it is estimated that all along 2020 approximately 6.300 new cases of leukemia will be diagnosed in Spain [12].

The emergence of oral lesions as a consequence of a leukemia is very frequent, especially in acute cases of the pathology. A lot of authors highlight the gingival enlargement as the most frequent manifestation in the oral cavity in the case of leukemia, although is not the only one [13-15]. Lynch and Ship described, in 1967, in a study that involved 155 patients, the existence of oral manifestations as the first sign in leukemia cases, these were petechiae or gingival bleeding (56%), oral ulcers (53%) and gingival hyperplasia (36%) [7].

More recently, Reenesh et al. found that in 5% of AML cases, gingival enlargement was the first clinic manifestation of the disease [13], shown in almost 67% of cases, gingival bleeding was present in 43,2% of AML cases and in 28,6% of ALL, followed by the appearance of ulcers [14]. Meyer et al. figure the percentage of ulcers existing in both AML and ALL around 36% and remark a higher rate of emergence of oral manifestations in leukemia than in other entities because of the immunological system are compromised [17]. Gingival enlargement in AML has been described in toothed patients, not in edentulous one, so it suggests that irritative factors related to teeth may play a role in its pathogenesis. In case of performing a biopsy it is noted a leukemic infiltrate, of monocytes cells, in gingival tissue but if it is made in the earliest phase of gingival involvement, it can result nonconclusive due to the low levels of leukemic infiltrate. However, this test is suitable for a proper diagnosis [18,19].

An ulcer is an elementary lesion, a breach in the oral epithelium, it courses with damage of both epithelium and lamina propria and affects the connective tissue exposing underlying nerve endings, reason which it results painful [20,21]. Its etiology is multiple, the most common causes are trauma, burns or secondary to another disease; here lies the importance of a correct diagnosis: if the ulcer is unique, all possible causal elements are removed and this lesion does not get better after fifteen days, it must be suspected an underlying pathologies such a neoplasm, among others [22]. The development of the ulcer in this kind of cases is the result of an infection produced by a neutropenia [19].

The presence of ulcers, among others symptoms, is a frequent reason why people seek dental care and, as it was shown, they can be an initial sign of leukemia, a entity that in an acute course and with a delayed diagnosis can provoke death in six months.

## Conclusion

Acute myeloid leukemia is a systemic condition that may be mortal. It has been shown that in several times it is displayed with changes in the oral cavity, the reason why is imperative for the dentist to know every oral structure and their changes or abnormalities in order to identify pathologies, as well as characteristic of the oral mucosa or consequence of any systemic disease. In this way, an early diagnosis can be established and carry out a proper therapy as fast as possible, with the final purpose to stop the pathology progression and also decrease the morbid-mortality. However, it is very important to reach and maintain a good communication between professionals, or even a further training about oral cavity pathologies by all physicians.

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## Case Report

# Oral Manifestations as First Clinical Sign of Lymphoma

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## Abstract

Lymphomas are a common neoplasia that sometimes has early oral manifestations. Most dentists misdiagnose them as periodontal disease or different dental infections.

We show a case of a 27 years old men that debuted with oral swelling and dental mobility. He was treated as for periodontal diseases until neurological involvement started and the patient was sent to our Postgraduate program where lymphoma was diagnosed by a gum biopsy. The case illustrates the common delay in the diagnosis that usually happens with this pathology.

## Keywords

Lymphomas; Oral Manifestations; Early Diagnosis; Blood Dyscrasias

## Key Points

Oral manifestations of lymphomas, Early diagnosis.

## Introduction

Lymphomas are the third most common cancer in the world and represent 3% of all malignant tumors [1,2]. They are a lymphoid tissue disease characterized by a malignant proliferation of lymphoid cells or their precursors [3].

Classically they have been classified into two big groups, Hodgkin lymphoma (HL) and no Hodgkin lymphoma (NHL). First-class lymphomas grow preferent in lymphoid nodes and only occasionally surplus infiltrate tissues around (3-4%). Histopathologically they present Reed-Sternberg cells. Their evolution is slow and predictable, and that improves the response to treatment even in the worst stadiums. They have a lapse of preference between 15-34 ages and older than 60 [2].

NHL can be classified in more than 20 different subtypes according to histologic and behavioral patterns, nodes involve in an aleatory way and clinical evolution is more unpredictable [4,5]. Growing in extranodal sites can be so fast in Burkitt lymphoma that they can double the size in less than one week [6]. Gastrointestinal involvement takes place in more than 50% of patients with extranodal lymphoma [7] it is the most frequent location followed by head and neck region which oscillate between 11 y el 33% [1]. NHL can be found at any age and doesn´t have a preferred age group [2] Lymphomas, Leukemia nervous system tumors, sarcomas and renal tumors are the most common neoplasia in early ages [8].

More recently the classification from the "World Health Organisation" (WHO) is being used [9]. The WHO divides

lymphomas by their cell type in: B cell lymphomas, T cell lymphomas, Natural Killer lymphomas, and Hodgkin Lymphoma. Diffuse large B cell lymphoma (DLBCL) is the most frequent NHL. There is a kind of DLBCL with very aggressive behavior showing similar traits to Burkitt lymphoma that WHO marks as unclassifiable [10-12]. The most common staging system is the Ann Arbor classification which is based on the number of regions with ganglion involvement, the presence of extraganglional involvement, the affectation above and below the diaphragm and the appearance of systemic symptoms, each representing a more advanced stage than the previous one [2,10].

According to their histological type, Lymphomas can show different behavior and aggressiveness, so a biopsy is key to find the appropriate treatment for each case. The choice of treatment should consider other variables also such as clinical findings [11].

Treatments used include radiation therapy, chemotherapy, growth factors that limit myelosuppression and marrow transplantation, and monoclonal antibodies that act against the antigenic surface of the affected cells.

Lymphomas are the second or third malignant entities in head and neck territory only behind epidermoid carcinoma and next to salivary glands tumors [4,7]. Oral manifestations of lymphomas are rare, only occur in 3% of all lymphomas, the percentage increases significantly if we talk about AIDS patients, in these cases the risk of lymphoma increases by 100 times compared to the rest of the population [2,13].

In maxillofacial territory the most common expression of lymphomas is the appearance of non-painful inflamed nodes, fast-growing painless swelling, and ulcers that do not heal and can be located all throughout the oral cavity (palate, gums, tongue, jugal mucosa, mouth floor, lips, salivary glands and breasts). This can be accompanied by tooth mobility and neurological symptoms such as paresthesia and anesthesia. Patients may also refer systemic signs and symptoms such as fever, weight loss, appetite loss, night sweat fatigue and itching [2,9,10,14].

Lymphomas are difficult to identify by their oral manifestations because they are often misdiagnosed as other diseases such as periodontal disease, osteomyelitis, or other tumors. This can delay diagnosis and worsen the prognosis [14-17].

## Case Report

A 27 years old man presented to his dentist with a swelling around mandibular left first molar he refers discomfort but no pain. A periapical X-Ray revealed moderated bone loss (Figure 1).

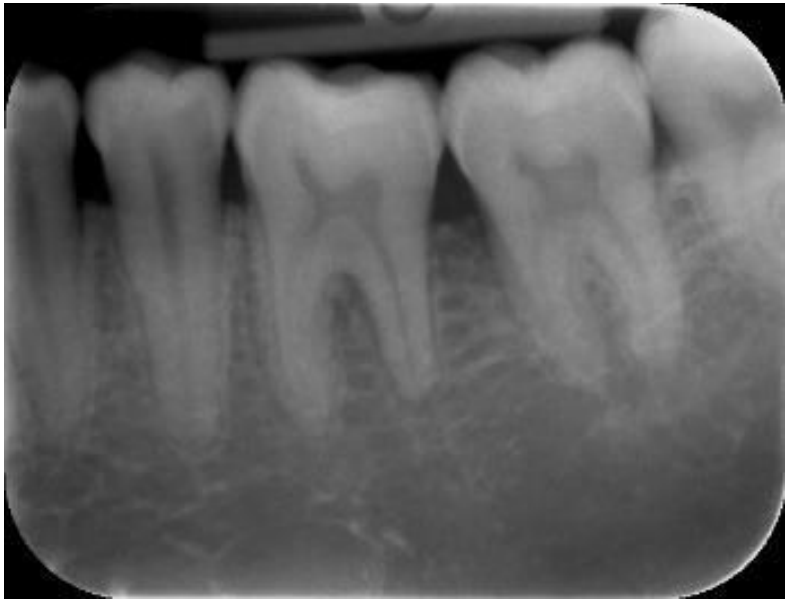


**Figure 1:** Initial status: Patient comes with swelling between first and second mandibular left molars. X-ray showed moderated bone loss between 36-37. Treated with antibiotics and periodontal cleaning.

Inspection showed swallowed gingiva in the mandibular area between first and second left molars. It was treated as a periodontal abscess with antibiotic (amoxicilin/clavulanic acid) and periodontal treatment.

Patient came to check after 10 days with no clinical improvement. Change of antibiotic was made (Doxiciclin) and other periapical X-ray (Figure 2) revealed more clearly bone loss between 36 and 37 so he insisted in periodontal treatment.

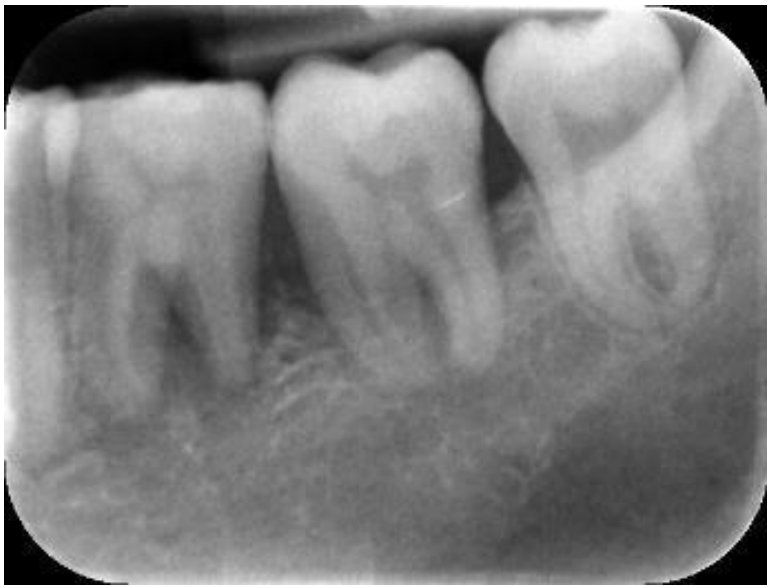
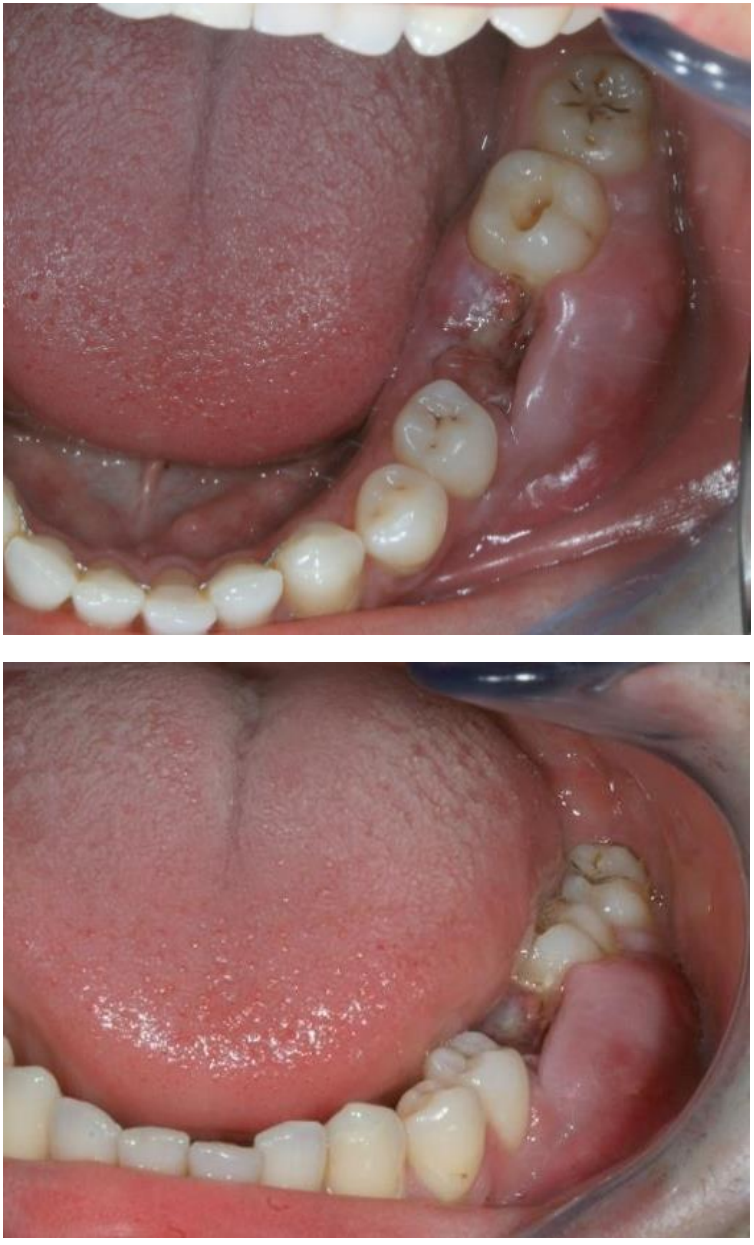


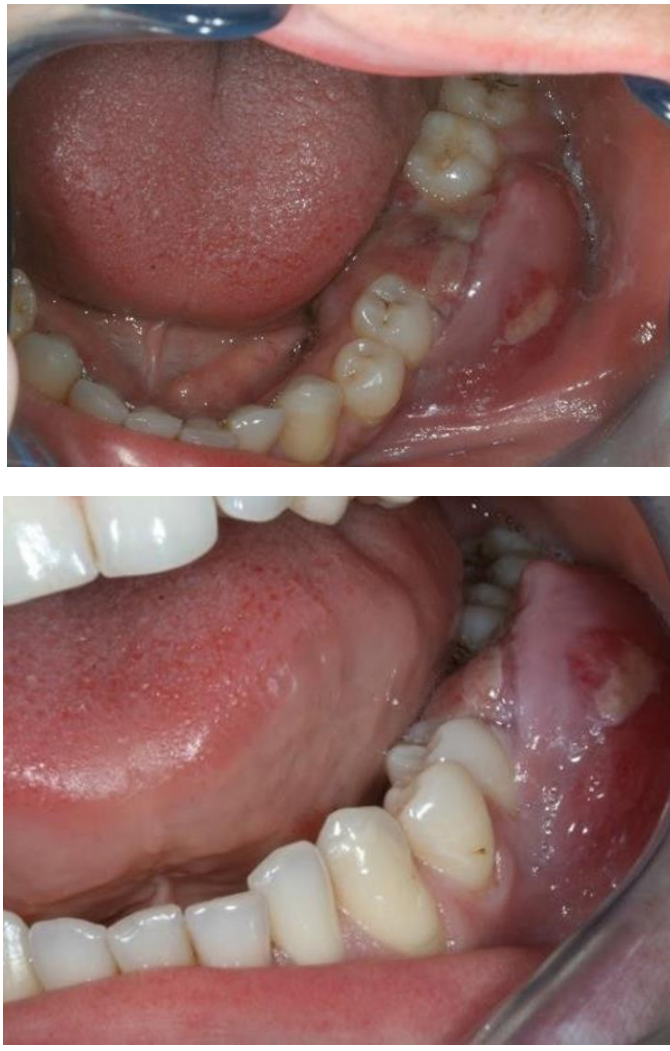
**Figure 2:** 1th review: Patient came to review with no improvement. Antibiotic regime was changed to Doxicicline and insisted on periodontal treatment.

By the time the patient attended his 2nd review the situation had worsened, the mobility increased, and the swelling was greater. The exodontics of 36 and cameral opening of 37 were proceeded but when the patient re-checked 5 days later, the injury continued to worsen (Figure 3 y 4) and the patient presented a slight paresthesia in the inferior left lip area so it was decided to refer this patient to our Postgraduate Program: MSc in Oral Medicine. University Rey Juan Carlos, Clinical Foundation (FCURJC). Alcorcón. Madrid. Spain.



**Figures 3 & 4:** After extraction and cameral opening the tumefaction does not subside and the patient refers a slight paresthesia of the lower left sector.

Intraoral examination revealed that swelling had spread relatively to the previous photographs occupying lingual and vestibular areas of 35, 36 and 37 had type IV mobility. We took photos (Figure 5 y 6) and requested for a panoramic X-ray a CT and a blood analysis, with the suspicion of neoplastic infiltration.



**Figures 5 & 6:** Images show the quick grow of the gingival area, extending to de premolar side. We ask for a CT, a panoramic X-ray and a blood test.

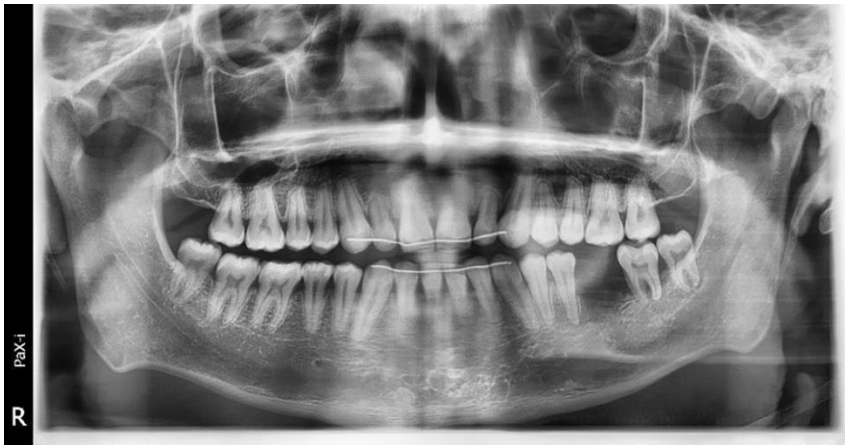
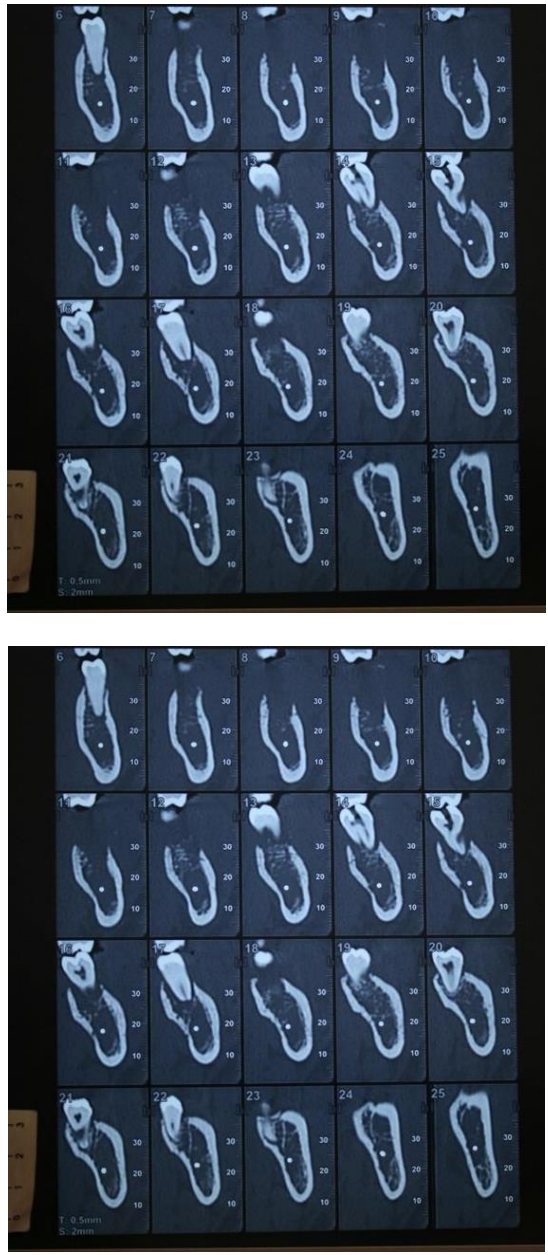



**Figure 7:** Panoramic x-ray: 37 shows furcation involvement.

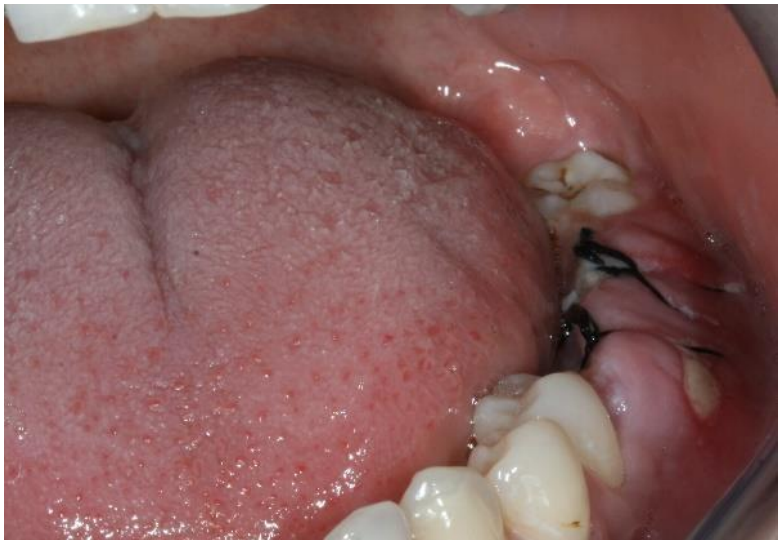
The blood test had no significant alterations but confirmed to us that the patient did not have HIV. CT revealed a bone injury in the area that could compromise the lower dental nerve, so we proceeded to take biopsy and exodontist of 37.

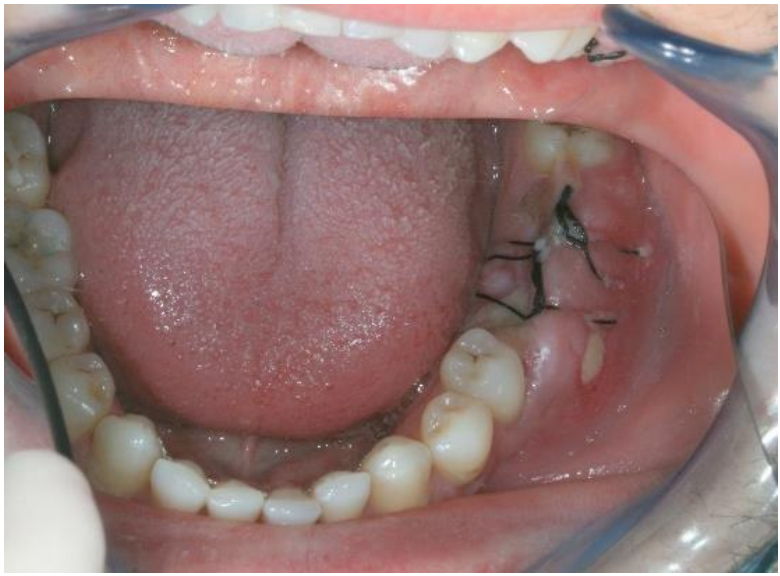
Histopathological results supported the diagnosis of DLBCL with some characteristics of Burkitt lymphoma the so-called unclassifiable LCBG according to WHO parameters, which we mentioned in the introduction [9,10].

The patient was sent to the to hematologist and was treated with radiation therapy and chemotherapy, currently undergoing the relevant revisions.



**Figures 8 & 9:** CBTC let us see bone involvement surrounding the area of dental nerve, causing patient´s paraesthesia.





**Figures 10 & 11:** Postoperative situation, after exodontics and biopsy.

## Discussion

Oral findings can be in some cases the first sign of lymphomas. They can appear as non-painful gingival swellings, accompanied

or not of tooth mobility. Sometimes the first finding is a dysesthesia or anaesthesia which are common signs of jaw involvement.

These characteristics can make the dentist get confused and misdiagnosed the lymphoma as a periodontal process. This involves in many cases the administration of antibiotics and tooth extractions as happened to our patient [1,9,14-17].

Most dentists do not handle blood dyscrasias in the differential diagnosis of oral lesions, but sometimes they debut with manifestations in the oral cavity. A correct diagnosis would take to early treatment of the disease with great benefit to the patient's health [2].

According to the study of [1] in 40.52% of the cases studied the initial diagnosis was wrong as so was the treatment applied by professionals. According to this we can conclude that it is necessary to train dentists in this field to improve diagnostic times. In the case of Burkitt lymphoma the survival rate descends from 97% in stage III to 27% at stage IV which exemplifies the importance of reaching the correct diagnosis early and effectively [16].

In the case we filed, between the patient's first appointment and his diagnosis elapsed about two months, which is not an excessive delay taking into account the timing of the anatomopathological study, but obviously it would have decreased reasonably if at the first appointment would have suspected the possibility of a neoplastic process, because of the clinical and epidemiological characteristics of the patient.

## Conclusion

Our case illustrates the common misdiagnose of oral lymphomas as other pathologies and highlight the importance of the dentist role in the early diagnosis. In cases that behave in an unexpected manner, dentists should be alert of lymphomas.

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## Case Report

# Osteoradionecrosis of the Jaws: A Case Report

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## Summary

Osteoradionecrosis of the jaws (ORN) is a condition that involves bone and mucosal lesions after radiotherapy treatments of the head and neck region. Its occurrence can lead to a significant decrease in quality of life and it is among the most severe oral complications of radiation therapy (RT). It appears more frequently in the mandible, more frequently in men with an approximate ratio of 1.6: 1, and an average age of approximately 50 years according to some reviews, with prognosis worsening as age progresses. Its treatment consists of actions aimed at

controlling the symptoms in early stages using multiple alternatives, infection control and debridement-type surgical interventions, removal of necrotic material, control of fractures and even large resection in advanced stages. We present a clinical case of a 76-year- old male patient with a long-standing lesion in the body of the mandibular related to a history of radiotherapy (conventional and brachytherapy) for malignant neoplasia in the floor of the mouth. Emphasis is placed on the importance of knowledge of the characteristics of this entity, risk factors, diagnosis, and the importance of correct dental management before and after head and neck RT treatments.

## Keywords

Osteoradionecrosis; Radiotherapy; Brachytherapy; Oncology; Head and Neck Cancer; Dentistry

## Key Points

- Osteoradionecrosis is a frequent complication in irradiated patients in the head and neck area.
- Depending on its stage, the dental management of patients with it varies from close monitoring to the need for major interventions and reconstructions.
- As a preventive measure, dental and periodontal hygiene is essential in head and neck cancer patients who may require radiotherapy as treatment.

## Introduction

Osteoradionecrosis of the jaws (ORN), is a condition that involves bone and mucosal lesion after radiotherapy treatments in the head and neck area. Its occurrence can lead to a significant decrease in quality of life [1] and it is among the most severe oral complications of radiation therapy (RT). It manifests itself as necrosis of bone tissues with no healing after RT, or secondary to surgical interventions in the oral cavity in previously irradiated patients. More classically, it is also defined as a devitalized and exposed area of bone that does not heal over a period of three to six months in the absence of local neoplastic disease in patients

treated with RT [2]. It is associated with a wide range of clinical presentations: from exposure of asymptomatic bone, to more advanced stages in which there is a large amount of affected tissue, severe pain and bone infection that may require surgical resection and reconstruction for its management [3].

Currently, the oncological treatment of malignant tumors of the head and neck largely depends on the use of radiotherapy, especially in advanced stages of the disease. It has been proven that around 50-60% of patients diagnosed with these maladies require their employment. According to the American Medical Association, based on the location of the radioactive source, radiotherapy can be divided into 2 subgroups: External and Internal Radiotherapy. The External RT involves high-energy radiation beams emanating from outside the body, while Internal RT, also referred to as Brachytherapy, involves radioactivity emanating from materials placed inside or near affected tissue therefore minimizing irradiation of healthy tissue and maximizing the radioactive concentration towards the target [4].

There are several hypotheses regarding the effects of radiation on bone, from fibroapoptotic changes in soft tissues and bones produced by an inflammatory reaction of endothelial cells followed by changes and abnormal fibroblastic activity, defects in the extracellular matrix and finally fibro-atrophy of the tissues. The classical model described by Marx describes the concept that radiation produces long-term biological effects, including decreased vascularization and hypoxia, consequently leading to slower wound repair, secondary infections and risk of necrosis. Alterations in the bone matrix are said to develop relatively slowly, whereas initial changes in bone remodeling (including osteocytes, osteoblasts, and osteoclasts) are thought to appear later (3). There is currently a certain consensus that it occurs in three stages. The first is a prefibrotic phase, in which endothelial cells undergo an acute inflammatory response, a second phase in which there is abnormal fibroblastic activity with loss of extracellular matrix, called the constitutive phase; and a later third phase or fibroatrophic phase in which a fragile matrix is formed in an attempt to remodel the tissue which is at greater risk of reactive inflammation when injured, and which could possibly

lead to a necrosis (4). Based on the vascular alteration in the irradiated bone, other theories suggest its susceptibility to infections after trauma, with the subsequent risk of necrosis, or the hypovascularity and hypocellularity of the irradiated bones [5].

There is a general consensus on the potential risk factors associated with the development of ORN related to oncological pathology [1,4-6], with treatment and/or with the patient's conditions, 4which are summarized in Table 1 [6].

Likewise, several accepted classifications or staging of this lesion exist, mostly derived from the proposal by Marx, and from which modifications as well as some proposed treatment methods have emerged [5]. Some of the classifications are summarized in Table 2.

It appears more frequently in the mandible, probably because the bone is more compact and is normally more exposed to radiation in head and neck oncological therapies. It occurs more frequently in men with an approximate ratio of 1.6:1, and with an average age of approximately 50 years according to some reviews, with prognosis worsening as age progresses. Its prognosis is directly related to the stage in which the lesion is found, with more advanced lesions having worse prognosis. Its treatment consists of actions aimed at controlling early-stage symptoms, with multiple alternatives [2] and infection control and debridement-type surgeries, removal of necrotic material, fracture control, and even major resection of the affected areas requiring major reconstructions [5-7].

**Table 1:** Risk factors associated with osteoradionecrosis: (Modified by Martos-Fernández et al [6].

| |
|---|
| ***Factors related to the tumor*** |
| - Tumor stage (>T1) (*) |
| - Tumor size (*) |
| - Bone invasion or proximity |
| ***Factors related to the treatment*** |
| - Mandibular osteotomy |
| - Neoadjuvant RT and/or followed by surgery |
| - RT dosage >60 Gy |
| - Short RT regimens with high doses per fraction (>1.8 Gy) |
| - Brachytherapy |
| - QT combined with RT (*) |
| ***Factors related to the patient*** |
| - Chronic pathologic local condition (periodontal disease) (*) |
| - Pre-RT dental health (*) |
| - Poor prosthetic adjustment |
| - Intraoral local trauma and/or biopsy |
| - Dental extractions pre-RT (<21 days) or post-RT (<2 years) (*) |
| - Smoking and alcohol consumption (*) |
| - Diabetes mellitus (*) |
| - Hypertension |
| - Malnutrition |
| - Immunodeficiency |
| - Connective tissue disorders |

*RT*, radiation therapy; *QT*, chemotherapy; *In addition to being

**Table 2**: Different classifications and treatments of ORN. Modified from [5].

| | ***Notami*** | ***Epstein et al.*** | ***Lyons et al.*** |
|---|---|---|---|
| **Type/Stage I** | ORN confined to dentoalveolar bone. | Resolved, healed.<br>(A) No pathologic fracture.<br>(B) Pathological fracture. | <2.5 cm length of bone affected (damaged or exposed); asymptomatic. Medical treatment only. |
| **Type/Stage II** | ORN limited to dentoalveolar bone or mandible above the inferior alveolar canal, or both. | Chronic persistent (nonprogressive).<br>(A) No pathologic fracture.<br>(B) Pathological fracture. | >2.5 cm length of bone; asymptomatic, including pathological fracture or involvement of inferior alveolar nerve or both. Medical treatment only unless there is dental sepsis or obvious loose, necrotic bone. |
| **Type/Stage III** | ORN involving the mandible below the inferior alveolar canal, or pathological fracture, or skin fistula. | Active progressive.<br>(A) No pathologic fracture.<br>(B) Pathological fracture. | >2.5 cm length of bone; symptomatic, but with no other features despite medical treatment. Consider debridement of loose or necrotic bone, and local pedunculated flap. |
| **Type/Stage IV** | | | 2.5 cm length of bone; pathological fracture, involvement of inferior alveolar nerve, or orocutaneous fistula, or a combination. Reconstruction with free flap if patient's overall condition allows |

## Clinical Case

A 76-year-old male patient came for a dental consultation in the department of oncology and immunocompromised patients in August 2009 for general dental evaluation, and complained of xerostomia and a non-healing ulcer on the internal aspect of the body of the mandible in the fourth quadrant. He reported the lesion to be asymptomatic with approximately one year of evolution, which had been increasing in size in recent months.

The family history comprised of both parents deceased; father due to leukemia, and mother with diabetes and hypertension; and a brother recently deceased due to lung cancer. In his personal medical history, he mentioned that he was a former smoker of 60 cigarettes daily from the age of 35 to 62 and arterial hypertension controlled via medication. He was diagnosed with oral squamous cell carcinoma in the floor of the mouth on the right side as a result of a casual finding in a dental consultation at another center in 2006. An incisional biopsy confirmed the diagnosis, and he was referred to his corresponding hospital for cancer treatment. He was treated with brachytherapy and subsequent surgical intervention, which involved excision of the lesion in the floor of the mouth and partial glossectomy on the right side, and submandibular, cervical, and supraclavicular lymphadenectomy on the affected side. Subsequently, 18 radiotherapy sessions were indicated and treatment ended in August 2007.

On clinical examination, he presented limited mouth opening, a depapillated tongue limited in function due to surgical scar, some occlusal and cervical caries, root stumps of 37, generalized mild gingivitis, poor and little functional saliva, and advanced attrition due to bruxism. His reason for consultation was an ulcerated lesion of approximately 1.5 cm diameter in the referred area and in relation to teeth 45 and 46. The lesion had a hard, bony, clean base with well-defined borders (Figure 1). Radiographically, an image compatible with osteomyelitis / osteonecrosis of the jaws was observed in correlation with the symptoms observed in the patient. He carried a report from the medical team treating him, which reported irradiation by brachytherapy with an implant

placed in the floor of the mouth in the fourth quadrant, and subsequent dose (IMRT) of 36 Gy oriented towards the same area, with involvement of the body of the mandibular. They also made an express request to avoid tooth extraction of any tooth, as a result an expectant management was decided; topical applications of chlorhexidine on the lesion and/or mouthwashes 2-3 times a day were recommended, as well as a strict periodic follow-up.

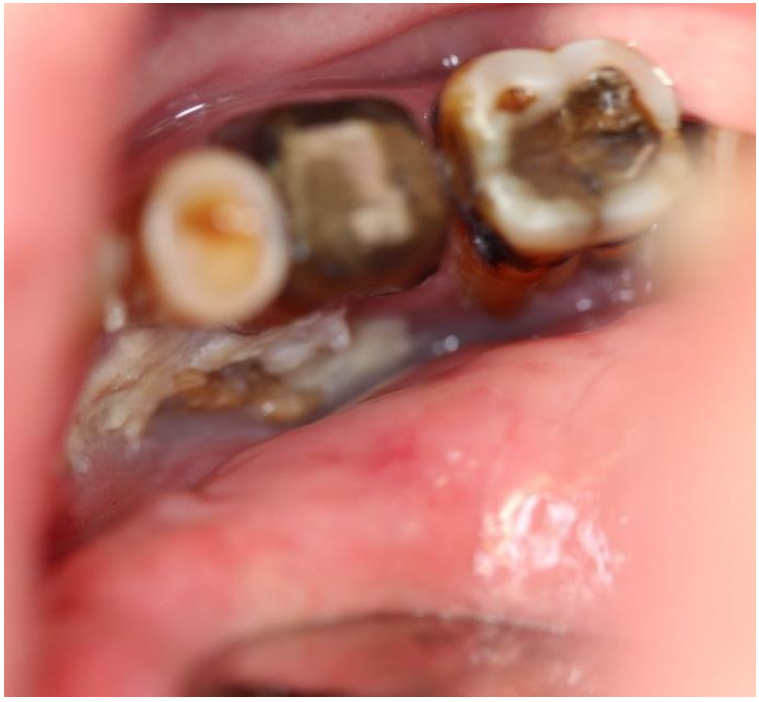

**Figure 1:** Initial condition.

The patient regularly attended the successive follow-ups, initially every month, then every 3 months, and thereafter every 6 months. He demonstrated sufficient collaboration and correct use of the hygiene techniques recommended in each consultation. In addition, the diagnosed carious lesions were treated, periodontal maintenance was performed and a night guard was made to control the bruxism.

In August 2014, he visited for a follow-up and exhibited an increase in the ORN lesion (Figures 2 and 3), and teeth 45, 46 and 48 with grade 1 mobility. An OPG was taken (Figure 4), and a radiographic image bigger than the one described in previous OPGs was encountered. Since then, we increased the periodicity of follow up, and communicationwith his medical team.

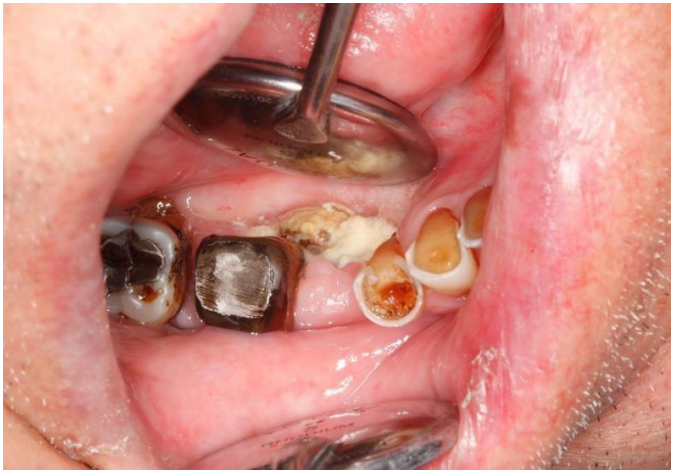

**Figure 2:** Photographic control, discrete increase in lesion area.

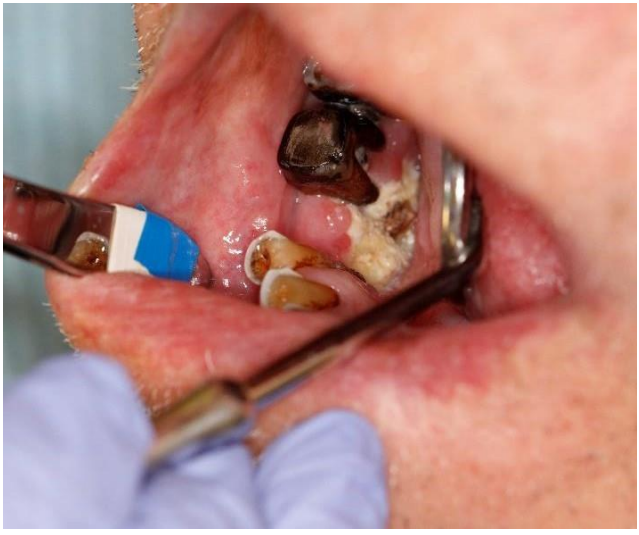

**Figure 3:** Photographic control, discrete increase in lesion area.

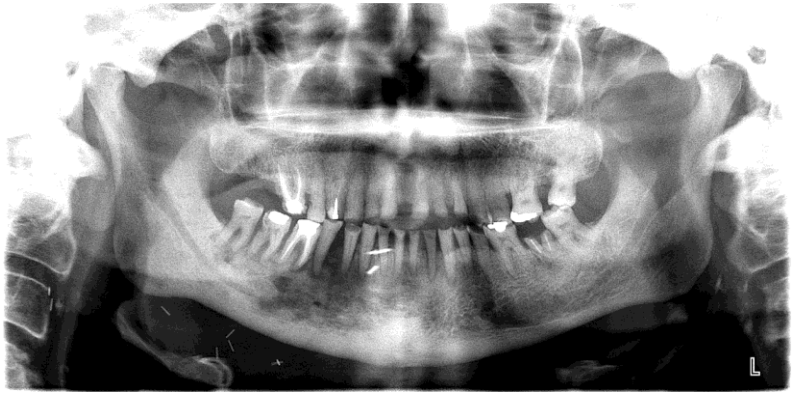

**Figure 4:** Radiographic control.

In 2016, no evolution of the lesion was observed clinically, except for an increase in the mobility of the teeth in approximation to the affected area. He also brought a report of a contrast neck CT scan performed by his medical team, where they reported absence of tumor recurrence or adenopathy and signs compatible with osteoradionecrosis of the right mandibular ramus. Successive follow up visits were programmed as before, but the patient did not attend these visits regularly.

In July 2019, he presented with acute pain in molars 36 and 37, and required an assessment of the possibilities of rehabilitation. The patient brought a medical report from his treating medical team. It stated that in May of the same year, due to a sustained increase in the size of the lesion observed in periodic follow up visits carried out in their department, mobility and spontaneous loss of the teeth involved, and given the evident risk of fracture, they decided to perform a right partial mandibulectomy with wide safety margins and reconstruction with a microvascularized fibular graft and a titanium support plate. Likewise, they authorized any dental, surgical and/or rehabilitative procedure necessary. Teeth 36 and 37 were extracted with no apparent complications, and rehabilitation was planned by means of removable prostheses, which the patient decided against. Thereafter, periodontal maintenance of remaining teeth and periodic follow up of his dental state and the operated area were programmed. Figures 5 and 6 show the current clinical appearance and radiographic aspect, respectively.

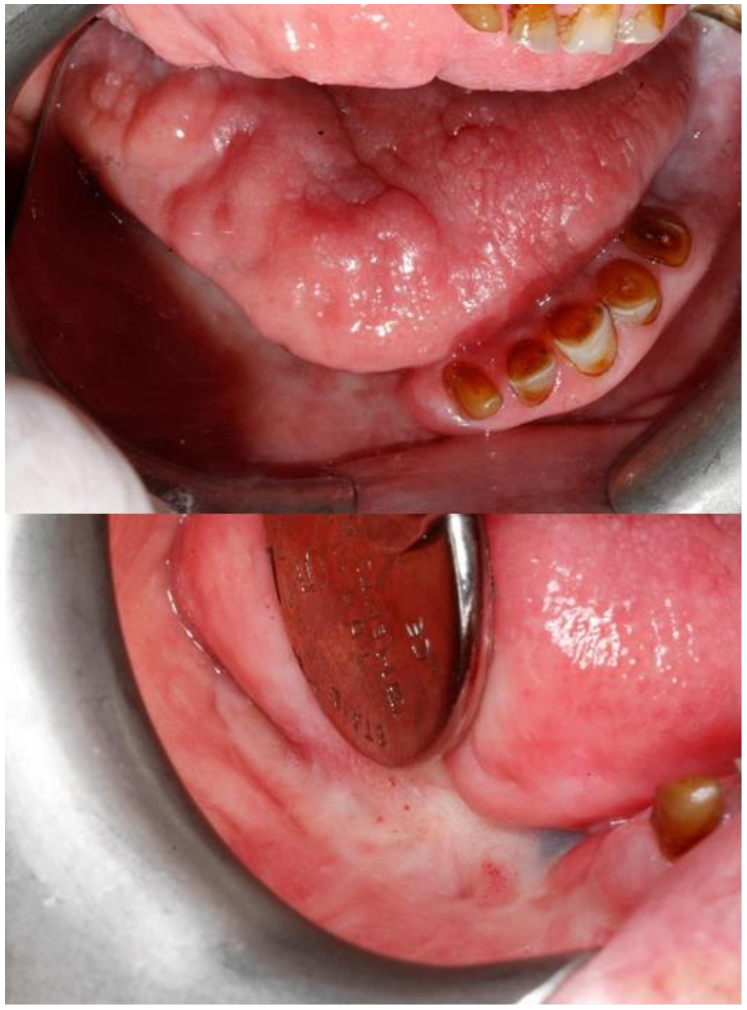

**Figure 5:** Clinical aspect after mandibulectomy and reconstruction.

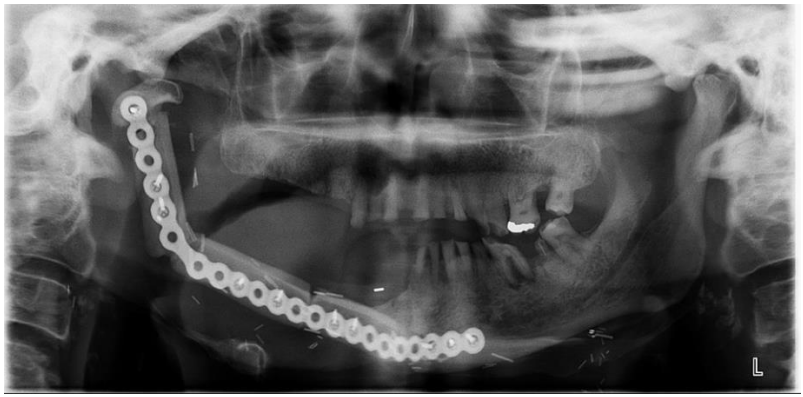

**Figure 6:** Radiographic aspect after mandibulectomy and reconstruction.

## Discussion

Radiotherapy is one of the fundamental pillars in the oncological treatment of head and neck cancers. It is useful from initial to advanced stages of oncological pathology, prior or concomitant to surgical or medical treatment, as well as for the management of recurrences and occurrences of primary second neoplasia in similar or adjacent locations [8-10]. In our case, it was employed due to the location of the patient's neoplasia, in the form of brachytherapy as a treatment strategy prior to surgical intervention, and afterwards as conventional or external source radiotherapy.

The most common complications associated with radiation toxicity are described according to the moment in which they appear, and can be classified as early (mucositis, xerostomia, dysphagia) and late (dental caries, osteoradionecrosis) [3,10-13], with ORN being the most important complication and with the worst prognosis. Among the clinical findings found in the patient, we demonstrated the presence of most of the sequelae related to late toxicity, namely, xerostomia, dental caries and ORN.

There is a variability in the statistics reported in relation to its prevalence, oscillating between 2.6% to 15% [14], and mostly between 4.6% - 7.4% [1,12]. It is generally associated with the dose/volume received, the patient's history (mainly history of

smoking), and the combination of chemotherapy treatment and comorbidities at the time of RT treatment [10]. Fortunately, advances in RT techniques, such as intensity-modulated radiotherapy (IMRT), have led to an improved planning and greater precision resulting in a decline in the number of the appearance of ORN lesions [7]. Moreover, currently, there is no great statistical difference in the type of radiotherapy applied according to the radiation source [1,12,14-16]. In our case, it would be reckless to affirm that brachytherapy has been the principal cause for the appearance of ORN lesion, although its location might lead one to believe so; Furthermore, the patient presents many of the predisposing conditions reported for ORN, the most important being the chronic smoking habit prior to his cancer diagnosis.

Likewise, it is difficult to identify accurately the moment in which the ORN lesion appeared in our patient; however, we calculated its initial appearance between 12/18 months after treatment according to the information provided in the anamnesis. Its time of the appearance in the mandibular bone has been reported to be an average of 10.9 months after RT (1.8-89.7) with 90% of cases appearing around 37 months after treatment [1], reporting a relative decrease in the risk of occurrence over time.

The characteristics of ORN have already been discussed in terms of its evolution and treatment, based on the control in early stages, antibiotic therapy, hyperbaric oxygen, and assessment of debridement or excision, and as reported in the literature, even pharmacological management with different options [6]. In the case presented here, a slow and "controlled" development of the lesion was monitored over time, by means of periodic follow-ups and hygiene measures. The patient denied relapse of smoking, reported correct medical condition, did not present any signs of oral or dental trauma except bruxism, or any dental treatment carried out in the affected area. However, owing to infrequent and distant follow-up visits on the patient's behalf, and probably due to relaxation in the hygiene strategies of the affected area, it is possible that the lesion worsened, which led his treating medical team to undertake the aforementioned surgical resolution.

There is a consensus regarding dental treatments in irradiated patients in the head and neck areas: they should be performed as early as possible prior to cancer treatment, based on dental and periodontal tissue hygiene [11, 17-19]. Although literature that denies the fact that pre-RT extractions reduce the risk of ORN can be found, there is a consensus that it is more than recommended to extract teeth between 14 and 21 days prior to the start of RT to decrease the risk of appearance of lesions [3]. During RT, the management should be limited to toxicities, and afterward, invasive procedures that increase the probability of ORN should be avoided. This is why currently the incorporation of the dentist in multidisciplinary teams for treatment of head and neck cancer is highly valued. It helps to avoid complications associated with treatment as far as possible and to carry out preventive and curative procedures in a timely manner [10,20].

## Conclusion

Concluding this case report, we highlight the importance of the dentist to identify this entity, its clinical characteristics, prognosis and treatment alternatives, as well as the risk factors associated with dental treatments in patients with a history of irradiation of the head and neck area. In the same way, the importance that dental and periodontal tissue hygiene can have in the prevention of the appearance of ORN in these patients prior to their oncological treatment, which is why we stress the importance of incorporating the dentist in the multidisciplinary team of head and neck oncology treatment.

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## Case Report

# Acute Necrotising Ulcerative Gingivitis in a Patient with Psoriasis Treated with Efalizumab: Consequences of the Treatment or Disease?

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## Abstract

Psoriasis is a chronic inflammatory disease that causes scaly patches of skin on an erythematous base. The pathogenesis is complex, but considerable evidence points towards the immune system playing a key role in its development. Compared to treatment with immunosuppressants, different drugs known as biological agents have had some success, including Raptiva

(Efalizumab), which has been associated with significant side effects.

The following is a case study of ANUG in a patient with psoriasis, treated with efalizumab.

## Key Points

Oral effects of immunosuppressive drugs, ANUG diagnostic, ANUG treatment

## Introduction

Acute necrotizing ulcerative gingivitis (ANUG) is an acute infection of the gums, localized or generalized, with a quick and sudden onset, causing intense pain, spontaneous bleeding gums, and interdental necrosis with "punched out" ulcerated papillae.

A series of secondary characteristics may be present, including: halitosis, the appearance of yellowish-white or grayish pseudomembrane covering the papillae, lymphadenopathy, fever and general discomfort [1,2].

The pathogenesis of ANUG is complex. There are several different factors, both local and systemic, that can lead to the condition appearing: poor oral hygiene, pre-existing gingivitis, anxiety and stress, poor nutrition, the use of different drugs, and diseases that lead to a compromised immune status (such as leukemia, neutropenia and HIV) [1,2]. The diagnosis is mainly clinical, but the patient's medical records and complementary exams are essential to rule out the possibility of systemic diseases or an underlying immunodeficiency [2].

Psoriasis is a chronic inflammatory disease characterized in most cases by scaly patches of skin on an erythematous base, and they can appear alongside other systemic symptoms. The pathogenesis is complex, but considerable evidence points towards the immune system (mainly T lymphocytes) playing a key role in its onset and progression. In comparison to conventional therapy with immunosuppressant drugs such as

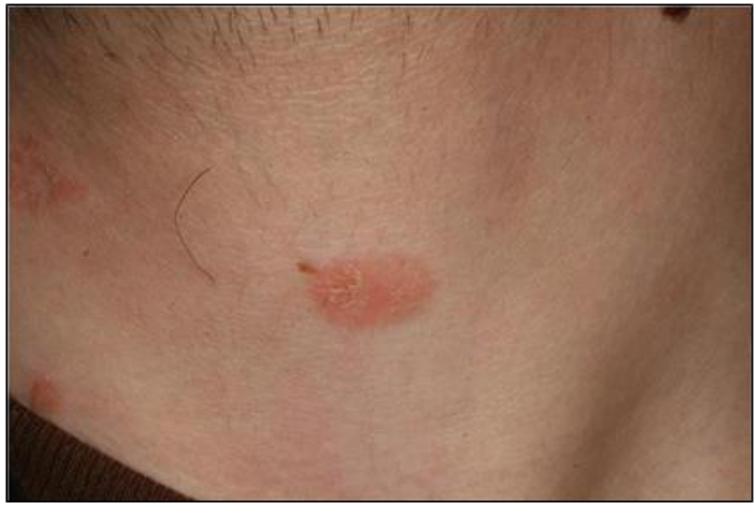
methotrexate, cyclosporine and hydroxyurea, in recent years drugs known as biological agents (including Efalizumab) have been used successfully, acting specifically on the immune and genetic mediators in the pathophysiological process [3].

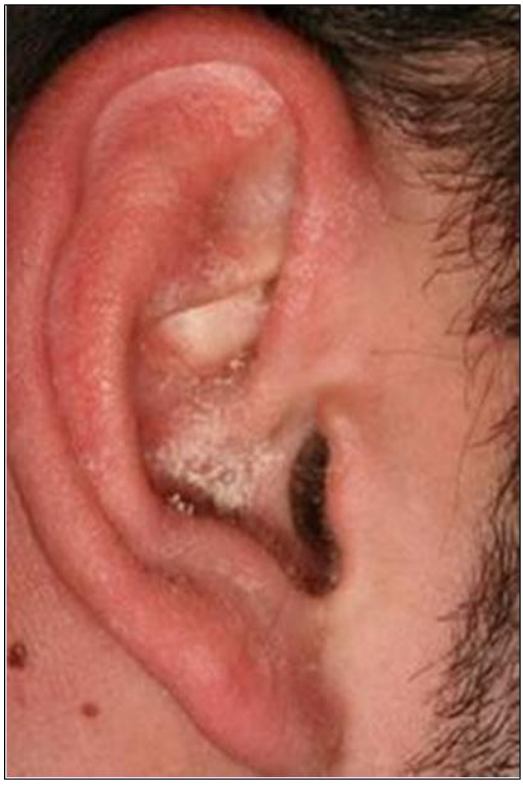
Efalizumab is described as a specific monoclonal antibody for integrin CD11a, which has been used successfully for the treatment of plaque psoriasis for a long time. However, it has been linked to major side effects, which saw the treatment removed from sale [4].

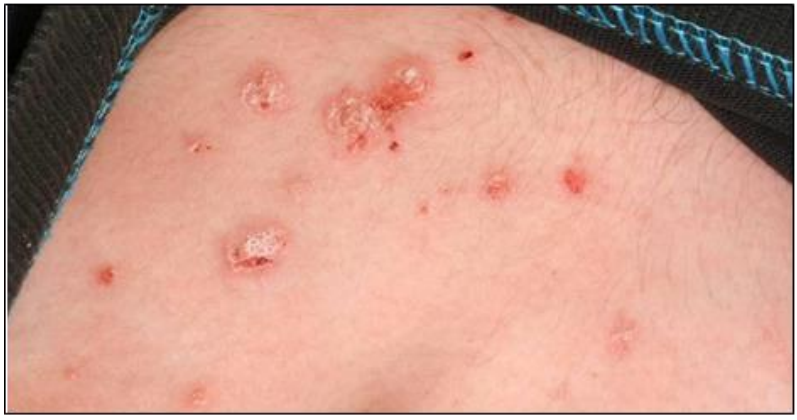
This article details a case study of ANUG in a patient with psoriasis, treated with efalizumab.

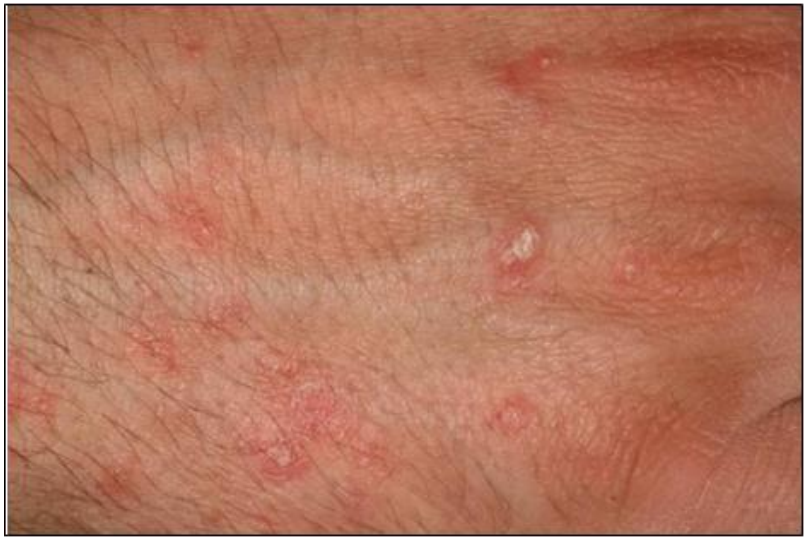
## Case Presentation

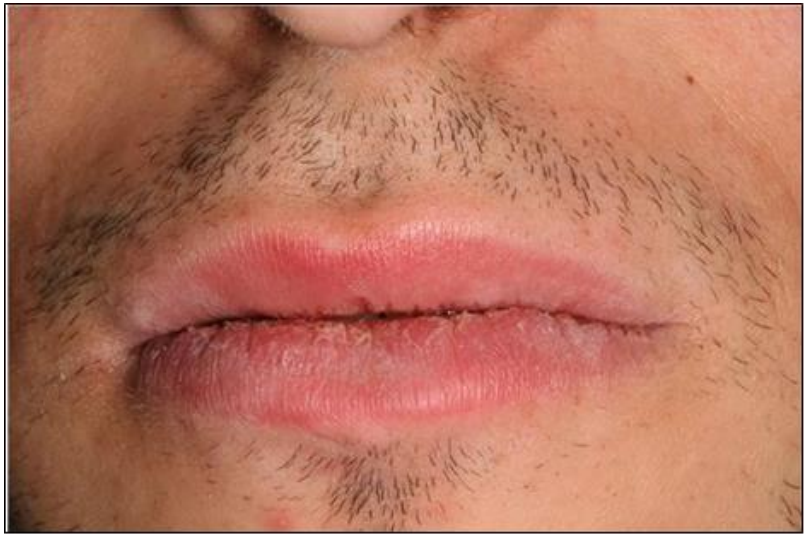
24 year old male with a history of psoriasis from 3 years olds, treated with topical corticosteroids (Figures 1-5). After years without improvement, he began using Raptiva (efalizumab), and continued treatment for 18 months. This drug is suspected of producing a state of immunosuppression in patients, leading to the emergence of some infections such as infectious mononucleosis and ANUG.











**Figures 1-5:** The appearance of psoriasis lesions.

The patient is a student of the Master's in Practical Orthodontics (University of Santiago de Compostela) and suffers from marked, spontaneous bleeding gums caused by brushing his teeth.

A clinical examination showed painful necrotic ulcers and bleeding of the buccal and labial gingiva on the maxilla and mandibule. The patient also has gingivitis and abundant plaque, as well as an acutely painful ulcer measuring 4 cm on the upper labial mucosa (Figures 6, 7). His functions are greatly impaired, and he suffers from halitosis and submandibular lymphadenopathy.

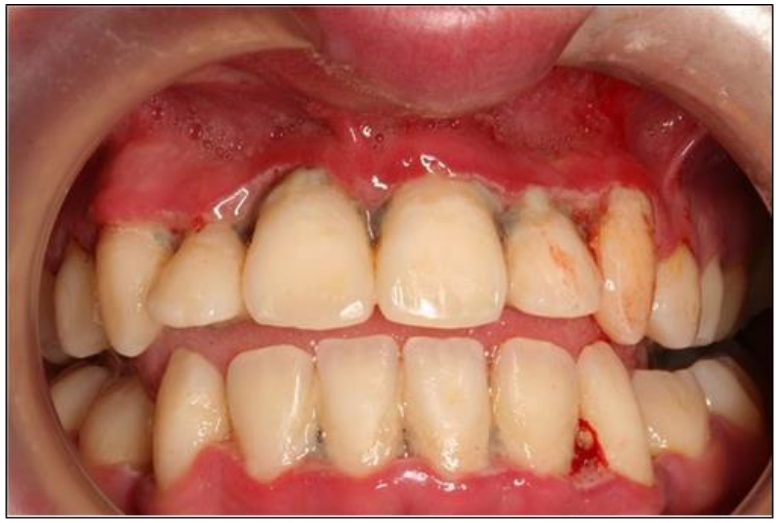


**Figure 6:** Painful necrotic ulcers and bleeding of the gingiva on the maxilla and mandible. ANUG diagnosed.

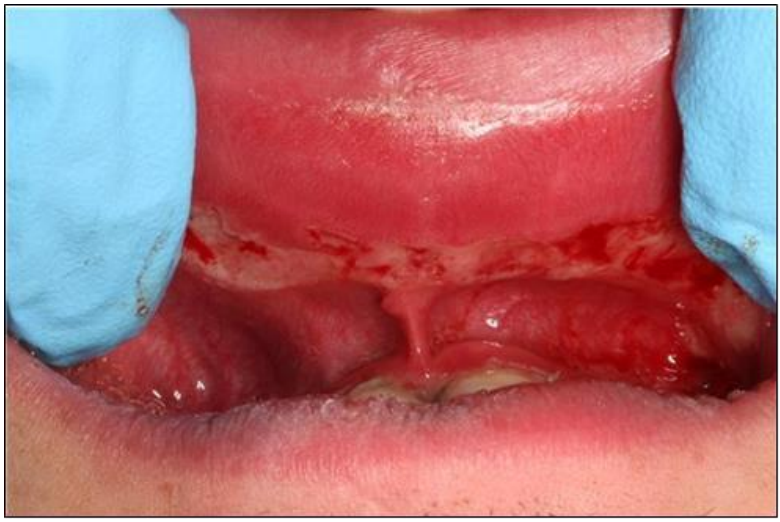


**Figure 7:** An acutely painful ulcer measuring 4 cm on the upper labial mucosa.

A blood analysis was requested to rule out a blood disorder, and an orthopantomography was also carried out, with no relevant data observed.

The clinical diagnosis of ANUG is confirmed.

It is treated with Augmentin Plus® 1000/62.5mg 2 pills/12 hours for a week and chlorhexidine rinses at 0.2% three times daily. After 7 days (Figure 8), tartar removal is carried out and an appointment scheduled to review the situation in a month, which shows a noticeable improvement (Figures 9, 10).

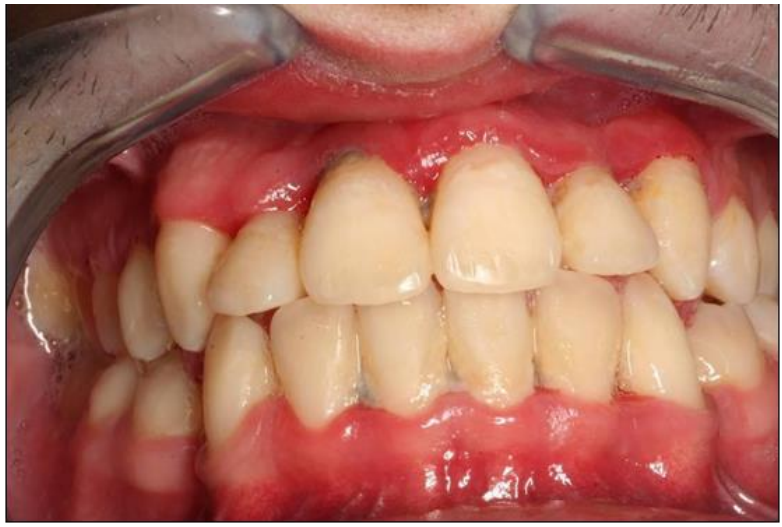
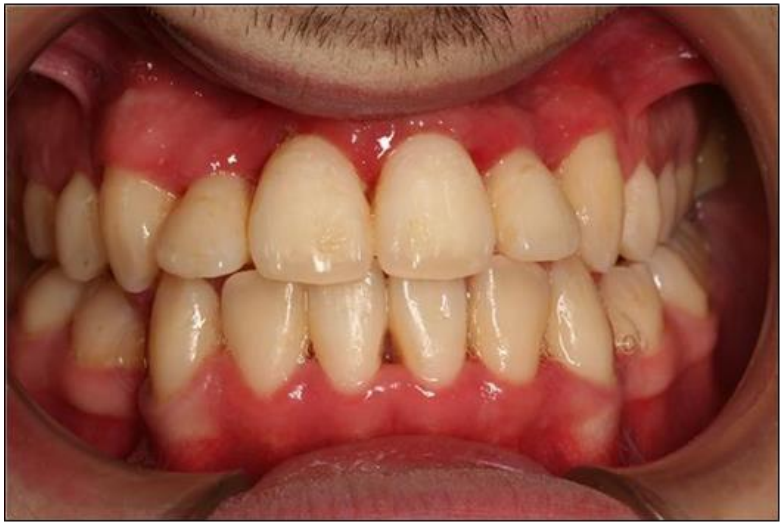
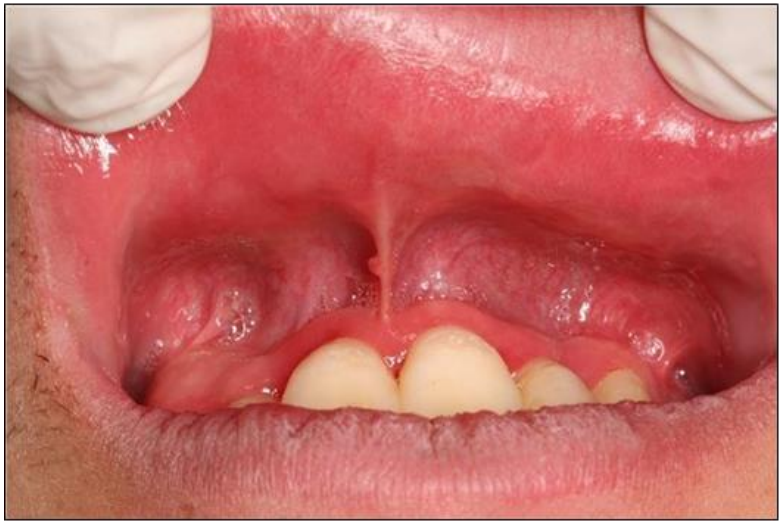


**Figure 8:** After 7 days treatment (Augmentin Plus® 1000/62.5mg 2 pills/12 hours for a





**Figures 9 & 10:** Healthy appearance of the gum and upper labial mucosa following.

## Discussion

Raptiva® is an effective drug when treating patients with moderate to severe psoriasis, especially in patients who do not respond to other treatments such as cyclosporine, methotrexate and PUVA, or who otherwise have an intolerance or contraindication [4].

It is described as a specific monoclonal antibody for integrin CD11a. It inhibits two steps in the pathogenesis of psoriasis: binding the CD11a (α-chain of LFA-1) and the interaction with ICAM-1, interrupting the formation of the immunological synapse, a critical step in the activation of the T cell dependent antigens [5].

This drug works by binding itself specifically to a leukocyte surface protein, interfering with the adhesion of T lymphocytes to other types of cells [6].

Several side effects have been associated with treatment with Efalizumab, such as mild to moderate infections, leukocytosis,

lymphocytosis, flu symptoms, hypersensitivity, arthralgia, psoriatic arthritis, back pain, fatigue, elevated alkaline phosphatase and transaminases, thrombocytopenia, urticaria, hemolytic anemia and erythema multiforme [7,8] as well as Guillain-Barré syndrome, Miller-Fisher syndrome, Progressive multifocal leukoencephalopathy (PML), encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections [2].

After Efalizumab was approved, the "Food and Drug Administration" (FDA) received notifications of three confirmed cases of death from PML in patients treated with this drug. This saw the Committee for Medicinal Products for Human Use (CHMP) recommend the drug be suspended [9].

Several published articles have demonstrated the possible association between Efalizmab and the occurrence of the following diseases: bullous pemphigoid [10], lupus [11], angioedema [12], cytomegalovirus [12], aseptic meningitis [6] and psoriatic arthritis [13,14].

Several factors that cause a predisposition to developing ANUG include stress and anxiety, smoking, poor oral hygiene, nutritional deficiency or HIV. All these factors lead to immunosuppression, in which there is a decrease in lymphocyte mitogenesis, antibodies and the impairment of polymorphonuclear leukocyte function, [15] which occurs in patients with HIV.
Numerous studies demonstrate the link between generalised depression of the immune system with the appearance of necrotising periodontal disease. It occurs relatively frequently in patients with HIV and is one of the seven oral lesions most commonly associated with this disease [16,17].

Recently, a hypothesis has been formulated that gingivitis and periodontitis share the same underlying inflammatory pathogenic process and underlying autoimmune process as psoriasis [18].

As ANUG is an acute infectious process, in our case it should be more related to the immunosuppression caused by treatment with efalizumab, rather than directly to the pathogenesis of psoriasis.

## Conclusion

The use of immunosuppressant drugs for various diseases can cause lesions in the oral cavity, as in this case of ANUG after using Raptiva® (Efalizumab); therefore these patients should be checked frequently.

New studies are needed to order to relate immunosuppression, caused by new drugs, with the emergence of infectious diseases in the oral cavity.

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## Case Report

# Oral Impact of Langerhans Cells Histiocytosis: Report of a Case

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## Abstract

Langerhans cell histiocytosis is a very rare disorder, based on a histiocytes-proliferative disorder, comprising various clinical presentations that follow a doubtful pattern, and can occur in both adults and children of either sex, with a considerably lower incidence in adults (1-2 per million).
Its diagnosis is made through histological analysis, using a conventional biopsy, including an immunohistochemical analysis.

The oral manifestations of the disease usually affect the gums, with the presence of ulcerations, loss of bone support, gingival recessions, swelling, pain, bleeding, etc.
In the present case, we report a 68-year-old woman who consults for presenting inflammation and dull gum pain with a course of evolution of 2 years.

## Key Points

Oral manifestations of Langerhans cell histiocytosis, Differential diagnosis of gingival lesions, Clinical, histological and immunohistochemical diagnosis in Langerhans cell histiocytosis.

## Introduction

Langerhans Cell Histiocytosis (LCH) is a histiocytes-proliferative disorder that is evidenced in various clinical presentations whose pattern is uncertain. This disorder appears when such cells migrate abnormally and disorderly to one or several body organs, such as lymph nodes, skin, bones, spleen, liver, lung and bone marrow [1,2].

This peculiar disorder is extremely rare, with only 1-2 cases per 1 million present among adults and a higher incidence in children (8-9 cases per 1 million) [1,2]. It may appear in people of both sexes, with a predilection for male sex [3].

Oral injuries may be the only presentation sign in patients diagnosed with LCH and it can even be the first sign of the disease. Bone injuries may appear on the skull, long bones and the jaw. On the latter, they appear as a defined radiolucent image that can simulate either a mild and localised or a severe and generalised periodontal disease, which may also cause severe pain, oral ulcers, periodontal disease and, on occasions, produce pathological jaw fractures [3-5].

It is a disease that causes great bewilderment due to the high variability in its progression, which fluctuates from spontaneous remissions of the disease to even death.

## Clinical Case

A 68-year-old woman came to the Master in Oral Medicine, Oral Surgery and Implantology at the University of Santiago de Compostela (Spain) in October 2017, sent by her periodontist for diagnosis and treatment of oral ulcerations and gums inflammation with approximately two years of progression. The patient came with severe and chronic pain of the gums, accompanied by great difficulty chewing. In her medical history, we point out that she suffers from Dermatitis, Diabetes Insipidus, Arthralgias and systemic Langerhans Cell Histiocytosis that affects the spleen and the pituitary; she has been treated with Vinblastine, Prednisone and Filgrastim.

In the intraoral examination, we observed an inflammatory lesion widespread in the entire gum, including the vestibular area as well as the palatal, maxillary and jaw areas, being more pronounced on anterior areas; she had ulcerated lesions, bleeding, gingival recession, calculus and noticeable tooth mobility (Figures 1,2). Complementary tests were performed: radiographic test, blood test and incisional biopsy.

The panoramic radiograph of the oral cavity (Figure 3) showed a generalized loss of bone insertion that affects both jaw and maxillary teeth, especially anterior teeth, also indicating a severe generalized chronic periodontitis. Periapical radiographs are done, showing the “floating teeth” on anterior areas.

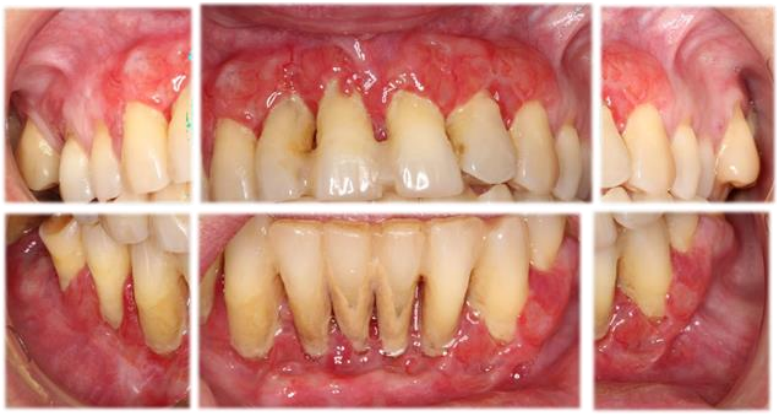

**Figure 1:** Gingival inflammatory lesions in the maxilla and mandible.

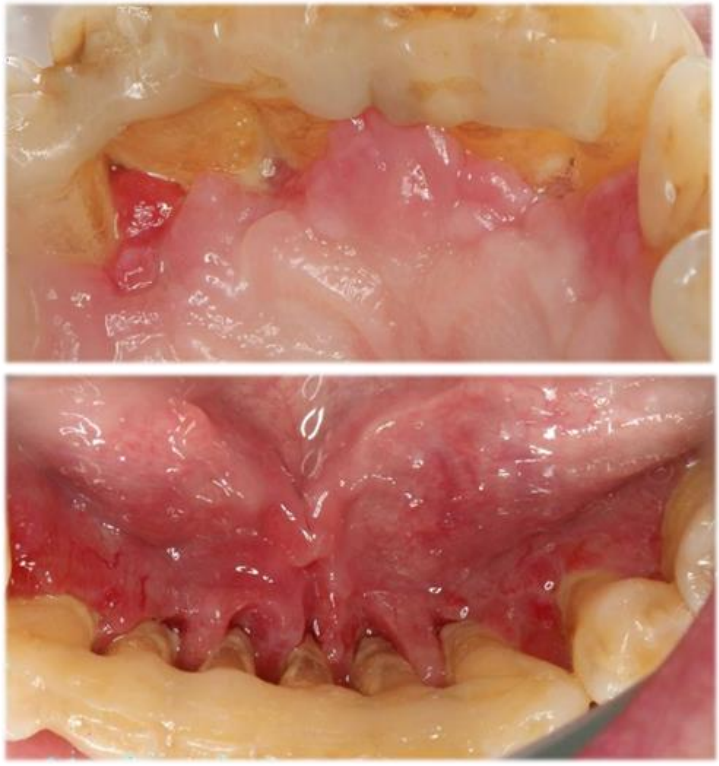

**Figure 2:** Palatal and lingual appearance of the gingival inflammatory lesion.

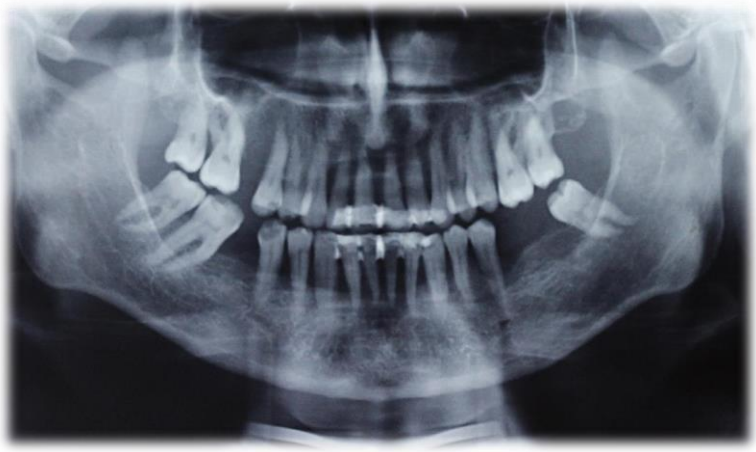

**Figure 3:** Panoramic radiograph of the patient where bone loss is observed, especially in the anterior mandibular area.

An incisional biopsy was performed on the vestibular gum of the first quadrant and was sent to the Pathological Anatomy Service of the University of Santiago de Compostela Hospital Centre. The histopathologic study revealed an ulcerated epithelium and a pathological process on the subepithelial connective tissue, with inflammatory mixed- cellularity (Figure 4). Through an immunohistochemical study, the diagnosis of Langerhans Cell Histiocytosis was confirmed, as the stainings with Langerin marker (Figure 5A) and surface antigen CD1a (Figure 5B) were positive.

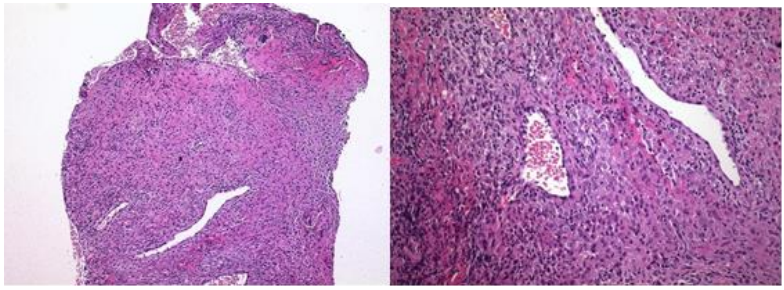

**Figure 4:** Histological aspect of the gum biopsy where ulceration and a pathological process that is occupying the subepithelial connective tissue with mixed inflammatory infiltrate and more increase can be seen cells with histiocytic appearance.

Corticoid intralesional infiltrations were made to our patient, specially 3 sessions of triamcinolone acetonide on aqueous solution injections (Trigon Depot®) for 3 weeks (Figure 6). Holding regular check-ups, we have seen a great improvement of mucosa lesions. Dental cleaning sessions and a resin dental splint were made, as the patient wanted to keep her natural teeth. In a check-up after 2 months of treatment (Figure 7), the function and aesthetic of the patient's teeth were restored, and the patient stated that the dull pain she had experienced during a period of approximately 2 years had ended (Figure 8).

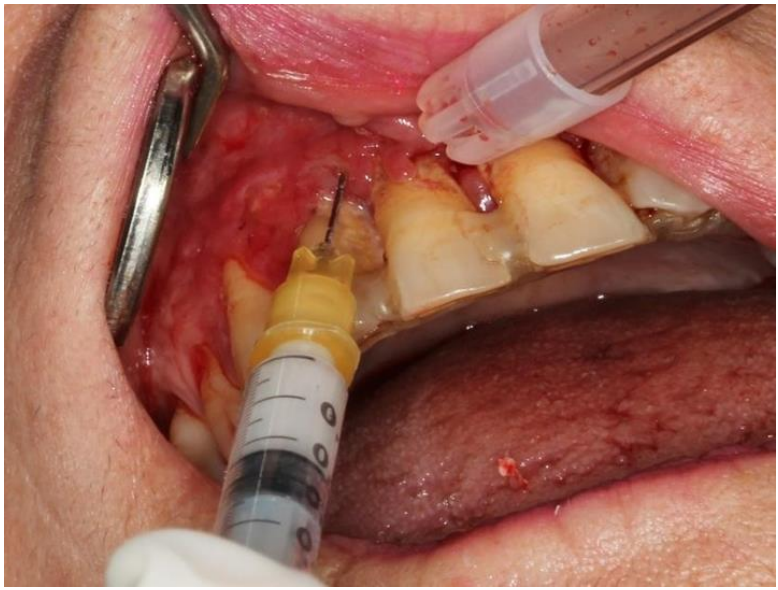

**Figure 6:** Corticoid intralesional infiltrations were made to our patient, triamcinolone acetonide on aqueous solution injections (Trigon Depot®) for 3 weeks (1/7 days).

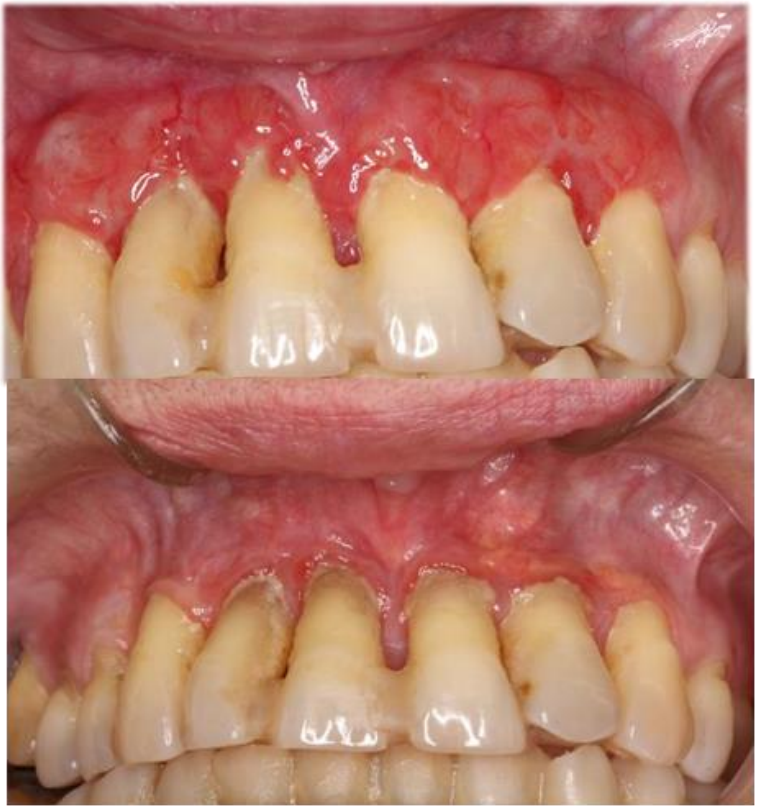

**Figure 7:** Appearance of oral lesions before (A) and after treatment (B) (3 intralesional infiltrations with triamcinolone acetonide on aqueous solution injections (Trigon Depot®) 1/week).

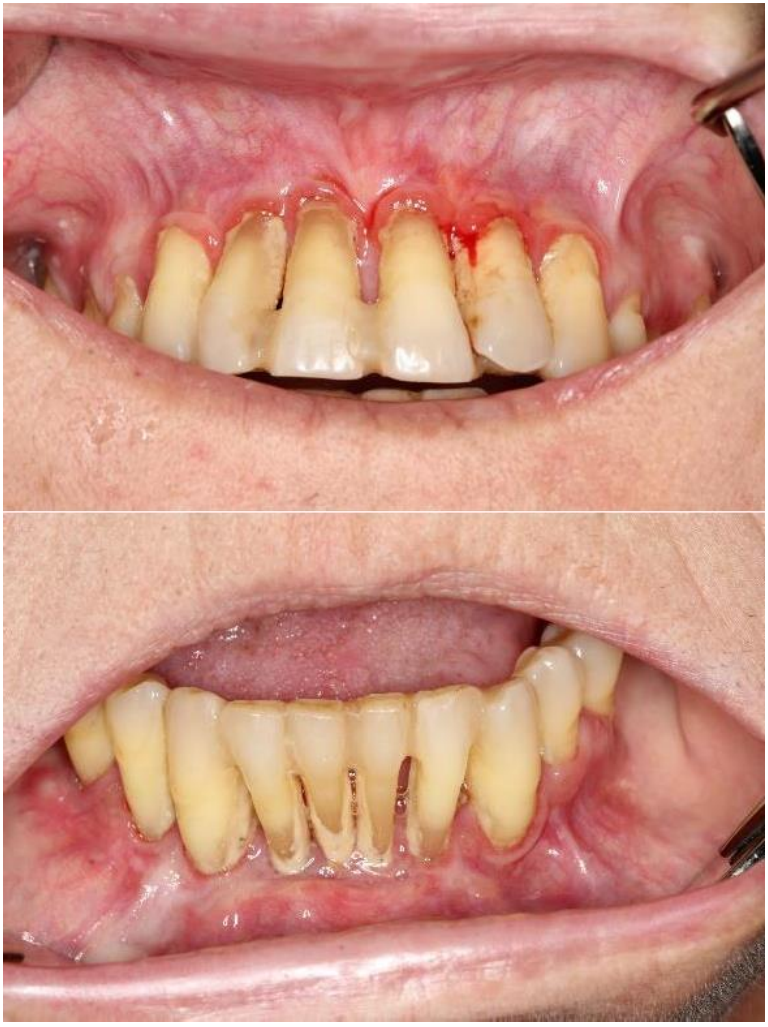

**Figure 8**: Appearance of oral lesions 6 months after treatment.

## Discussion

Oral manifestations can be the first and only presentation sign in patients diagnosed with LCH. In our case, in 2010, the patient's haematologist diagnosed her with LCH, affecting the spleen, the pituitary and the hypothalamus. Oncologists and haematologists are the professionals that usually assume the main role in these

patients' treatments. However, due to the possible involvement of several systems and organs, it is advisable to adopt a multidisciplinary approach in order to monitor the disease. In the particular case of oral location, lesions are associated with a variety of different signs, symptoms and loss of function, which may significantly affect patients' quality of life.

Currently, the Histiocyte International Society classifies this disease according to the number of organs affected: Histiocytosis that affects just one system, whether uni- or multifocal; and multisystemic histiocytosis, affecting two or more organs [3], as it is the case of our patient.

As a consequence of a histiocytosis that affects the hypothalamus-pituitary axis, a rare disorder may appear, as in the case of diabetes insipidus (DI), being the only sign of LCH or an early manifestation of it. In patients with multisystemic LCH, the risk of developing DI is 4 to 6 times higher than in those patients with LCH that affects just one system [3].

The clinical presentation of LCH may vary greatly depending on the affected area. At the oral level, alveolar bone loss implies gingival recession, destruction of the keratinised gum, presence of periodontal pockets, swelling and, together with the loss of bone support, it leads to a greater tooth mobility, simulating "floating teeth". Ovoidal, erythematosus and very painful ulcerations can also appear [2]. Its diagnosis is done with the histological test, making a biopsy with conventional cold scalpel, under electron microscopy techniques where we can see typical Birbeck granules. The immunohistochemical test is considered to be the pathognomonic test for the diagnosis, being able to detect the positivity of surface CD1a and Langerin markers. In the case of the involvement of the oral cavity, a radiological test through panoramic, periapical and even CT scans must be carried out in order to determine the location and the degree of bone involvement [6,7].

The therapeutic basis of LCH with multiorganic involvement is based on the use of corticoids, radiotherapy and chemotherapy. In most cases, these patients respond positively to the

combination of steroids and cytotoxic agents, in cases where the disease appears with multiple bone injuries. Some studies show that recurrence rate is significantly reduced when the injuries are treated with vinblastine and systemic corticoids for 6 months [3]. When the jaw is involved and it is an isolated and localised bone injury, surgical curettage may be used; it is also recommended to extract the teeth with symptoms, marked mobility and periapical lytic injuries, as well as dental cleaning, scaling and root planing sessions [3]. Corticoid intralesional infiltrations were made to our patient, specially 3 sessions of triamcinolone acetonide on aqueous solution injections (Trigon Depot®) for 3 weeks. Holding regular check-ups, we have seen a great improvement of mucosa lesions. Dental cleaning sessions and a resin dental splint were made, as the patient wanted to keep her natural teeth. In a check-up after 2 months of treatment (Figure 1. C, D), the function and aesthetic of the patient's teeth were restored, and the patient stated that the dull pain she had experienced during a period of approximately 2 years had ended.

Regarding prognosis, patients with a multiorganic histiocytosis need repeated treatments and have a higher mortality rate than patients with unifocal lesions [3]. In the case of our study, the patient has a systemic disease in control for 6 years, and although the oral manifestation of the disease is currently stable, it is necessary to monitor lesions, as we cannot rule out that such oral manifestation is not an indication of a possible systemic reactivation of the disease.

## Conclusions

LCH is a rare disease of systemic involvement that can affect oral cavity, which can be the first and, often, the only manifestation of the disease. It is important to have an adequate knowledge of the clinical presentation and the complementary tests necessary for its diagnosis. Radiographic, histopathologic and immunohistochemical studies are essential for such diagnosis. In oral manifestations, besides systemic treatment, local corticoids are needed for a better evolution of the disease.

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## Case Report

# Black Tongue Secondary to Paraneoplastic Cushing's Syndrome

Carmen Menéndez Valdés, Eva María Otero-Rey, Catalina Barba Montero, Manuel Somoza Martín, Mario Pérez-Sayáns García, Berta Rivas Mundiña, José Manuel Suárez-Peñaranda and Andrés Blanco Carrión

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## Abstract

The study presents the case of a 44-year-old woman who comes to our unit at the University of Santiago de Compostela (Spain) due to the presence of black tongue. Progression time of 3 years. Asymptomatic. Currently diagnosed with a neuroendocrine tumour, an atypical lung carcinoid. Through clinical, analytical and pathological data, and once the differential diagnosis is done with other pathologies involving this colour change, the clinical suspicion reached is that black tongue is secondary to a paraneoplastic Cushing's syndrome.

## Key Points

Differential diagnosis of oral melanotic macules, Atypical pulmonary carcinoid with neuroendocrine abnormalities. Oral lesions in paraneoplastic Cushing's syndrome.

## Introduction

Atypical lung carcinoid is a rare subtype of lung cancer. It belongs to a spectrum of neuroendocrine tumours [1]. These are a group of neoplasms arising from cells in the neuroendocrine systems, found in most organs of the human body [2]. They were defined for the first time in 1972, but their classification was not standardised until 1998. They can be classified into four subtypes according to their biologic aggressiveness: typical carcinoid, atypical carcinoid, neuroendocrine giant cell carcinoma, and small cell carcinoma [3].

Neuroendocrine lung tumours represent approximately 20-30% of all the neuroendocrine tumours, and around 25% of lung cancers. Lung carcinoids are the rarest, as they represent just 1 to 5% of all lung malignant lesions, with an incidence rate of 5 to 10/1,000,000 people/year [4,5]. These are less aggressive and generally follow a painless course. Most studies found a higher incidence rate in females than in males, and in Caucasians compared to African American individuals.4 Survival is generally favourable, with a global survival rate of 5 years in 61 to 88% for atypical carcinoids and 90% for typical carcinoids [6].

It is a functionally active neuroendocrine tumour that secretes an excess of peptides or amines, eventually resulting in specific clinical symptoms, such as carcinoid syndrome due to excess secretion of serotonin, or paraneoplastic Cushing’s syndrome due to excess secretion of ectopic ACTH [7].

Paraneoplastic syndromes are rare in lung carcinoids. Carcinoid syndrome, considered to be characteristic, is more common in gastrointestinal carcinoids, while only 1 to 3% of those that originate in the lungs show clinical manifestations. Others, such

as paraneoplastic Cushing's syndrome (1 to 2% of cases), are even rarer. However, when a thorough endocrinological evaluation is performed on patients with lung carcinoid tumours, data on the hypersecretion of ACTH can be found in up to 15% of cases, although it has no clinical manifestations in most of them [8].

As in Cushing's disease, main symptoms and signs include central, primary or secondary obesity, amenorrhoea in female patients, hirsutism, acne, purple stretch marks, easy bruising, hypertension, imbalance in glucose metabolism, fatigue, muscle weakness, mental changes or emotional disturbances, hyperpigmentation and acanthosis nigricans [9]. Patients' Cushing's syndrome may not be characteristic because its clinical presentation could be masked by the symptoms of the underlying tumour [7].

Hyperpigmentation can affect any part of the body, including mucosa, as in this specific case of lingual involvement.
Regarding treatment, neuroendocrine tumours that secrete ectopic ACTH must be respected. When a complete surgical resection is impossible, tumour chemotherapy, steroidogenesis inhibitors, mifepristone or bilateral adrenalectomy can be treatment options in order to control this type of tumours [10].

The aim of this study is to assess the lingual colour change and the differential diagnosis with other pathologies involving this colour change, as well as the selection of the appropriate diagnostic tests in order to relate it to a possible systematic pathology.

## Clinical Case

A 44-year-old woman comes to the Master in Oral Medicine, Oral Surgery and Implantology at the University of Santiago de Compostela (Spain) due to the presence of a dark discolouration of the tongue. At clinical examination, we can see a black-blue colouration that affects the entire tongue dorsum. We also see melanotic macules of a lower intensity in the upper and lower vestibular, marginal gum and in the ventral side of the tongue

(Figure 1). The patient reports that macules appeared 3 years ago. The patient does not show symptomatology and there is no apparent causal relationship. On later visits, melanotic macules can be seen on skin.

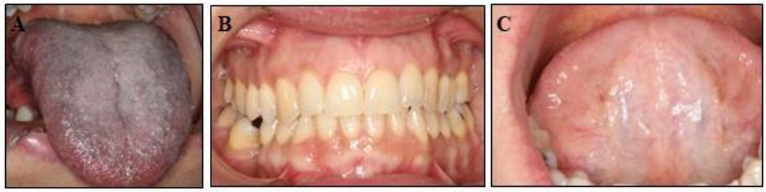


**Figure 1:** Clinical examination of oral cavity, where a dark discolouring of the dorsum of the tongue and a slight hyperpigmentation of the gum and the ventral side can be observed. **(A)** Tongue dorsum. **(B)** Vestibular gum. **(C)** Ventral side.

There is no relevant family history. Regarding personal history, the patient had hepatitis A when she was a child, and she suffers from allergic rhinitis, migraines, hypertriglyceridemia, depression, hypothyroidism and uterine fibroid. Regarding medical history, the patient reports that she is allergic to mites and bees. She does not have any toxic habits. Regarding dental history, she was diagnosed with black hairy tongue and acanthosis nigricans. Currently, she has been diagnosed with stage IV atypical lung carcinoid. She is subjected to a treatment involving: intravenous Octreotide 30 mg, Levosulpiride 250 mg and Omeprazole 20 mg.

On her first visit, the patient provides us with a blood test and a tongue dorsum biopsy report from 1 year ago. In the blood test, we can see altered levels in triglycerides (301.0 mg/dL) and a slightly altered in haemoglobin (10.1 g/dL), iron (49.0 µg/dL) and ferritin (9.0 ng/mL). In the anatomical-pathological analysis, squamous epithelium related to lingual filiform papillae with no relevant alterations was noted. PAS-D and Grocott's stains were negative for fungi.

As complementary test, a new blood test with basal cortisol and ACTH levels is requested, in case there is a hormonal disorder. We can see that haemoglobin and iron are still low, and

triglycerides are high. Regarding hormone levels, ACTH is high (113.0 pg/mL), while cortisol levels are normal (15.6 μg/dL).

We perform a new incisional biopsy of the dorsum of the tongue, on the discoloured area. The anatomical-pathological description is as follows: chronic inflammatory residual signs with post-inflammatory hyperpigmentation. On the pathological anatomy images with optical microscopy and hematoxylin/eosin staining, we can see normal tissue without pathological alterations; under higher magnification, we can see the presence of melanophages, which are the cause of this hyperpigmentation (Figure 2).

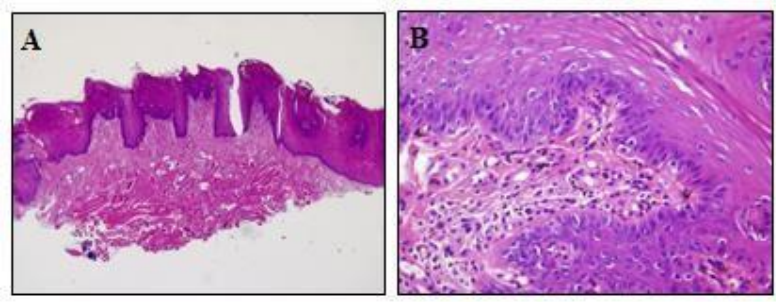


**Figure 2:** Histopathology. Epithelial hyperplasia with ortho and parakeratotic hyperkeratosis. On the basal layer, there are small regenerative signs, but no dysplasia. On the subepithelial connective tissue, there is an accumulation of inflammatory cells, predominantly lymphocytes, as well as melanophages and moderate dilation of superficial blood vessels. **(A)** 10x. **(B)** 40x.

The patient attends check-ups. Melanotic macules on the oral cavity remain stable in several check-ups. This is not the case for the melanotic macules on skin, which continue to appear, indicating that it is an active pathology.

## Discussion

The importance of differential diagnosis of pigmented oral lesions lies in the fact that it allows us to distinguish among different scenarios. They can respond to exogenous pigmentation, the manifestation of a physiological phenomenon, a local or systemic disease or neoplasms. A specific therapeutic handling is required for each of these circumstances.

Differential diagnosis is sometimes difficult, and it requires a careful evaluation. Thorough oral, systematic, family and pharmacological research is essential to guarantee an accurate diagnosis [11].

Some exogenous substances such as chemical agents, amalgam, graphite, drugs, tobacco or chromogenic bacteria may cause a discolouration in normal tissues [12]. Our patient does not have a history of these substances; thus, we can reject them as the cause of pigmentations.

Blood and vascular alterations such as petechiae, purpura, ecchymosis, bruises, haemangiomas and vascular tumours are frequent among endogenous pigmentations.[11] They can be flat or slightly raised lesions, and they vary in colour from red to bluish- purple, depending on the type of blood vessel involved (capillaries, veins or arteries) and the depth of the lesion. These lesions generally show paleness when a vitropression test is performed, as blood is inside vascular spaces and the pressure causes it to move from the lesion [13]. Considering the clinical examination, the negative vitropression test and the biopsy results, in which vascular proliferation is not observed, we can reject these alterations.

Melanotic pigmentation can be focal, multifocal or diffuse in its presentation. Melanin is a pigment derived from tyrosine and is synthesised by melanocytes, which normally appear in the basal layer of the epithelium [15]. A pathological production of melanin on the oral mucosa can be associated with a variety of aetiologies such as tumours, metabolic diseases, dysplastic processes or endocrine disruptions [11].

Although they are rare, both nevus and melanoma can appear in the oral cavity [16]. The pigmentation colour on mucosa can vary from brown to blue or black [12]. Nevus are benign tumours on skin and mucosa, characterised by melanin production. They appear as small, well-defined macules. Hard palate, gum, oral mucosa and lips are the most common oral areas, with a higher incidence in women and an average age of 35 [17]. On the other hand, melanoma is a malignant neoplasm that arises from

melanocytes on skin or mucosa [18]. They are much less common on mucosa than on skin, being hard palate and gum the most common oral areas [19]. In our study, we reject tumoural aetiology given the histopathological findings and the fact that there is no clinical coincidence.

Haemochromatosis is the most common metabolic alteration that causes melanotic hyperpigmentation. It is an increased iron absorption in the intestine which results in a systemic overload. This disorder may be congenital or acquired. If it is not treated, it can lead to diabetes mellitus, cirrhosis, cardiac failure and skin hyperpigmentation. The main oral manifestation is hyperpigmentation due to iron deposits in the adrenal cortex. It varies from greyish-blue to brown [13]. We reject this alteration, since our patient shows lowered ferritin levels.

We reject dysplastic processes such as neurofibromatosis, Peutz-Jeghers syndrome or Albright syndrome, as they are normally congenital processes and provide a different clinical presentation.

Addison's disease is characterised by a deficient hormone production in the cortex of the adrenal gland, which leads to increased ACTH production [20]. Mucocutaneous pigmentation is often one of the earliest clinical manifestations [11]. Oral pigmentation areas include lips, gums, oral mucosa, hard palate and tongue. Other signs and symptoms of Addison's disease are anorexia, sickness and postural hypotension [21]. In our patient's case, Addison's disease is unlikely, because of the absence of these symptoms and the normal cortisol level.

Cushing's syndrome linked to non-pituitary tumours is characterised by the variability of its clinical presentation and by the heterogeneity of associated underlying tumours [22]. The increase in ACTH production induces the stimulation of melanocytes, which are responsible for diffuse pigmentation on skin and oral mucosa [13]. Patients with paraneoplastic Cushing's syndrome may have a wide variety of systemic complications [11]. From descriptions of first cases, characteristic data of these patients are considered to be the

following: myopathy, weight loss and hyperpigmentation [23], with mucocutaneous pigmentation being one of the first signs of this disorder [24]. Pigmentation will eventually be solved if the underlying source of the disease is properly treated [11]. The typical clinical presentation of weight gain and centripetal distribution is more common in non-paraneoplastic Cushing's syndrome [25]. Other symptoms such as high blood pressure, asthenia, muscle weakness, easy bruising and depression must also be considered. Patients with paraneoplastic Cushing's syndrome may have some or all of these symptoms and signs, depending on the underlying tumour [23]. In our case, the presence of skin macules, atypical lung carcinoid and increased ACTH levels lead us to believe that the main cause of black tongue results from the effect of paraneoplastic Cushing's syndrome.

The relevant information of this case is the appearance of black tongue caused by melanin metabolism alteration as a side effect of a non-pituitary neuroendocrine tumour, such as this carcinoid lung tumour secreting ectopic ACTH.

## Conclusions

Hyperpigmentation of oral mucosa is due to different local, systemic or pharmacological causes. A good clinical examination of the oral cavity and the rest of the body, as well as analytical and histopathological tests, are necessary for its diagnosis. Only in this way, once the differential diagnosis with the various possible causes is performed, do we think that the main cause is the paraneoplastic Cushing's syndrome secondary to the previously diagnosed atypical lung carcinoid. It is a rare instance in which the first manifestation is the change of lingual colour related to increased ACTH levels.

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## Case Report

# Oral Ulcers Associated to Methotrexate Toxicity: Case Report and Review of the Literature

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## Abstract

**Introduction:** Methotrexate (MTX) is an immunomodulatory drug, a folic acid antagonist, which is mainly used in autoimmune diseases treatment at low-dose and, at high-dose as a chemotherapeutic agent. Adverse reactions have been reported in long-term treatment with low-dose MTX, such as oral ulcers.

**Case Report:** A 91-year-old female patient, with a medical history of rheumatoid arthritis treated with Methotrexate since

2013, reported painful oral ulcers on the ventral surface of the tongue and retrocommissural mucosa, additionally, the patient declared asthenia and weight loss during the last month. The blood test results showed pancytopenia. She was transferred to the hospital and a biopsy of the oral ulcers and a spinal puncture to rule out another pathology were performed. The definitive diagnosis was MTX intoxication, the treatment consisted of the suspension of the drug administration. At this time, the patient is stable.

**Conclusion:** Oral ulcers caused by low-dose methotrexate (MTX) are known as a side effect of this drug, furthermore they are usually not identified by dentists as a side effect of the treatment. A careful medical and pharmacological anamnesis, along with a recent complete blood test assessment is required in patients with low-dose MTX treatment. Dentists should be aware of the possible side effects of MTX on the oral mucosa.

## Keywords

Methotrexate; Low-Dose Methotrexate; Oral Ulcers; Lymphoproliferative Disorders

## Key Points

- MTX is an antiproliferative, anti-inflammatory, and immunoregulatory drug that contributes to therapeutic management of inflammatory and malignant diseases.
- MTX therapy is commonly supplemented with folic acid to prevent side severe effects.
- Moderate adverse effects are: alopecia, ulcerative stomatitis, and gastro-intestinal intolerance. Severe adverse effects are: pneumonitis, leukopenia, pancytopenia, and myelosuppression.
- Mucositis and oral ulcers being one of the first manifestations of toxicity. The frecuency rate of appearance of oral ulcers in patients treated with low doses of MTX is 11 to 17%
- Patients who present pancytopenia, asthenia, and weight loss

associated with oral clinical manifestations, it is important to rule out lymphoproliferative and myelosuppressive acute syndromes, considering that MTX can cause bone marrow disorders

- The management of oral ulcers in these patients, are cessation of the drug administration and folic acid therapy

## Introduction

MTX's history dates back to 1948, with an initial report written by Sidney Farber and the successful use of aminopterin, an antifolate with the treatment of childhood leukemia. The first published study on Methotrexate (MTX) was in 1962 by Black et al. [1], in patients with rheumatoid arthritis (RA) and psoriatic arthritis (AS), showing favorable results in both pathologies. Robert Willkens et al.[2,3], reported in 1980 one of the first cases series of patients taking MTX, with an improvement of more than 75% of patients using doses ranging from 7.5 to 15 mg per week [2,3].

MTX is an antiproliferative, anti-inflammatory, and immunoregulatory drug that contributes to the therapeutic management of inflammatory and malignant diseases. Various mechanisms of action have been proposed; as an antitumor drug its mechanism is well known, as it interferes which the metabolism of folic acid and prevents cell division [4,5]. However, several hypotheses have been studied that could explain the effect of MTX on rheumatoid arthritis. One of the hypotheses, which has the most evidence, is the one that associates the effect of MTX with the extracellular release of adenosine, resulting in the suppression of inflammation [6].

It is currently used as an anti-inflammatory and immunoregulatory treatment in diseases such as: rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, psoriasis and psoriatic arthritis, Reiter's syndrome, prophylaxis of graft-versus-host disease in allogeneic bone marrow transplantation. Additionally, as an antiproliferative agent in neoplasms such as: childhood acute lymphoblastic leukemia, choriocarcinoma, non-hodking lymphomas and solid tumors [7].

MTX is available enterally and parenterally (subcutaneously, intramuscularly, and intravenously). The dose and route of administration differ according to the indication, from 20 mg/ $m^2$ - 500mg/$m^2$ used as chemotherapy, either orally, intramuscularly or endovenous and as an anti-inflammatory, the doses range from 10 to 25 mg/week orally or subcutaneously due to its high bioavailability and efficacy [7-10].

Oral MTX is absorbed from the gastrointestinal tract, while subcutaneous administration facilitates the arrival of the drug in the vascular system, preventing incomplete gastric absorption, minimizing liver degradation and increasing its clinical efficacy. The drug binds to plasma proteins and is distributed along the body in its free fraction, by serum albumin until it is excreted mostly unchanged bythe kidney. MTX plasma concentrations are used as a predictive value of the toxicity and efficacy [6-9].

Alterations in the absorption, distribution and excretion of MTX can increase blood levels of the drug and increase its toxicity [8]. Drugs such as probenecid, loop diuretics, and phenylbutazone can reduce the renal clearance of MTX [6]. Other concomitant factors that raise the concentration, producing adverse effects are advanced age, weight loss, increased dose, liver and kidney failure [11-13].

Among moderate side effects, alopecia, ulcerative stomatitis, and gastro-intestinal intolerance have been frequently described, while pneumonitis, leukopenia, pancytopenia, and myelosuppression have been described as severe adverse effects [10,14-19]. The most acute reaction is pneumonitis, which, despite being rare, can cause mortality in up to 17% of the patients [6]. Methotrexate therapy is commonly supplemented with folic acid to prevent side severe effects.

Currently, MTX is a drug frequently used by rheumatologists and although its adverse effects have been described, sometimes are unknown in the field of dentistry, with mucositis and oral ulcers being one of the first manifestations of toxicity. Subsequently, we present a case of pancytopenia and oral ulcers associated with low doses of Methotrexate.

## Clinical Case

A 91-year-old female patient, with no know allergies, diagnosed with osteoporosis, rheumatoid arthritis and heart failure, polymedicated with: Dabigatran 110mg, Furosemide 40mg, Alendronate 70mg, Hydroferol 0.266mg, Methotrexate 17.5mg, Pregabalin 25mg and Folic acid 5mg, total edentulous and a full prosthesis worn for more than 20 years. The patient arrives at Bellvitge Dental Hospital - University of Barcelona, reporting "a fuchsia stain on the tongue and burning sensation in the mouth" (Figure 1.A), which impede eating.

During the clinical examination, we weren´t able to observe any coloration, although the patient presented a fungal component in the tongue. Her family member provides us with a photograph of the tongue the days before the visit (Figure 1.B), which we associate with the extrinsic coloration of one of the tablets she took daily. When exploring the oral cavity, ulcerated lesions were observed on the left ventral surface of the tongue and retro-commissural mucosa, of approximately 18mm and 10mm respectively (Figure 2. A-B). They presented a fibrin membrane in the upper layer with erythematous áreas, providing a blister appearance. Throughout the anamnesis, the patient reported that the ulcers had a 4 weeks evolution, the patient declared asthenia with weight loss (5Kg) since last month.

The prostheses she was wearing and its settlement in the alveolar ridges, weren´t correct, which suggested the first diagnosis of presumption of traumatic ulcers, taking into account that the poor adaptation of the prostheses had produced the ulcers. Another differential diagnosis to take into consideration was pemphigus, nevertheless the Nikolsky test was carried out, having a negative result. Finally, analyzing the patient's medical history, methotrexate intoxication was suggested (Table 1).

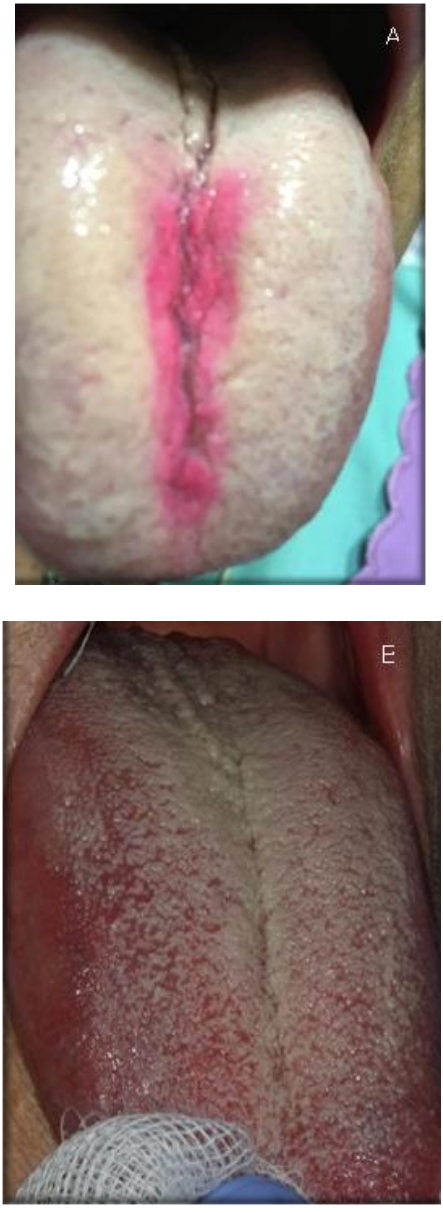


**Figure 1:** A) Extrinsic staining by pharmacological tablet. B) Coated tongue/Candidiasis.

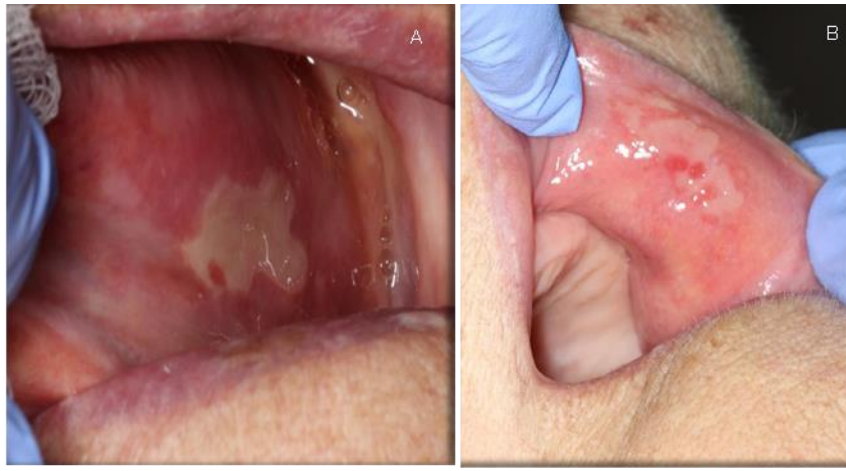


**Figure 2:** A) Ulcer on the left ventral surface of the tongue. B) Ulcer in the retro- commissural mucosa. First visit.

**Table 1:** Differential diagnoses, etiology, clinical features and diagnosis.

| | **Etiology** | **Clinical features** | **Diagnosis** |
|---|---|---|---|
| Traumatic ulcers | Prosthetic maladjustment. | Variable size. Acute pain. Yellowish fibrin coating, clean and non- bleeding appearance. Surrounded by an erythematous area. Location: lateral sides of tongue and retro-commissural mucosa. | -Remove etiological agent |
| Pemphigus vulgaris | Antibodies (IgG) against desmoglein 3. | Multiple and poorly defined blisters, different size, thin roof that breaks easily producing erosions or superficial ulcers, irregular and very painful. Location: mucocutaneous friction areas. | - Positive Nikolsky Sign -Histology Immunofluorescence |
| Pemphigoid | Antibodies (IgG, IgA, C3) against hemidesmosomas. | Blisters that break result in erosion. When the ampoule breaks present a white membrana on erosive surface Location: gingival and palatal mucosae. | - Positive Nikolsky Sign -Histology Immunofluorescence |
| Ulcers induced by MTX | Drug toxicity. Side effect. | Variable size, homogeneous, well defined, clean surface, acute pain. Location: lips, tongue. | -Clinical History -Hematological study -Drug suspension |

We insisted on increasing oral hygiene, not using the prosthesis for the next 15 days, an updated medical report of the pathologies and their pharmacological control, results of previous tests and a current test was requested, rinsing solution with Acetonide of triamcinolone 0.1%, Lidocaine 1%, Clotrimazole 1%, Aloe Vera 30%, Saccharin sodium 1% and strawberry essence was prescribed; 2 times a day for 15 days and a control was scheduled after 2 weeks.

The patient attended after 15 days, no significant differences were found, there were no significant changes in the oral ulcers size, despite the treatment with corticosteroids. Although the ulcers located at the retro-commissural area were erythematous (Figure 3. A- B), the patient still referred to oral burning sensation and difficulty while eating, her family member reported that the patient also presented injuries in the abdominal area, therefore we examined the abdomen (Figure 4), genital and anal mucosa, the last two didn´t present any alteration. We suggested that the abdominal injuries could be related to the administration of MTX, since the route of administration was subcutaneous in the abdominal area. We asked her if there was any pattern of appearance of the lesions with the injection of the drug, but no confirmatory answer was obtained. Laboratory results revealed mild pancytopenia (Table 2).

The case was studied and possible presumptive diagnoses were proposed, including: neutropenic ulcers, ulcers due to methotrexate toxicity, herpes, pemphigus, pemphigoid, paraneoplastic pemphigus. Comparing previous blood tests (December 2018 and June 2019) with normal values, we wrote a clinical report with a presumed diagnosis of the lymphoproliferative syndrome and pancytopenia associated with oral ulcers, requesting a hospital evaluation by the hematologist, rheumatologist, and dermatologist. The oral corticosteroids were suspended and a biopsy of the oral ulcers, was requested to confirm the diagnosis.

The patient was hospitalized in her referent center for 15 days. The results of the biopsy in the oral ulcers showed nonspecific ulcers; The specialists also performed a bone marrow aspiration

(BMA) which did not show hemopathy, for which myelodysplastic or lymphoproliferative syndrome was dismissed. The final diagnosis was methotrexate toxicity, the drug administration was ended and Prednisone was prescribed with a descending schedule if there were outbreaks of rheumatoid arthritis.

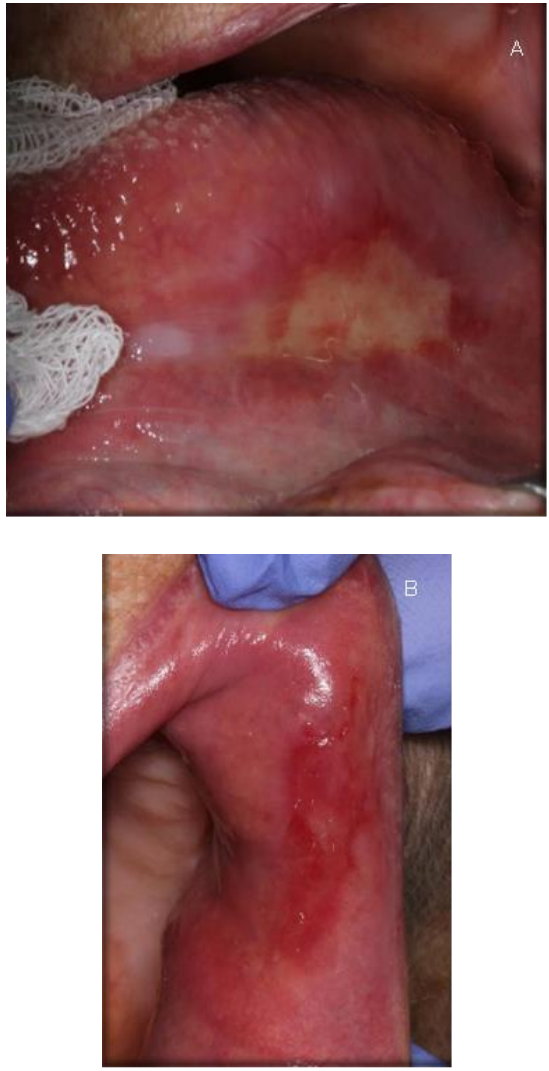


**Figure 3:** A) Ulcer on the left ventral side of the tongue. B) Ulcer in the retro-commissural mucosa. 15 days later.

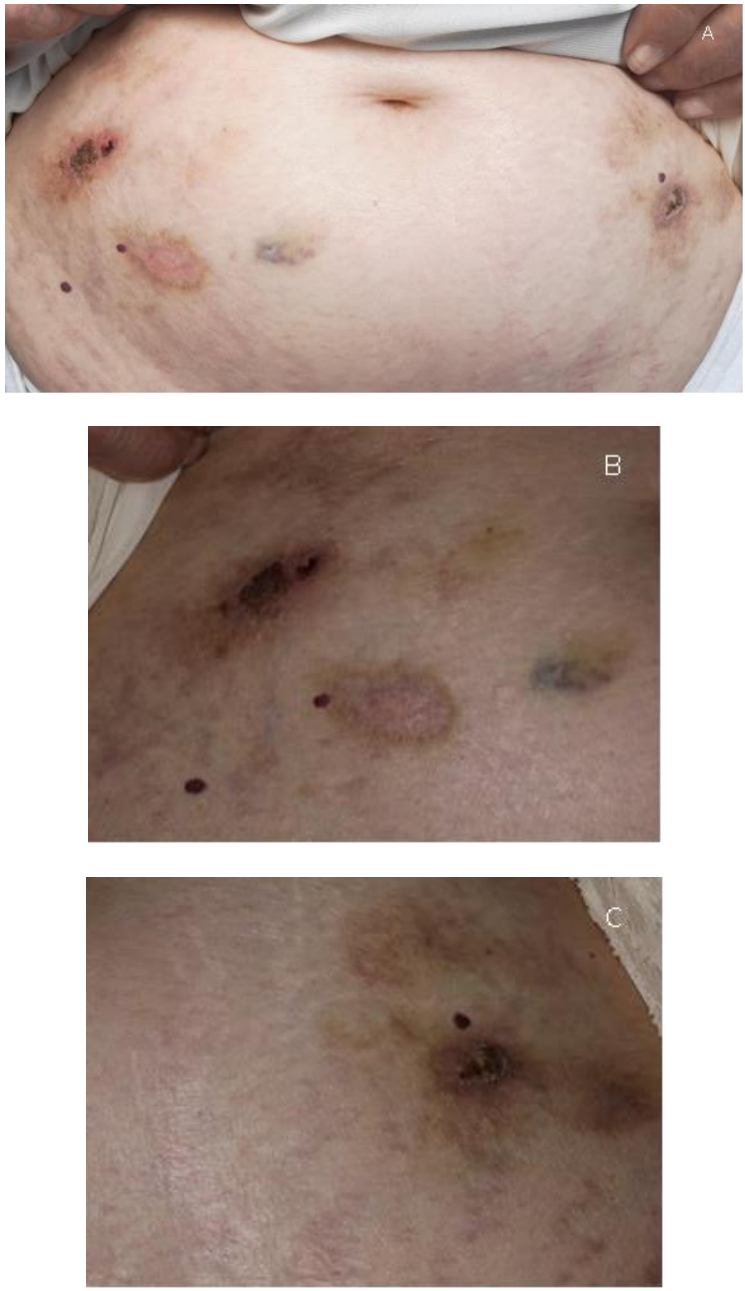


**Figure 4:** A, B and C: Mixed hematoma lesions, crusts and scar in abdominal area.

**Table 2:** Laboratory Tests.

| | | | |
|---|---|---|---|
| Red blood cell count | 3.03 | x10E12/L | 4.00 – 5.20 |
| Hemoglobin | 11.1 | g/dL | 12.0 -15.0 |
| Hematocrit | 33.3 | % | 36.0 – 45.0 |
| Mean corpuscular volume (MCV) | 109.9 | fL | 80.0 – 98.0 |
| Mean corpuscular hemoglobin (MCH) | 36.6 | pg | 27.0 – 33.5 |
| Reticulocytes | 31.5 | x10E9/L | 50.0 – 100.0 |
| Leukocytes | 1.56 | x10E9/L | 4.00 – 11.00 |
| Neutrophils % | 37.8 | % | 40.0 – 80.0 |
| Neutrophils | 0.6 | x10E9/L | 2.0 – 7.0 |
| Lymphocyte | 0.7 | x10E9/L | 1.2 – 3.5 |
| Platelets | 95 | x10E9/L | 140 – 400 |
| Erythrocyte sedimentation rate (ESR) | 57 | mm/h | 0 – 20 |
| C-reactive protein | 1.52 | mg/dL | 0.03 – 0.50 |
| Parathyrin level | 112 | pg/mL | 14.5 – 87.1 |

## Discussion

Methotrexate is safe and effective in various rheumatological disorders. Although it is important to beware of the side effects associated with its administration. Advanced age, duration of treatment, weight loss, the interaction with other drugs that modify folate metabolism, low levels of folic acid, and renal function disturbance can lead to the development of pancytopenia.

Pancytopenia is an idiosyncratic effect of MTX, several studies have affirmed it [16,18-20] including Ajmani et al. (2017) [16] study, which presented a case series of 46 patients with pancytopenia associated with MTX with an average dose of 10mg/week. The main signs reported were oral mucositis (37 patients), followed by temperature (24 patients), diarrhea and gingival bleeding, concluding that the low level of white blood cells is indicative of a poor prognosis and a higher mortality rate. Patients who present pancytopenia, asthenia, and weight loss associated with oral clinical manifestations, it is important to rule out lymphoproliferative and myelosuppressive acute syndromes,

considering that MTX can cause bone marrow disorders. The literature reports cases and case series that demonstrate the similarity of the clinical characteristics of lymphoproliferative acute syndromes with methotrexate toxicity [20,21]. It is necessary to highlight the patient's clinical-pathological history to exclude any neoplastic disorder.

Oral ulcers were found, with a high rate, in patients treated with low-dose MTX ranging from 11-17% [20-22]. A systematic review was carried out by Chamorro-Petronacci et al. (2019) [23] regarding the management of oral ulcers in these patients, they reported cessation of the drug administration and folic acid therapy in 29.17% of the patients, abandonment of the treatment without any added therapy in 25%, abandonment of the treatment plus antibiotics and corticosteroids therapy in 12.5%, and finally abandonment of the treatment and additionally folic acid and corticosteroids therapy in 8.33%. Indicating that the average remission time of the lesions was 20 days.

## Conclusions

Dentists should take into consideration the differential diagnoses of ulcerations in the oral mucosa such as: aphthous stomatitis, autoimmune disorders, allergic reactions, viral and bacterial infections, syndromic diseases and adverse drug effects. Furthermore, a detailed medical and pharmacological history of the patient, keeping in mind the complete blood count. Communicating with their doctor to establish a correct diagnosis and accurate management of oral pathologies is fundamental.

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## Case Report

# Oral Manifestations of Crohn's Disease: A Case Report

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## Abstract

**Introduction:** Crohn's disease (CD) is a chronic, autoimmune, recurrent and idiopathic inflammatory disease. Oral manifestations of CD occurs in 8-10% of patients. In this article, a clinical case of a patient presenting oral manifestations related to CD is going to be presented.
**Clinical Case:** 26-year-old patient, diagnosed with CD 6 years ago. He came to our department to assess oral lesions compatible with manifestations of CD.

**Discussion:** Orofacial granulomatosis (OFG) is related to different granulomatous inflammatory pathologies, including CD. The OFG is considered an oral lesion specific of CD. There are different treatments for CD manifestations, the first choice is usually corticosteroids.
**Conclusions:** To approach the correct diagnosis and clinical management of oral manifestations of CD, a multidisciplinary approach is necessary.

## Keywords

Crohn's Disease; Oral Manifestations; Oral Granulomatosis; Biological Treatments

## Key Points

- Oral manifestations of Crohn's disease.
- Differential diagnosis of orofacial granulomatous diseases.
- Clinical and histological diagnosis of oral lesions of Crohn's disease.
- Treatment of oral lesions of Crohn's disease.
- Use of local corticosteroids.

## Introduction

Inflammatory bowel diseases (IBD) are characterized by a chronic inflammatory process in the digestive tract mucosa. One of them is Crohn's disease (CD) [1].

CD is a chronic, autoimmune, recurrent, and idiopathic disease (2,3). It can affect any part of the digestive tract from the mouth to the anus, although, it is more frequent in the area surrounding the ileocecal valve [3–5].

The incidence and prevalence of CD is increasing. The highest incidence in the world is in Australia (29,3 / 100.000), followed by Canada (20,2 / 100.000) and Northern Europe (10,6 / 100.000) (2.6). Regarding prevalence, it is higher in Europe (322 / 100.000), Canada (319 / 100.000) and the USA (214 / 100.000) [2].

The aetiology of CD remains unknown [6]. Its pathogenesis is not fully established, but it is believed that arises in genetically susceptible patients as a consequence of an alteration in the homeostasis of the immune system of the intestinal mucosa by an environmental sensitization and several triggering factors [2,6].

Clinical presentation of CD is heterogeneous, depending on the location, the extension, the pattern and the degree of activity of the disease [6]. A triad of moderate chronic diarrhoea, weight loss and abdominal pain has been found to be characteristic [2]. Abdominal pain is usually located at the level of the iliac fossa. The presence of diarrhoea will depend on the location of the disease. If the condition is located at the iliac level, the diarrhoea is usually profuse and without pathological products. However, if it is located at the level of the colon, it is smaller in volume, but presents mucus and blood. Other symptoms such as discomfort, fever and asthenia can also be found [6].

CD is a recurrent disease, which goes through periods of relapse and remission and has a prodromal period that can last up to 10 years. Its cycles of inflammation lead to the development of complications such as fistulas or stenosis [2].

In patients with CD, an early diagnosis is necessary. Once the diagnosis of the suspected disease has been established, the combination of clinical, biochemical, endoscopic, radiological and histological criteria is necessary [2,6].

Oral manifestations of CD are usually observed in 8% - 10% of patients [7]. They can manifest at any stage of the disease, before the intestinal manifestations, at the same time as these or even after their appearance [8]. They are divided into two subgroups: disease specific and non-specific [7,8]. Specific lesions are characterized by the presence of non-necrotizing granulomas, which only appear in patients with CD [8]. Among the specific lesions we can mention: oral stone mucosa; inflammation of the lips, cheeks and / or face, being the lips being the most commonly affected; fissures on the lips and tongue; mucogingivitis and linear and deep ulcers with hyperplastic

mucosa in the vestibular depth. Among the non-specific lesions we find: recurrent aphthous stomatitis (RAS), vegetative pyostomatitis, angular cheilitis, glossitis, lichen planus, decreases in salivary levels, caries, candidiasis, halitosis, odynophagia and dysphagia, perioral erythema, recurrent oral abscesses, lymphadenopathy and metallic dysgeusia [7.8]. These nonspecific lesions are caused by malnutrition, chronic inflammation, and drug side effects [8].

The objective of this work is to present a case of oral manifestations of Crohn's disease in order to understand the wide range of clinical symptoms that can be shown and the importance of a good diagnosis and multidisciplinary treatment by both the specialist doctor and the odontostomatologist.

## Clinical Case

26-year-old female patient who attends the Oral Medicine, Surgery and Implantology service of the Faculty of Medicine and Dentistry of the University of Santiago de Compostela (Spain), for presenting a facial swelling at the level of the left cheek with one month of evolution. She has no other symptoms.

As a relevant medical history, the patient had been diagnosed with Crohn's disease for 6 years, with a Montreal classification of A2, L3, B1. He was on treatment since 2016 with injections of Humira® (Adalimumab), a monoclonal antibody that is part of the group of biological medications, fortnightly. He had no relevant family history or any other known pathology or allergy, nor a history of previous trauma or glandular pathology.

Upon extraoral clinical examination, a swelling anterior to the parotid gland was observed, not painful, not adhering to deep planes and with a soft consistency (Figure 1A, B). Intraorally, a gingival enlargement was observed at the level of the second quadrant, more pronounced at the level of the canine and premolars, and a stone-like lesion in the left jugal mucosa (Figure 2A, B, C). Both extraoral and intraoral lesions were asymptomatic.

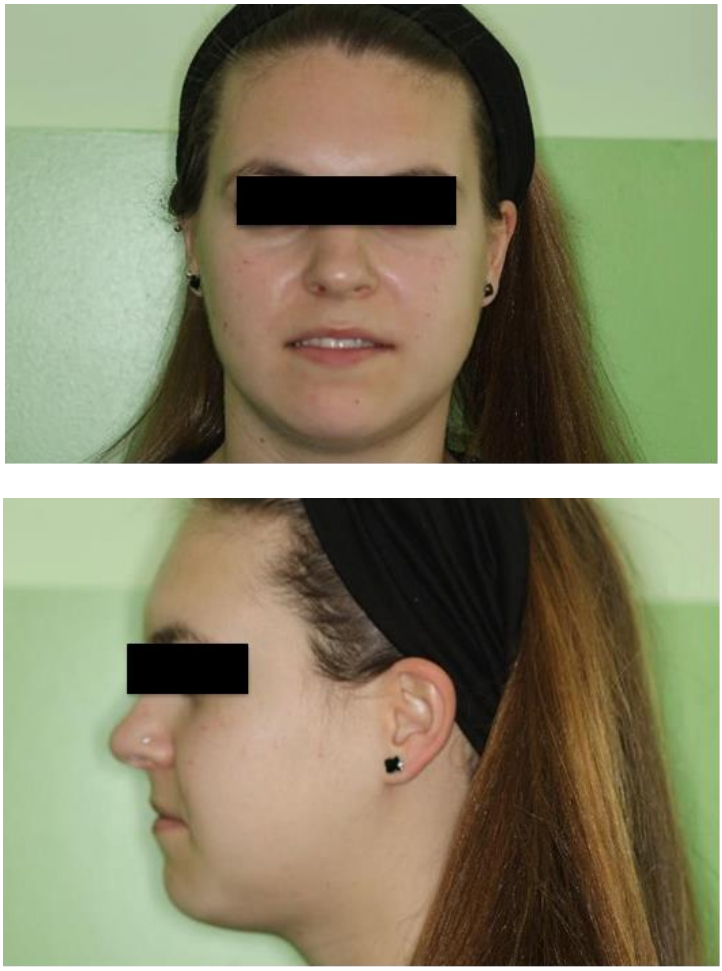


**Figure 1:** Extraoral photographs. A. Front-view of the left hemifacial swelling. B. Lateral-view.

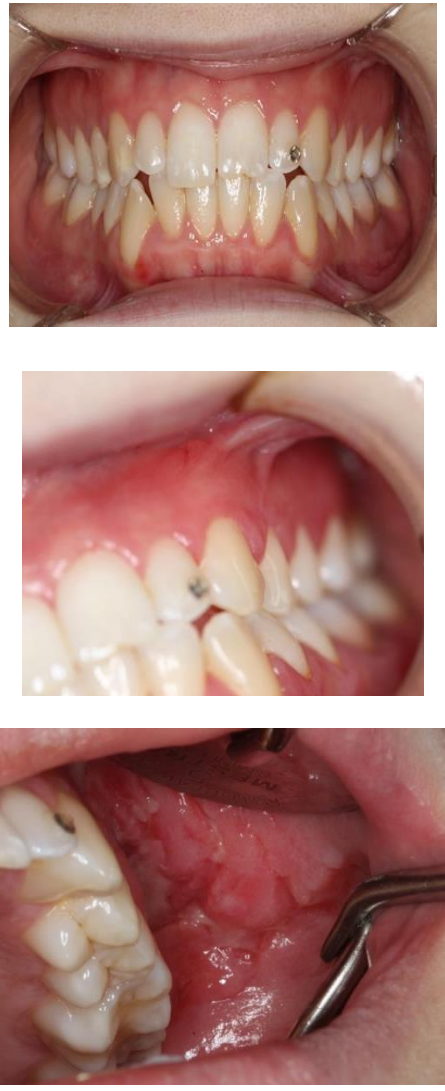
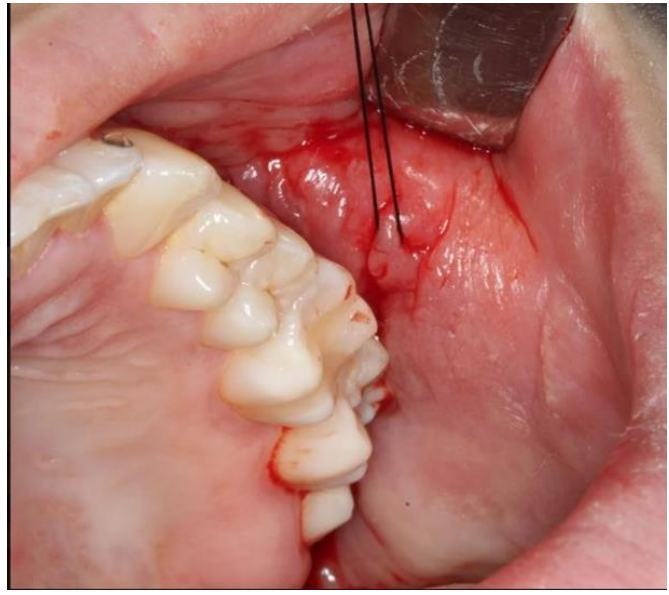


**Figure 2:** Intraoral photographs. A. Front-view. B. Gingival inflammation of the 2nd quadrant. C. Cobblestone lesion in the left jugal mucosa.

Initially, a differential diagnosis was made between the following pathologies that could cause swelling of the left side of the face: infectious pathology of dental origin, inflammatory pathology of the parotid gland, infectious pathology of the parotid gland, glandular or mesenchymal tumors, trauma and

granulomatosis. As there was no previous history of trauma or related dental signs or symptoms, the possibility of an infectious dental disease or trauma was excluded. In turn, due to the anterior situation of the swelling of the parotid gland, any pathology that could be involved was ruled out. Due to the presence of intraoral lesions related to the extraoral swelling, a granulomatosis was suspected, which could be because of the CD presented by the patient.

The patient underwent the following complementary tests: a panoramic radiograph (to assess a possible dental condition), a blood test (whose parameters were within normal limits), and an incisional biopsy of the stoned lesion of the left jugal mucosa. (Figure 3A, B).



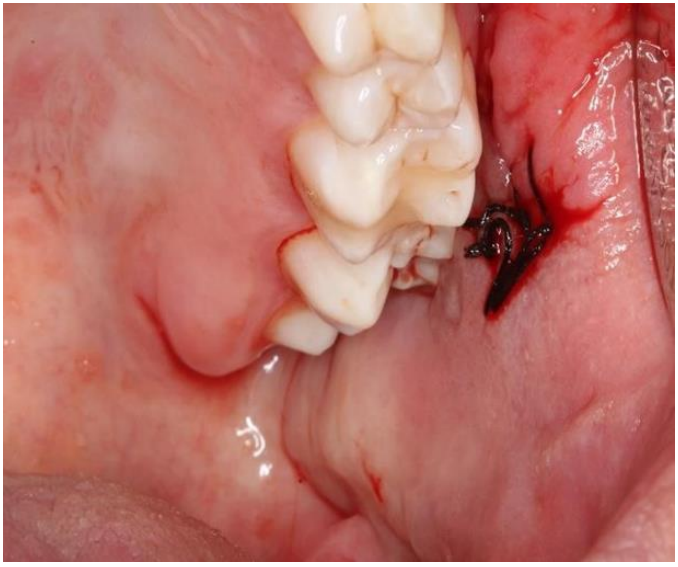


**Figure 3:** A) Biopsy zone in the left jugal mucosa. B) Suture closure (silk, 4-0).

The pathology report of the incisional biopsy indicated a granulomatous inflammation compatible with Crohn's disease. At the microscopic level, the histological study revealed a dense inflammatory infiltrate that mainly affects the subepithelial connective tissue and extends to the hyperplastic surface epithelium (Figure 4). The predominant cells are plasma cells with abundant lymphocytes, and non-necrotizing epitheloid granulomas with giant cells are easily found (Figure 5A, B). PAS staining was performed which did not reveal the presence of fungi.

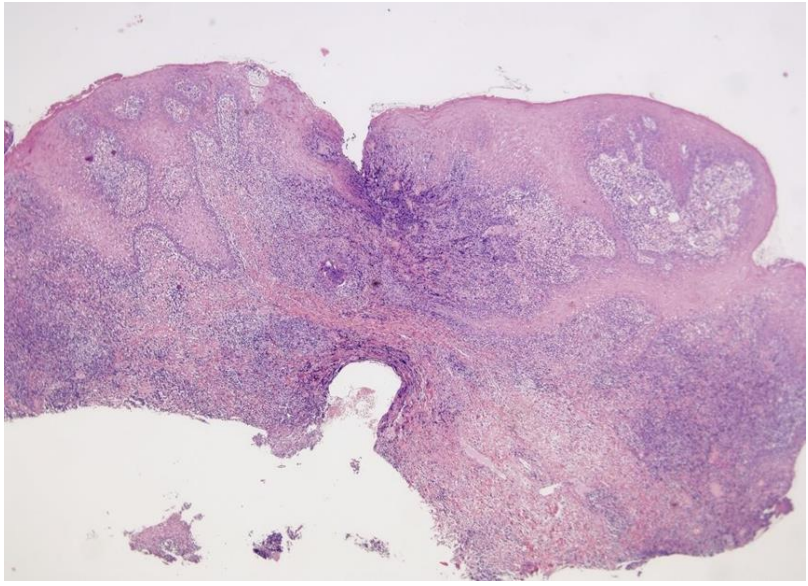
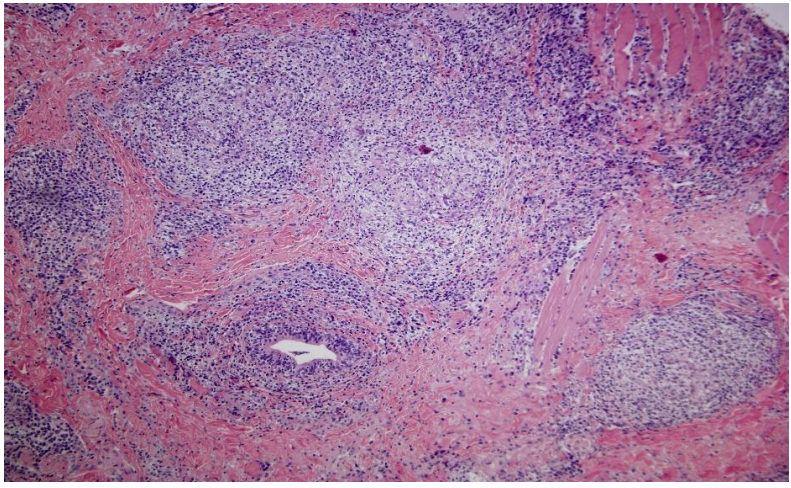


**Figure 4:** Inflammatory infiltrate in connective tissue extending into an hyperplastic epithelium.



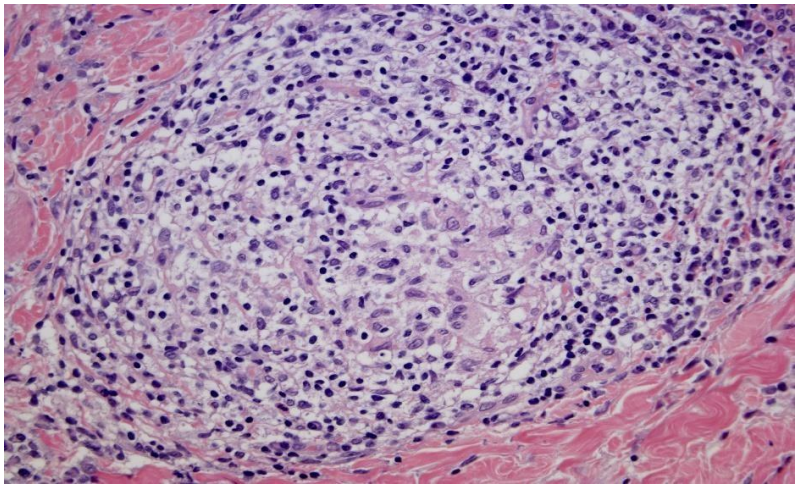


**Figure 5:** A) Accumulations of inflammatory cells. B) Non-necrotizing granuloma formed by giant cells, macrophages, and lymphocytes.

Based on the results of the biopsy, we concluded that the patient's lesions were oral manifestations of the already diagnosed Crohn's disease.

The patient was initially treated with hyaluronic acid and amoxicillin 750 mg every 8 hours for 7 days. Such treatment was chosen, assuming that the lesions were caused by an infection with a dental origin. When the patient came to our service after receiving the biopsy results and corroborating the initial suspicion diagnosis. She was prescribed 0.5% triamcinolone acetonide in aqueous solution to rinse 3 times a day for a month. After one month, due to an insufficient improvement of the lesions, we began with intralesional corticosteroid injections of triamcinolone acetonide 40 mg / ml solution for injection (Trigon Depot®). Corticoid were injected into the lesions, every 7 days, using a previously emptied anesthetic carpule. Since the patient did no present any symptoms, the aim of the treatment was to improve the aesthetic appearance of the mucosa. Corticoids would reduce inflammation and therefore the mucosa bulging.

After 5 weeks (5 doses) of intralesional injections, the improvement of the lesions was evident, decreasing the oral

inflammatory process, both intra- (Figure 6 A, B) and extra-orally (Figure 7 A, B). After one year of follow-up no recurrences were found.

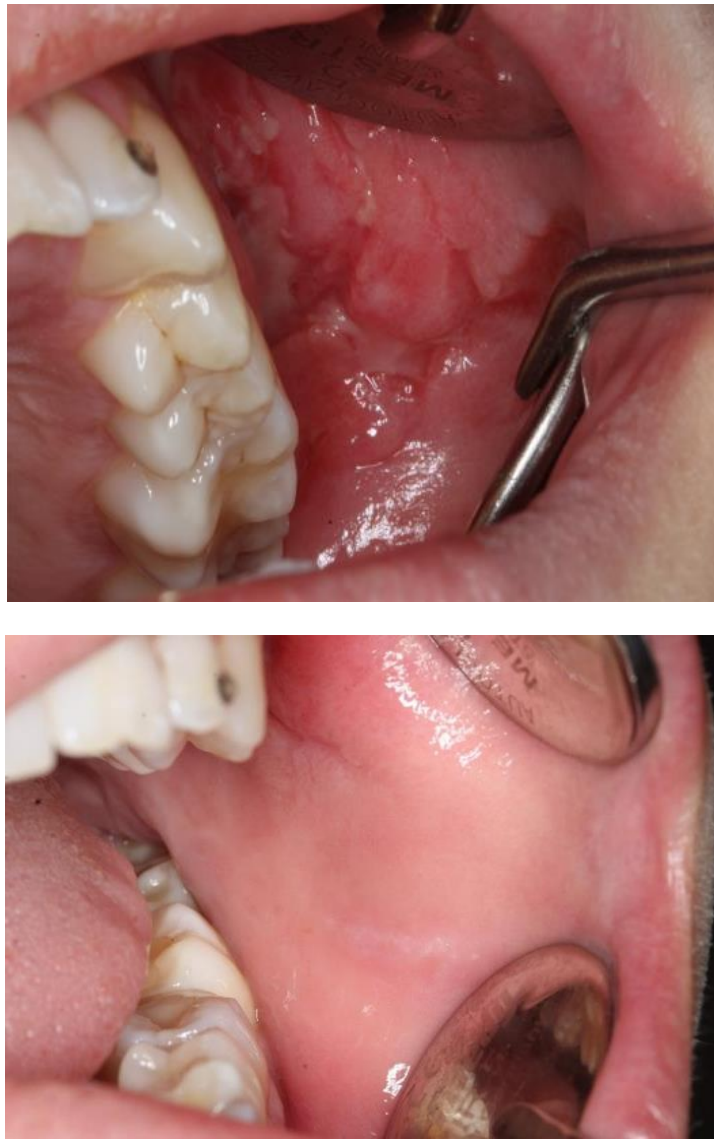


**Figure 6:** A) Evolution of the cobblestone lesion in the left jugal mucosa B) after 5 intralesional injections of triamcinolone acetonide 40 mg / ml in injectable solution.

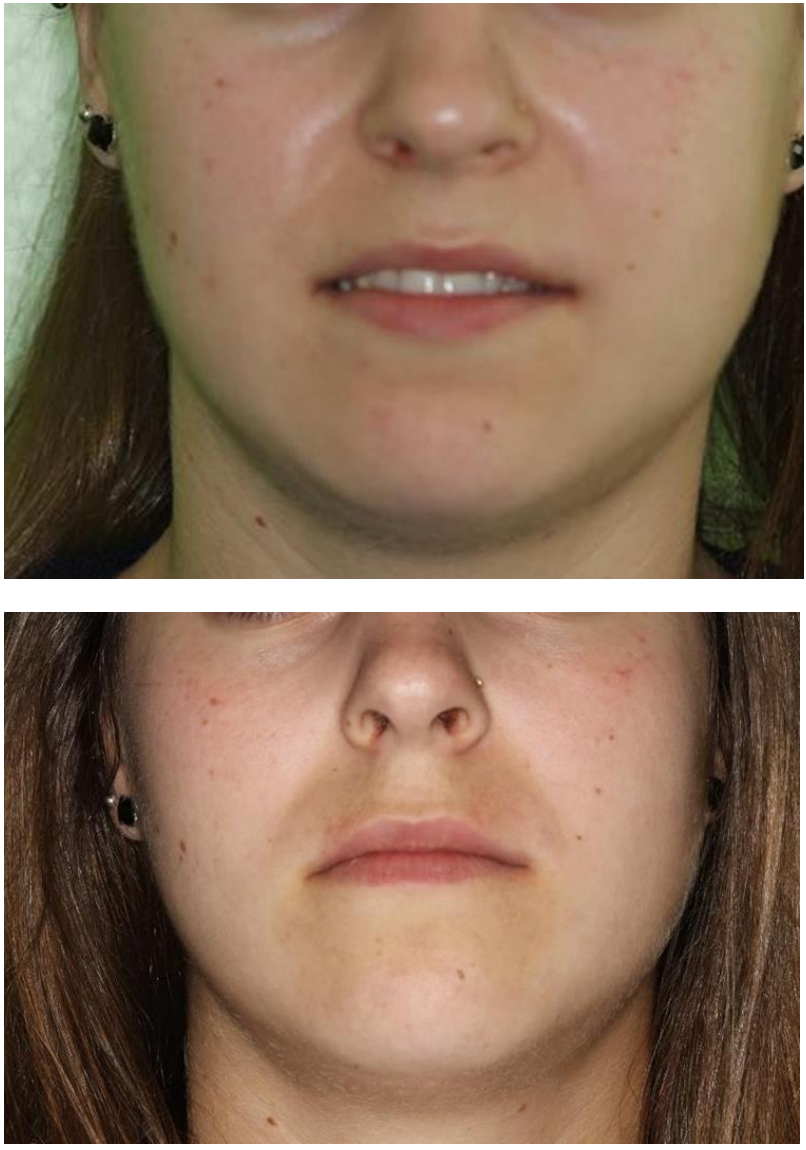


**Figure 7:** A) Extraoral photographs before and B) after 5 oral intralesional injections and a decrease in the swelling of the left side of the face.

## Discussion

Orofacial granulomatosis (OFG) is a chronic inflammatory disease that affects the soft tissues of the face in a greater extent [9,10]. It is characterized by the presence of granulomatous inflammation in the orofacial region, which can cause swelling of the face or lips. Intraorally it is characterized by the appearance of cobblestone lesions, mainly located in the posterior part of the jugal mucosa, or gingival enlargement, as in the currently described patient [10,11]. Histopathologically, it is characterized by the presence of non-necrotizing granulomas and the predominance of epithelioid cells [12,13].

OFG may be caused by systemic granulomatous conditions, such as CD, which according to Sarra et al. (9) it is frequently impossible to distinguish to idiopathic OFG, both clinically and histologically [13,14]. OFG in relation to CD can appear as an initial manifestation even before intestinal manifestations; however, it is difficult to know if these manifestations will appear in those patients already diagnosed with CD [12].

The management of systemic CD is not totally related to the control of oral manifestations [13]. According to Bandzar et al. [15] Nowadays, there is no cure for CD, all existing treatments are symptomatic.

Several studies have demonstrated the presence of elevated levels of TNF-alpha, a cell signaling cytokine, which causes chronic outbreaks [15,16]. For this reason, TNF-alpha blockers such as liximab, certolizumab and adalimumab have started to be used on its treatment. Adalimumab, is the drug used by the medical specialist in our patient. Natalizumab and the alpha-4 integrin blocker are also very effective in the remission of the disease [15,1]). Furthermore, other treatments such as human hormones, antibodies directed against pro-inflammatory cytokines and T cells, and anti-inflammatory cytokines, have shown promising results [15,17].

Regarding the oral manifestations of CD, a spontaneous remission is very unlikely [9]. In a high number of cases, the oral

manifestations can be controlled by the systemic treatment of the disease, but it is necessary to control the intestinal pathology to be able to remit the oral manifestations. A wide variety of treatment options with variable results is available, usually focusing mainly on corticosteroids rinses or gels, in non- severe cases [13,18]. Intralesional steroids are used in more severe cases, especially in cases of prominent lip or facial swelling [13,18+. In cases of resistance to topical and intralesional corticosteroids, systemic corticosteroids are used [13,18]. Other alternative treatments could be immunosuppressants or immunomodular agents, such as tacrolimus or methotrexate, among others [13,18].

The prognosis and evolution of oral lesions is closely related to the evolution of other intestinal disorders. These patients need continuous monitoring throughout their life, since recurrences and new outbreaks are very common. As a result, the efficacy of the treatment and the regulation of the dose of the drug used must be continuously evaluated [2,15].

It can occur in the mouth, and coinciding with the appearance of new intestinal outbreaks oral lesions may recur, so it will be necessary to review these patients by the odontostomatologist once or twice a year. If new lesions appear, treatment with topical corticosteroids will be indicated and, if necessary, intralesional injections [18]. After a one year follow-up, the previously described patient did not present recurrences, however, lifetime controls will needed.

## Conclusions

CD is a chronic inflammatory pathology that can affect the entire digestive tract, hence we can find oral manifestations even before intestinal manifestations appear.

The correct diagnosis and management of these injuries is very important. For a proper diagnosis, it is necessary to know the different lesions, specific or nonspecific, that can occur in the oral cavity.

For a correct management of the treatment of the disease, the relationship between the specialist doctor and the odontoestomatologist is important. In order to achieve remission of oral manifestations, good control of the disease is necessary. Topical or intralesional corticosteroids are the treatment of choice depending on the severity of the lesions.

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## Case Report

# Cardiovascular Patients and Their Management in Dentistry: Update

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## Abstract

Cardiovascular disease (CVD) is the leading cause of death in industrialized countries, as well as being an important cause of morbidity in these populations. Consequently, we will find many

patients who attend dental offices with this disease. On the one hand, it has been shown that patients with CVD present more dental and periodontal pathology and, on the other hand, that dental and periodontal pathology can aggravate the cardiovascular state of our patients. Besides, most of these patients are under treatment with various medications, highlighting antiplatelets and anticoagulants. As dentists, it is necessary to know what measures to take with these patients to perform treatments safely.

## Points of interest

- We have to know what cardiovascular disease is and what it means to our patients.
- The patient must be evaluated as a whole, so maintaining a good state of oral health can improve his cardiovascular pathology.
- We must know the medication that the patient takes and know what measures to take in each case, to offer comprehensive and safe treatment to our patients.

## Introduction

Atherosclerosis is an inflammatory-based disease, which is due to the accumulation of lipids and fibrous tissue in the arterial walls. Despite lifestyle changes and new pharmacological approaches to lower plasma cholesterol levels, cardiovascular disease remains the leading cause of death in Europe, the United States, and most of Asia [1-3]. Atherosclerosis lesions occur mainly in large and medium arteries and can trigger ischemia with irreversible lesions [1]. It has been identified that a high inflammatory activity is responsible for the process of atherogenesis and endothelial dysfunction, which lead to cardiovascular disease [1,4].

In Spain in 2015, the group of diseases of the circulatory system remained the leading cause of death, with a rate of 267.6 deaths per 100,000 inhabitants. Likewise, they were the first cause of death in women (286.9 deaths per 100,000 inhabitants), and the second in men (247.6) [5]. These data are reinforced with those

obtained in 2017, where atherothrombotic diseases are the first cause of death in women and the second in men [6].

In the human species, atherogenesis is a process that extends throughout life. However, the growth of atheroma plaques is likely to be discontinuous, with periods of relative inactivity interrupted by rapidly evolving episodes. After an "asymptomatic" phase, which lasts, generally for decades, atherosclerosis may become evident. Its clinical expressions can be "chronic" as is stable angina pectoris associated with exertion or intermittent claudication. It can also manifest more acutely and seriously, such as myocardial infarction, stroke, acute ischemia of the lower extremities, or sudden cardiac death [7].

Today, the main cause of atherosclerosis is known to be an excessive serum concentration of low-density lipoprotein (LDL-c) cholesterol. However, other cardiovascular risk factors must also be taken into account, which also plays a very relevant role in their origin, including smoking, obesity, diabetes mellitus (DM), hypertension (HT), and other factors such as excessive concentrations of apolipoproteins (apo) B and homocysteine among others [8-10], or even dental and periodontal pathology [11,12].

Under normal conditions, the arteries of medium and large-caliber are composed in their innermost part by an intimate layer, formed by endothelial cells, basement membrane, and loose connective tissue, the latter consisting mainly of smooth muscle cells and fibroblasts. In the middle layer of these arteries, we find smooth muscle cells and elastic tissue, and in the most superficial layer, called the adventitia layer, we find connective tissue, vessels, and nerves [13]. These endothelial cells of the intimate layer, when in a state of rest or non-aggression, present a smooth surface allowing the flow to be laminar, not adherent to leukocytes or platelets and release vasoconstrictor and vasodilator substances that regulate blood pressure [1].

When toxic substances from tobacco, increased LDL-c, bacterial toxins, etc. appear in the bloodstream, that is to say, risk factors associated with atherosclerosis, mediators of inflammation are

released, causing endothelial cells previously in a resting state to activate. This fact assumes that endothelial cells present molecules in their cell wall, making their surface adherent to leukocytes and platelets [1,14]. Also, there is an increase in the permeability between these cells and an increase in the production and release of vasoconstrictor substances, proinflammatory cytokines, and growth factors, causing endothelial dysfunction, which is described as an imbalance in the bioavailability of active substances of origin. endothelial that predisposes to inflammation, vasoconstriction, and increased vascular permeability, and that can facilitate the development of arteriosclerosis, platelet aggregation, and thrombosis; in addition to causing an irreversible thickening of the intimate layer [14].

Once endothelial permeability is increased, LDL-c particles will enter the intimate tunic of the vascular wall, where they oxidize and become toxic, causing further endothelial dysfunction and inflammatory response. There will also be the recruitment of circulating monocytes, generating a feedback loop [2].

Subsequently, the monocytes will enter the vascular wall, transforming after activation into macrophages. These cells gobble up the oxidized LDL-c particles, transforming into foam cells, prototype cells, and primaries of atherosclerosis [1,13]. Foamy cells will undergo apoptosis, releasing cholesterol particles into the environment, causing a greater inflammatory response, and therefore more endothelial dysfunction [13]. Besides, the foam cells activate the smooth muscle cells, causing them to begin migrating to the innermost layer.

It is at this point where we can talk about the formation of the fatty stria, which is a non- elevated lesion, characterized by presenting oxidized LDL-c particles, lymphocytes, macrophages, foam cells, debris, and cholesterol crystals [10,15].

Likewise, throughout this inflammatory process, endothelial cells secrete proinflammatory substances, cytokines, and growth factors, which stimulate smooth muscle cells. These migrate from the middle layer to the intima and are the main protagonists of the proliferative component of the atheroma plaque, where they deposit collagen after its transformation to fibroblasts [10,15].

From this point, we can speak of atheroma plaque. Collagen secreted by smooth muscle cells creates a fibrous capsule that surrounds the entire center of the lesion, called the "necrotic nucleus" or "lipid nucleus." In this case, the lesion is elevated, protruding into the vascular lumen, and may cause partial or total occlusion, or rupture of the fibrous capsule with embolization of fragments of the plate at a distance, or the appearance of thrombosis and vascular occlusion due to the formation of a blood clot [10,13,15].

According to the characteristics of the plate and the place itself; as well as the spread of the thrombus, and taking into account the most frequent events of atherothrombotic cardiovascular disease, we can speak of reversible or irreversible cerebrovascular ischemic stroke, if it occurs in the cranial region, of angina pectoris (stable or unstable), acute myocardial infarction or sudden death in the coronary zone or, if it occurs in the lower limbs, we will speak of arteriopathy of the lower extremities with intermittent claudication [16].

On the other hand, in numerous studies, it has been shown that patients with CVD have a worse oral health status versus patients without this disease [17]. Most studies evaluated its relationship with periodontal disease (PD) [18], but it has also been related to caries [19], apical periodontitis [20], the number of teeth [21], oral hygiene [22], and even with mucosal pathology such as oral lichen planus [23]. Not only this, but it also seems that PD treatment can improve the systemic inflammatory state of patients, thus reducing the risk of CVD [22,24], although this finding still generates considerable controversy [25]. Now, if we try to look at it from the other point of view, that is, if we ask ourselves if people with CVD have a higher incidence or progression of suffering PD, the answer is that there is not enough evidence to support or reject this possible association [18]; However, it seems that if a patient suffers from CVD and PE, they could be at greater risk of having a second ischemic accident [26], but there are still authors who do not find such a relationship [27] (Figure 1).

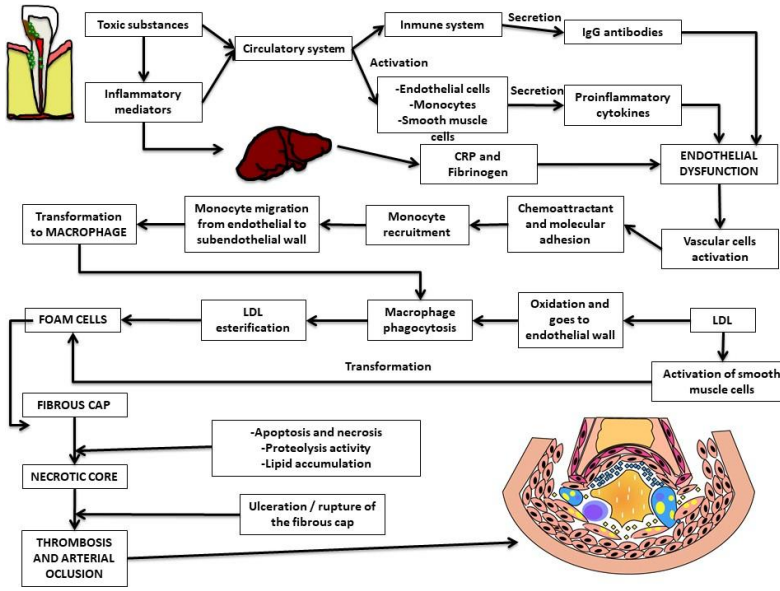


**Figure 1:** Diagram that relates dental and / or periodontal pathology to cardiovascular disease.

To treat a patient who has suffered an atherothrombotic accident, we will have to wait 6 months from the cardiovascular event, when it is considered safe to treat the patient. The risk of reinfarction during non-cardiac surgery is 30% in the first 3 months, 10% from the third to 6 months, and 5% from the sixth month [28]. Some authors recommend delaying surgery for at least 9 months after a cerebrovascular event, supporting that it is not until then that the risk of reinfarction decreases considerably [29,30].

On the other hand, we will have to take into account the anesthesia that we are going to use. In dentistry and more specifically in oral surgery, the use of vasoconstrictor anesthetics is very frequent, since they reduce toxicity, increase the anesthetic effect, and improve hemostasis [31- 33]. The combination of a local anesthetic with a vasoconstrictor causes the diameter of the nearby vessels to decrease (alpha-adrenergic effect), but on the other hand, they can increase the heart rate and can cause vasodilation in skeletal muscles and internal organs (beta effect - adrenergic) [31,34]. Due to this, the use of vasoconstrictors in

patients with cardiovascular disease can lead to confusion and controversy [31,35]. The psychological factor and its influence on homeostasis must be taken into account. An episode of stress or anxiety can lead to the exaggerated production of endogenous catecholamines, causing unwanted hemodynamic and metabolic disorders [36,37]. A study reported that stress-induced release of catecholamines could be more than 10 times greater than the basal level; Furthermore, in stressful situations, such as pain and anxiety, the release of endogenous catecholamines could reach higher concentrations than the low concentrations of epinephrine used in dental local anesthetics [38,39]. For this reason, the use of vasoconstrictor anesthetics in patients with controlled CVD and/or controlled arterial hypertension is not discouraged today. Therefore, it is recommended to aspirate before injecting, not to use more than 0.036mg of epinephrine and in case we need to reinforce anesthesia, we will do it without a vasoconstrictor [40].

Once the patient has suffered a transient ischemic accident, most of them are polymedicated. In general, they are usually taking a lipid-lowering agent, usually a statin, an antihypertensive agent, a beta-blocker, a gastric protector, in some cases a hypoglycemic agent, and one or two antiplatelet agents (AG) and/or anticoagulant (NOAC).

The GA, NOAC, and new oral anticoagulants (DOAC) that we most frequently find in Spain are presented in Table 1.

**Table 1:** AG, DOAC, and NOAC most frequently used in Spain. Adapted from Rubio Alonso LJ et al. [41].

| Type of medicine | Name of the drug | Trade name (Spain) |
|---|---|---|
| **AG** | Acetylsalicylic acid | Adiro®, Bioplak®, Tromalyt® |
| | Clopidogrel | Plavix® |
| | Prasugrel | Effient® |
| | Ticagrelor | Brilique® |
| **DOAC** | Acenocumarol | Sintrom® |
| | Warfarin | Aldocumar® |
| **NOAC** | Dabigatran | Pradaxa® |
| | Rivaroxaban | Xarelto®, Eliquis® |

AG: Antiplatelet; NOAC: oral anticoagulant; DOAC: New oral anticoagulants

Before performing any dental treatment in our patients with cardiovascular pathology, we will have to take into account that the patient is medically controlled and we will have to assess the dental intervention that we are going to perform, differentiating it into a dental procedure that does not usually cause bleeding and a dental procedure that usually causes bleeding, either low or high risk (Table 2) [42]. For patients taking AG, NOAC, or DOAC we will have to be careful with procedures with a high risk of bleeding and we will take special measures considering each case.

**Table 2:** Classification of dental interventions based on the risk of bleeding, recommended by the Scottish Dental Effectiveness Program (SDCEP) [43].

| **Dental procedure that does not usually cause bleeding** | **Dental procedure that usually causes bleeding** | |
|---|---|---|
| | Low bleeding risk | High bleeding risk |
| -Local anesthesia due to infiltration, intraligamentous or blockage of the mental nerve or inferior dental nerve<br>-Basic periodontal study<br>-Removal of plaque or supragingival tartar<br>-Restorations with supragingival margins<br>-Endodontics<br>-Impressions and other prosthetic procedures<br>-Placement and adjustment of orthodontic appliances | -Simple extractions (1-3, small surgical wound)<br>-Incision and drainage of intraoral abscesses<br>-Periodontal study with complete probing<br>-Removal of root plaque<br>-Restorations with subgingival margins | - Complex extractions (more than 3, large surgical wound<br>-Flap lifting<br>-Surgical extractions<br>-Periodontal surgery<br>-Pre-prosthetic surgery<br>-Periradicular surgery<br>-Crown lengthening<br>-Implant surgery<br>-Gingivoplasty or gingivectomy<br>-Biopsies |

Before treating a patient who has suffered an atherothrombotic accident and who is taking antiplatelet or anticoagulant medication, it is important to balance the risk of bleeding after a dental procedure and the patient's thrombotic risk. The risk of hemorrhage has to be assessed by the dentist, while the thrombotic risk has to be analyzed by the specialist doctor and it is him who will decide to continue, withdraw or replace antithrombotic treatment [41,44,45]. Given that in most cases these are chronic treatments, it is expected that the patient with antithrombotic therapy throughout his life will undergo a surgical intervention, which may require the prompt withdrawal

of the drug. This fact is of great importance since premature discontinuation of antiplatelet therapy is associated with an increased risk of cardiovascular events, including stent thrombosis [45,46].

## Management of Patients on Oral Antiplatelet Therapy

There are a large number of patients who are under medical treatment with GA as a primary prevention mechanism for a cardiovascular accident. They are usually taking a single AG once a day. On the other hand, patients who have suffered an atherothrombotic accident, as a general rule, are taking two GA, during the first year after the cardiovascular event. This double anti- aggregation is prescribed due to the high risk of reinfarction that exists during the first year [47].

The patient who comes to the dental consultation in the first 6 months after the atherothrombotic event, is generally doubly antiplatelet. In this case, dentists should only treat the emergency (as it is only the emergency, we will not take into account the type of procedure, whether it is a high or low risk of bleeding) and always in a hospital setting due to the high risk of recurrence of the event and it is not recommended to modify the anti-aggregation guideline; hemostatic measures should always be prepared after the procedure. On the other hand, if the patient comes between the sixth and the twelfth month after the event, we will have to differentiate whether the consultation is urgent or not. If urgent, after evaluating it with your specialist doctor, it is recommended to do the procedure without stopping the medication and with hemostatic measures prepared for after the procedure. If the consultation is not urgent, the patient could be treated, with the above considerations, generally without suspending or modifying the medication, but it is recommended to wait up to a year, at which point the patient normally stops taking one of the AGs, so the bleeding would be less. Finally, if the patient comes one year after the event, any type of procedure can be done without the need to suspend or modify the AG treatment [42,48] (Figure 2).

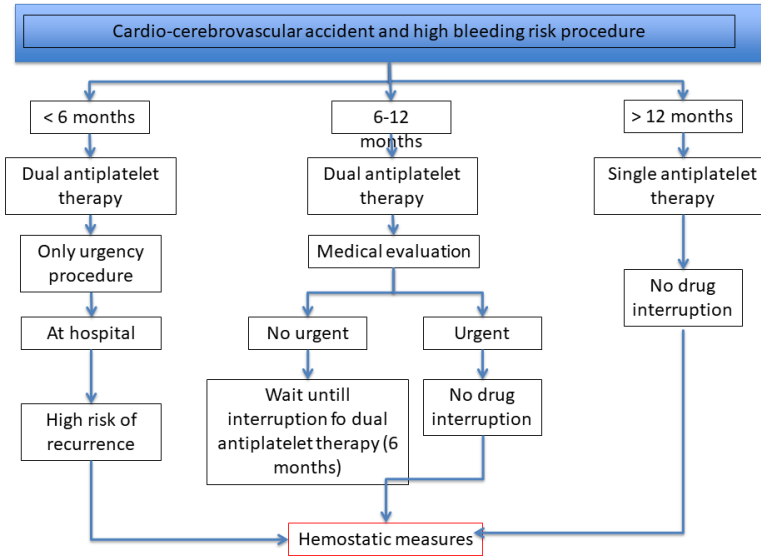


**Figure 2:** Diagram of decisions to treat an antiplatelet patient.

Most of the societies, as we have commented, do not recommend the suspension of antiplatelet therapy (Table 3).

**Table 3:** Recommendations of different societies for oral treatments in patients on antiplatelet therapy.

| YEAR | GROUP - ASSOCIATION | RECOMMENDATION |
|---|---|---|
| 2015 [49] | American Dental Association | Continue with antiplatelets for dental procedures |
| 2014 [50] | The Society for Neuroscience in Anesthesiology and Critical Care (supported by the American Society of Anesthesiologist) | e with antiplatelets for simple extractions |
| 2013 [51] | American Academy of Neurology | Continue with aspirin for dental procedures |
| 2012 [52] | American College of Chest Physicians | Continue with aspirin for dental procedures |
| 2007 [53] | American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association | e with antiplatelets for dental procedures |

## Management of Patients Receiving Oral Anticoagulants

Before performing a surgical dental procedure on a patient taking oral anticoagulants (NOACs) or new oral anticoagulants (DOACs), there are no agreed criteria on what steps to take; in fact, there are significant and inconsistent variations, although in most cases they do not recommend stopping NOACs and consulting their doctor if they are taking DOACs [42].

Oral anticoagulants (NOAC and DOAC) are widely used drugs in Spain, used to prevent the formation of blood clots and thus prevent the risk of strokes [54].

If a patient goes to the dentist for a high-risk bleeding procedure and is undergoing treatment with a NOAC, there is the possibility of having the patient monitored, since we can assess what state of anticoagulation he is in, employing the INR (International Normalized Ratio) test [54]. The normal INR range for these patients is between 2 and 3.5, with some exceptions of high specific risk [55]. If the patient is within the normal INR values ($\leq$3.5) (provided that no more than 72 hours have elapsed since the test), we will not suspend the treatment and we will have hemostatic measures prepared. If, on the other hand, the patient has an INR> 3.5, it will have to be assessed whether we can regulate this figure or because of the thrombotic risk, the patient must have a higher INR. If the INR value can be regulated, an inter-consultation with your specialist doctor will be necessary, so that he may try to modify the NOAC regimen and thus be able to stabilize the patient in a more adequate INR range. If, on the other hand, the patient has to have high INR values and it cannot be regulated, we will consult with his doctor so that he may consider replacing the NOAC with low molecular weight heparin (LMWH) and returning to the NOAC afterward (42,54,56) (Figure 3).

On the other hand, DOACs have been introduced in the last decade, since they are the same or safer and more effective than warfarin or acenocoumarol, in addition to having a more favorable profile in the balance between bleeding and thrombotic risk and does not need to be monitored [4,55,57].

The most recent information on the management of patients under treatment with DOAC suggests that low-risk bleeding procedures do not require interruption of DOAC in patients with correct renal function (42). It is also recommended, when possible, that the procedure be carried out when the DOAC concentration is as low as possible, that is, 12 or 24 hours after the last intake, depending on whether the medication is taken once or twice a day, since that it is not advisable to carry out an intervention at the peak of maximum plasma concentration of the drug [42, 58] (Figure 4).

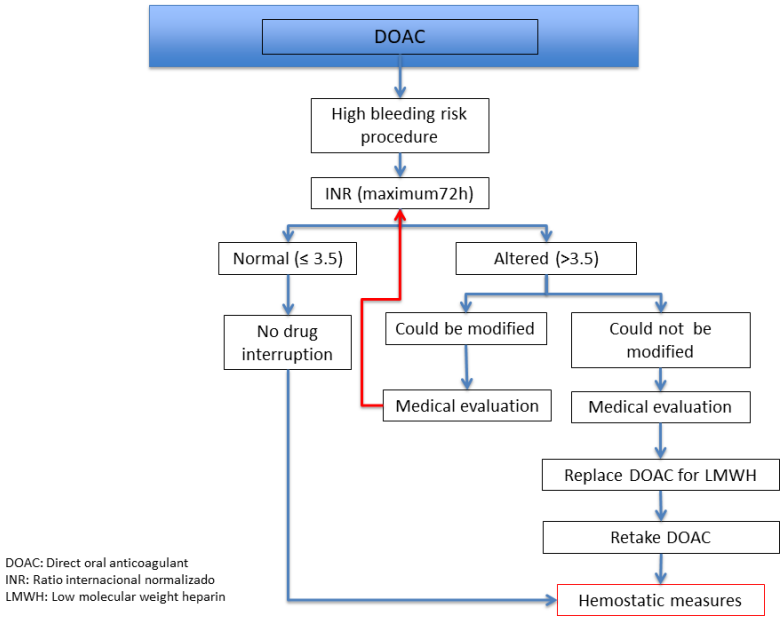


**Figure 3:** Diagram of decisions to treat a patient with direct oral anticoagulants (DOAC).

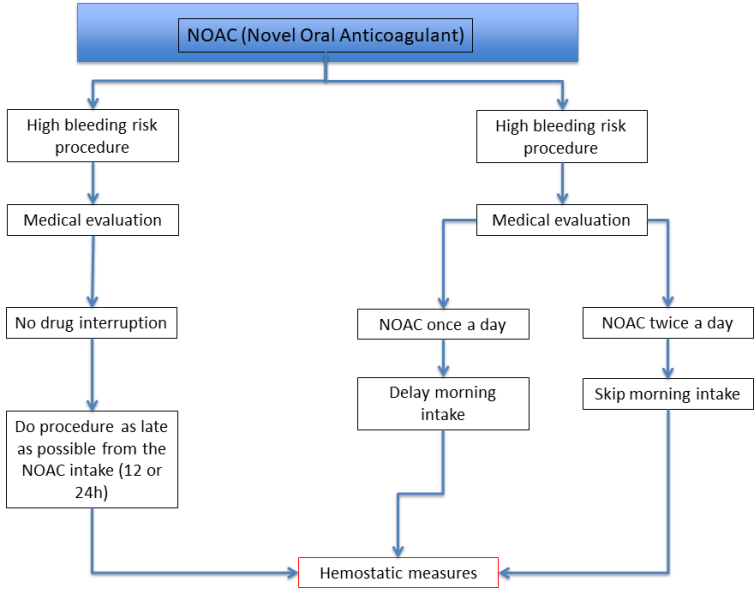


**Figure 4:** Diagram of decisions to treat a patient with new oral anticoagulants (NOAC).

For those patients undergoing treatment with DOAC and who require a dental procedure with a high risk of bleeding, it is recommended to delay taking the medicine in the morning, in the case that it is only taken once a day, or that the morning dose is skipped if the drug is taken twice a day [58] (Figure 4).

Due to the short time, it takes for DOACs to reach maximum plasma concentration, resuming the medication once hemostasis has been established (between 6-8 hours), provides rapid restoration of anticoagulation after the dental intervention [59].

## Conclusions

- Cardiovascular diseases represent the first cause of death in developed countries.
- It has been shown that patients with cardiovascular disease have a higher prevalence of the dental and periodontal disease, with periodontal disease being the most studied one.
- The first 6 months are considered of risk after a cardiovascular

event, although sometimes this period should be extended to one year due to the state of polypharmacy in which the patient is.

- We must know and know how to master the medications that patients with ischemic heart disease take to offer the best treatments and alternatives when treating our patients in dental clinics.

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## Case Report

# Pemphigus and Pemphigoid: Clinical Cases

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## Abstract

This section describes the two most frequents vesiculoulcerative diseases groups that can affect oral cavity. On one hand, the pemphigoid and, on the other hand, the pemphigus but in a superficial way, because this disease will need multidisciplinary and hospital control.

Some of the aspects that we detail in pemphigoid section are applicable to all chronic vesiculoulcerative diseases from the oral cavity. On the other hand, the detail in this section brings us

closer to the complexity of antigens and antibodies that are involved in this type of disease. This complexity often exceeds the skills of the dentist, especially if we consider their infrequency.

Finally, we present two clinical cases, one of pemphigus and the other of pemphigoid, to assess how the dentist can deal with these pathologies.

## Point of Interest

- Review the differences between the two most significant groups of bullous diseases that can occur in the mouth.
- Analyze the diagnostic complexity of this type of disease.
- Review the role of the dentist in said diseases.

## Introduction

Bullous diseases present clinical pictures that are not very similar to each other. The elemental lesion in these diseases is a blister. They can primarily affect the skin, the skin annexes and / or the mucosa, or these diseases can develop due to other systemic diseases. Bullous diseases are also classified according to their etiology, we can group them into different sections (Table 1) [1,2].

**Table 1**: Bullous diseases. Adapted from Pulido Pérez & Suárez Fernández [1].

| **Classification of bullous diseases** | |
|---|---|
| **BULLOUS AUTOIMMUNE DISEASES** | **OTHER** |
| *A. Intraepidermal* | **Enfermedades bullosas hereditarias** |
| -Pemphigus vulgaris, vegetative pemphigus | *A. Group of hereditary epidermolysis bullosa* |
| (Pedomain of mucosal lesions) | -Intraepidermal: simple epidermolysis bullosa |
| (Mucocutaneous lesions) | - Intralamine lucid: junctional epidermolysis bullosa |
| -Pemphigus foliaceus, Fogo selvage | - Sublamina densa: dystrophic epidermolysis bullosa |
| -Pemphigus IgA | - Mixed: Kindler syndrome |

| | |
|---|---|
| -Paraneoplastic pemphigus (may have subepidermal involvement) | B. Enfermedad de Hailey-Hailey (intraepidérmica) |
| *B. Subepidermal* | **Bullous diseases of metabolic cause** (subepidermal, except for zinc deficiency) |
| -Bullous pemphigoid | *A. Group of porphyrias (porphyrias with skin involvement)* |
| -Scar pemphigoid (of mucous membranes) | -Perphyria cutaneous late |
| -Gestational pemphigoid or herpes gestationis | -Porphyria variegata |
| -Linear IgA bullous dermatosis | -Hereditary coproporphyria |
| -Dermatits herpetiforme | -Congenital erythropoietic porphyria |
| -Acquired epidermolysis bullosa | -Erythropoietic protoporphyria |
| -Bullous lupus erythematosus | -Hepatoerythropoietic porphyria |
| -Bullous lichen planus | -Pseudoporphyria |
| | B. Bullosis *diabeticorum* |
| | *C. Déficit de zinc (intraepidérmica)* |
| | **Bullous vasculitisc(subepidermal)** |
| | **Infectious diseases** |
| | *A. Intraepidermal:* herpes simplex, herpes zoster, staphylococcal impetigo |
| | *B. Subepidermal:* bullous scabies, ecthyma gangrenosum (Pseudomonas aeruginosa), deep mycoses (zygomycosis, aspergillosis, fusariosis ...) |
| | **Toxicodermias** |
| | *A. Intraepidermal:* erythema multiforme exudative, Stevens-Johnson syndrome, toxic epidermal necrolysis |
| | *B. Subepidermal:* Fixed drug rash, palmoplantar erythrodysesthesia |
| | **Blisters induced by physical agents (subepidermal):** thermal burn, cryotherapy, radiodermatitis ... |
| | **Coma-induced blisters (subepidermal)** |
| | **Culicosis bullosa or blistering after insect bites** (intraepidermal, subepidermal) |
| | **Other:** mastocytosis, Grover's disease (transient acantholytic dermatosis) |

**Table 2**: Autoimmune bullous diseases. Adapted from Pulido Pérez & Suárez Fernández [1] y van Beek N, et al [3].

| **ENFERMEDADES BULLOSAS AUTOINMUNES** | **Autoanticuerpos** | **Antígeno** | **Características clínicas** | **Test diagnóstico** |
|---|---|---|---|---|
| *A. Intraepidérmicas* | | | | |
| -Pénfigo vulgar, pénfigo vegetante | | | Erosiones de las membranas mucosas, ampollas flácidas / erosiones de la piel | -IMD: ICF IgG / C3<br>-IFI esófago de mono: ICF IgG<br>-ELISA, IIF: Dsg3 + Dsg1 ± |
| (Pedominio de lesions mucosas) | IgG | -Desmogliena 3 | | |
| (Lesiones mucocutáneas) | IgG | -Desmogliena 1<br>-Desmogleina 3 | | |
| -Pénfigo foliáceo, *Fogo selvage* | | -Desmogliena 1 | Ampollas flácidas / erosiones de la piel, erosiones y placas de descamación | -IFD: ICF IgG / C3<br>-IFI esófago de mono: ICF IgG<br>-ELISA, IIF: Dsg1 + |
| -Pénfigo IgA | IgA | -Desmocolina | Pustulas principalmente en zonas intertriginosas | -IFD: ICF IgA / C3<br>-IIF esófago de mono: ICF IgA<br>-ELISA, IIF: Dsc1, 2, 3 Dsg 1, 3 IgA + |
| -Pénfigo paraneoplásico (puede tener afectación subepidérmica) | IgG | -Desmogleína 1,3<br>-Desmoplaquina I, II<br>-Periplaquina<br>-Envoplaquina<br>-Plectina<br>-BPGA1<br>-¿Otros? | Erosiones predominantes de la mucosa oral y los labios, neoplasia (neoplasias malignas hematológicas, timoma, enfermedad de Castleman) | -IFD: ICF IgG / C3 ± BMF<br>-IFI esófago de mono: ICF IgG ± BMF Vejiga de rata / mono: urotelio +<br>-ELISA, IIF: Dsg3 +, envoplakin + |
| *B. Subepidérmicas* | | | | |
| -Penfigoide ampolloso | IgG | BP180/BPAG2/ colágeno XVII | Ampollas tensas, erosiones, | -IFD: BMF, n-pattern<br>-IFI esófago |

| | | | | |
|---|---|---|---|---|
| | | | eritema, placas urticariformes, severa picazón | de mono: BMF<br>-IIF SSS: blister roof<br>-ELISA, IFI: BP180 +, BP230 + |
| -Penfigoide cicatrizal (de membranas mucosas) | IgG | -BP180/BPAG2/ colágeno XVII<br>-Laminina 332<br>-Integrina b4 (subunidad)<br>-Antígeno p200-laminina y 1<br>-¿Otros? | Lesiones predominantes en la mucosa (oral> conjuntival> nasal) | -IFD: BMF, n-pattern<br>-IIF monkey esophagus: BMF<br>-IFI SSS: blister roof and/or blister floor<br>-ELISA: BP180+, BP230+<br>-IB: LAD-1+; IB: BP180+; IB, IIF: laminin332+; IB: integrins+ |
| -Penfigoide gestacional o herpes *gestationis* | IgG | BP180/BPAG2/ colágeno XVII | Vesículas, placas urticariformes, eritema principalmente en el área periumbilical;severa picazón | -IFD: BMF, n-patern<br>-IFI esófago de mono: BMF<br>-IFI SS: blister roof<br>-ELISA,IIF BP180 +, BP230 + |
| -Dermatosis bullosa IgA lineal | IgA | -Antígeno 120 KDa del dominio extracelular de BP180/BPAG2<br>-BP180/BPAG2/ colágeno XVII<br>-Colágeno VII<br>-¿Otros? | Vesículas en los márgenes de la lesión (a modo de rodete de perlas) | -IFD: BMF, n-pattern (IgA)<br>-IFI esófago de mono: BMF (IgA)<br>-IFI SSS: blister floor (IgA)<br>-IB, ELISA: BP180 + (IgA), LAD-1 (IgA) + |

| | | | | |
|---|---|---|---|---|
| -Dermatits herpetiforme | IgA | Transglutaminasa epidérmica (TGe) | Severa picazón, vesículas, eritematosas y, a menudo, pápulas excoriadas sobre las superficies extensoras de las extremidades y la región sacro-glútea. | -IFD: fluorescencia de puntos en papilas dérmicas ya lo largo de la membrana basal<br>-IIF esófago de mono: endomysium + (IgA)<br>-ELISA: TG + epidérmico, TG + de tipo tisular, GAF + (IgA) |
| -Epidermolisis bullosa adquirida | IgG | Cilágeno VII | Ampollas tensas y erosiones de la piel y mucosas. | -IFD: u-pattern<br>-IFI esófago de mono: BMF<br>-IFI SSS: blister floor<br>-ELISA, IIF: COL7 + |
| -Lupus eritematoso bulloso | IgG | Cilágeno VII | Lesiones en piel concomintantes y en boca de aspecto liquenoide | |
| -Liquen plano bulloso | -- | -- | Su presentación es rara en boca. Ampollas asociadas a lesiones liquenoides | IFD: Negativa |

Col7, type VII collagen; Dsg, desmoglein; Dsc, desmocollin; IFD/IFI, directa/indirecta immunofluorescencvia; BMF, membrna basal fluorescencia; ICF, intercellular fluorescencia; SSS, salt- split skin; IB, immunoblotting; LAD-1, soluble ectodomain of BP 180; GAF, coeliac disease-specific gliadin epitopes; blister flor; suelo de ampolla

When the etiology is autoimmune, autoantibodies are deposited against normal components of the epidermis [3]. In the group of pemphigus, the main antigen is desmoglein 1 and 3; that will cause acantholysis, that is, the loss of intercellular union between keratinocytes, this involves the formation of intraepidermal bullae (4). In bullous pemphigoid (PA) and its variants, autoantibodies are produced against components of the basement membrane and in the dermatitis herpetiformis, autoantibodies are specifically directed against epidermal transglutaminase (enzyme expressed in the epidermis and dermal papillae) [1 -5].

From the clinical point of view, we will review the group of pemphigoids extensively and, more superficially, that of pemphigus, which is less important for the dentist, except in its capacity for early diagnosis when the disease debuts with exclusively oral manifestations [3].

## Pemphigoid Group (Subepidermal Bullae)

Thus, within subepidermal autoimmune bullous diseases, several entities have been defined [1-3,6]:

i) Bullous pemphigoid (BP), which is primarily a skin disease;
ii) Mucous membrane pemphigoid or scar pemphigoid, which primarily affects mucosal.
iii) Epidermolysis Bullosa Acquisita (EBA).
iv) Linear IgA Bullous dermatosis.
v) Dermatitis herpetiformis so is primarily a skin disease and associated with celiac disease.
vi) Bullous lupus erythematosus.

In this review, we will review the most prominent aspects in connection with the oral cavity and we will focus specifically on its therapeutic alternatives.

### Bullous Pemphigoid (BP)

It is the most common presentation of autoimmune bullous diseases, with about 10–40 cases per million/population/year [7]. Its incidence usually increases with age and its severity is

associated with the fragility of the affected patients. On many occasions, it is a secondary manifestation of drugs. The mortality rate per year remains high, ranging from 13 to 38%. (8). Although its relationship with neoplastic diseases is not clear, whenever it occurs at an early age it should be investigated. [9,10,11]. Antibodies are directed against a component of the basement membrane, the BP180 protein. Also, there is a clear inflammatory component, which destroys the dermo-epidermal junction.

At the cutaneous level, it presents with erythematous-edematous plaques, of urticarial appearance, associated with intense itching (sometimes before the lesions). Blisters appear on these lesions, sometimes months after the onset of symptoms (there are cases in which they do not appear). [12]. It mostly affects the lower trunk and flexor areas, and the head and neck are usually excluded. Mucosal involvement is rare, but for some authors, it can be affected by up to 40%, especially the oral mucosa. [13]. There may be atypical presentations, such as palmar-plantar form, pediatric the pediatric presentation limited to the vulva, or nodular pemphigoid (erythematous nodules). [1].

Histologically, there is a bulla separating the epithelium from the connective tissue with an inflammatory infiltrate in eosinophils (sometimes associated with serum eosinophilia). Direct immunofluorescence studies show a continuos linear band of inmunoreactants, usually IgG and C3. In the gestational variant and some mucosal pemphigoids, the deposits are observed on the epidermal side (roof); while bullous epidermolysis, bullous lupus erythematosus, antip-200 pemphigoid, and anti-laminin 332, are shown on the dermal side (soil) [1-3].

The gestational variant (Herpes gestationi) usually presents in the third trimester or just in the immediate postpartum (it can affect 1: 20-50,000 pregnancies) and the most affected area is the peri-umbilical area It can affect the baby in up to 10% of cases [14,15]. Oral involvement is rare and can be associated with other autoimmune processes such as thyroiditis or alopecia areata, among others [3].

## Treatment

In this group of diseases, three objectives are pursued: control inflammation, usually with corticosteroids, tetracyclines and/or nicotinamide; control the production of antibodies, with corticosteroids and/or immunosuppressants and limit the sequelae. (1,3). From the dentist viewpoint we can propose 5 lines of action that we list here and will develop later:

- 1st line. Topical treatment for the oral cavity, if the outbreak is not very serious. [2,16]
- 2nd line: Start systemic treatment if the outbreak at the oral level is more important or is associated with skin manifestations. With this option, between 60 and 90% of patients are usually controlled in between 1 and 4 weeks of treatment. [1,2,17].
- 3rd line. If there is no complete response and/or there is regrowth, tetracycline and nicotinamide can be added or dapsone (50-150mg/Kg/day) can be used. In this case, if we are not experts in this type of pathology, the most appropriate is to refer the patient to a specialist (1,2).
- 4th line. If the previous alternatives fail, we can resort to immunosuppressants or drugs such as tacrolimus or similar, but as in the previous case, the most appropriate thing will be to refer the patient. [1,2,18,19].
- 5th line. Other alternatives may be immunotherapy or monoclonal antibodies. In most cases, these therapeutic options will be outside the daily chore of dentists. [20]
- This treatment scheme, which we will develop later, will be valid, in general, for the dentist to start the treatment of any bullous disease.

## Mucous Membrane Pemphigoid (MMP)

Also called cicatricial or mucosal pemphigoid, it is a rare chronic disorder that can cause scarring. It can affect only the skin, only the mucous membranes, or both. Some authors attribute up to 2 cases/million people/year [21]. When only the mucous membranes are affected, it is called mucous membrane pemphigoid (PMM), and it is called ocular pemphigoid when

only the ocular membranes are involved [22]. The risk of scar healing depends on the affected area, thus in the eyes, it can cause recurrent ectropion, trichiasis and formation of corneal films. For this reason, it may require aggressive treatment based on its initial presentation. Skin lesions can appear more or less localized in 25-30% of cases [1,2]. Ocular affectation at the onset of the disease can be frequent. In a retrospective study from the 70s, 162 patients participated, the involvement was 67% [23].

Antigens can be against: i) BP180. It is a transmembrane collagen, known as collagen XVII and is a component of the epithelial cell hemidesmosome. The dense plaque of the hemidesmosome binds to keratin 5 and keratin 14 within the keratinocyte. The BP180 passes through the lamina lucida. The noncollagenous portion of the domain (N-terminus) is located near the cell membrane and the collagenous portion of the domain (C-terminus) extends over the lamina lucida and projects into the lamina densa. Serum antibodies from patients with bullous pemphigoid target primarily the N-terminus of BP180, whereas sera from patients with scarred pemphigoid target the C-terminus. This variability in antibody target may explain the clinical differences observed between patients with bullous pemphigoid and scar pemphigoid [24,25]. Targeting the N term would result in a more superficial blister with little chance of healing, as seen in bullous pemphigoid. Targeting the C term would result in a deeper separation, which would be more likely to heal, as seen in cicatricial pemphigoid. ii) Laminin 332 (formerly known as epiligrin or laminin- 5). It is a transmembrane protein that connects the α6-β4-integrin of the keratinocyte hemidesmosome to the non-collagen domain 1 (NC1) of collagen VII. Collagen VII is the accessory for the anchoring fibrils that secure the basement membrane to the dermis. Laminin 332 helps to strengthen the attachment of the epidermis to the dermis by shear forces. When this expression is very evident, it is called antilaminin pemphigoid 332 (previously called antiepilligrin). iii) β4-integrin. α6-β4-integrin is a component of the hemidesmosome that binds to transmembrane laminin 332 and that binds to collagen VII. Serum and IgG fractions from patients with scarred pemphigoid have been shown to target the

intracellular portion of α6-β4integrin, suggesting that this may have a pathogenic role in scarring pemphigoid. A recent study demonstrated that sera from patients with ocular scar pemphigoid reacted to β4 integrin. iv) p200-laminin (anti-p.200 pemphigoid) and other antigens that are not fully described [26,27].

We have already commented that its exact prevalence is unknown. A French study attributes 1.16 per million per year and another German 0.87 per million per year, and it seems more frequent in women, 7 to 1 [28,29]. HLA-DQB1 * 03: 01 is considered a marker of susceptibility to the disease. There is an interesting work from the year 2000 by Fleming & Korman [30] that says that while the ocular mucosa is affected in 50-70% of cases, 85% of patients have oral involvement, being the gingiva (64%), the buccal mucosa (58%), the palate (26%), the alveolar crest (16%), the tongue (15%), and the lower lip (7%) are the most frequent locations [30,31].

Histologically it presents with a subepidermal blister with a dermal lymphohistiocytic infiltrate, variable in the number of neutrophils and eosinophils (in skin biopsies, frequently, there is the infiltration of plasma cells). It is a non-specific lesion and can be observed in other immune disorders, such as bullous pemphigoid, linear IgA bullous dermatosis and epidermolysis bullosa acquisita, among others that we will describe later. Fibrosis may be present in older lesions [32].

## Clinically

*A.* The mouth is usually the most affected, and even the only location. All areas can be affected: the buccal mucosa, the gums, the tongue, the vermilion of the lips and the palate, it can also spread to the posterior pharynx [32]. Desquamative gingivitis is common. In mild cases, it is characterized by erythema and gingival edema. The involvement, which can be moderate to severe, is manifested by paresthesia and scaling, with blisters, erosions, and ulcers. Patients may complain of bleeding gums after brushing their teeth, and mild chewing trauma can cause flaking. A long period of inflammation and difficulty in

maintaining oral hygiene can cause cavities, tooth loss, gum tissue, and alveolar bone [33]. Scars are not common but can present as reticulated white lesions, with adhesions, limiting movement.

*B.* In the ocular mucous membrane, a progressive scarring formation is quite common to cause blindness. Inflammation can also be slowly progressive.

The patient may experience nonspecific symptoms of eye irritation such as burning or have scaly lesions associated with a decrease in tears, mucin, and possible secondary infections. It can affect only one eye, but, commonly, in a period of one or two years the other is affected equally. It is rare to find whole blisters but at the ending to find synechiae. Healing usually begins with the lower eyelid and fibrous strands that connect the conjunctiva with the eyeball (symblepharon). These are best seen by pulling the eyelid up. Finally, there is a scarring of the conjunctival sac (ankyloblepharon). Associated with a decrease in the production of tears with entropion (inward turning of the eyelid), trichiasis (eyelash turning), and keratinization of the corneal epithelium with ulcers and decreased visual acuity, and even blindness [34].

*C.* Nasopharyngeal involvement is less frequent (nasal lesions with crusts, epistaxis, or chronic sinusitis with altered airflow), if there are adhesions it can obstruct the airways. If the larynx is affected, a sore throat or hoarseness may occur and if there are permanent scars it may cause difficulty in speaking and difficulty in the airway. If the esophagus is involved, pain, dysphagia, odynophagia, and stricture may occur [34,35].

*D.* Pemphigoid rarely involves the genital and anal mucosa. Erosions and ulcerations can cause considerable discomfort to the genital skin, and scars can cause narrowing of the urethra and vagina [36].

*E.* Scarring pemphigoid skin lesions are rare and occur in two clinical presentations. The first subtype presents as a more generalized rash of tight blisters without healing. The second subtype presents as blisters on an erythematous base that occurs in

localized areas, resulting in an atrophic scar, most common on the head and neck. If the scalp is affected, it causes alopecia [37]. It is important not to confuse it with Brunsting-Perry pemphigoid, which was once thought to be a form of scarring pemphigoid. This presents as a bullous healing eruption of the skin of the head and neck without the involvement of the mucous membrane. Today this is believed to be a phenotype of acquired epidermolysis bullosa [38,39]

For diagnosis, a biopsy of injured skin is recommended for histopathology, in which we will observe subepithelial bleb with mixed infiltrate with eosinophils. And another from a perilesional area for direct immunofluorescence (DIF). Immunofluorescence usually shows IgG and C3 as a linear band in the area of the basement membrane 3,25,40]. Occasionally a linear deposit of IgA can be seen. Indirect immunofluorescence is positive in a small percentage of cases for IgG and IgA. It is best done in a separate sample with NaCl 24-48 hours, which allows us to mark the epidermal side. Using ELISA (enzyme- linked immunofluorescence) it will detect anti-BP180 or anti-laminin 332 antibodies, among others [3,25,40-42].

**Treatment**

As in bullous pemphigoid, the goal should have three pillars: 1. Decrease the production of antibodies. 2. Decrease inflammation. 3. Prevent sequelae.

*Differential diagnosis* should be done with:

i) Bullous pemphigoid is the most common autoimmune subepidermal bullous disorder, with an age of onset of 65 to 75 years. It usually affects the mucosa little and the lesions do not cause a scar. [1,2].
ii) Bullous systemic lupus erythematosus is an autoimmune subepidermal bullous disorder that develops in patients with systemic lupus. The rash consists of erythematous macules, plaques, and blisters that tend to occur in areas exposed to the sun and do not usually produce scars. Oral lesions can occur [61,62].

iii) Paraneoplastic pemphigus is a rare autoimmune disease associated with malignancy, most often non-Hodgkin's lymphoma and chronic lymphocytic leukemia. It is characterized by a painful, erosive stomatitis and polymorphous skin lesions that may resemble bullous pemphigoid, lichen planus, or erythema multiforme. It responds poorly to treatment if the underlying disease is not treated [63].

iv) Pseudocular cicatricial pemphigoid. If there is only ocular involvement, it is a mimic of scar pemphigoid. This is a rare complication from the use of medicated eye drops in the treatment of glaucoma. Ocular involvement is unilateral. The progression generally stops once the eye drops are discontinued. There are no mucosal skin lesions.

v) Acquired epidermolysis bullosa (EBA) and bullous dermatosis of linear IgA that we will comment on later.

The *prognosis* depends on the sequelae of the scars. Patients require long-term follow-up to monitor for complications resulting from scarring and possible relapse.

Our mission in these patients will be to inform them about the chronic nature of the disease, its possible recalcitrant course and the possible serious complications. We must provide patients with information on the appropriate oral hygiene techniques based on the oral manifestations they present.

## Acquired Epidermolysis Bullosa (EAA)

It is a rare autoimmune subepidermal bullous disorder that causes autoantibodies against collagen VII, as in bullous lupus. The blisters are usually tense, not inflammatory. They are located especially on the extensor surfaces and are usually caused by friction or trauma. The oral mucosa may be affected, blisters appearing from mere chewing trauma. The blisters heal with scars and meliceric crusting. They are usually resistant to treatment and may be associated with underlying systemic diseases [64-66,67,68].

## Linear IgA Dermatosis (DAIL)

Its characteristic is IgA deposits in the epidermal basement membrane, it is rare and may encompass several diseases. In its presentation, it may resemble dermatitis herpetiformis, bullous pemphigoid, or scarring pemphigoid. It is the most common autoimmune bullous disease in children (chronic bullous dermatosis of childhood) and usually affects the facial area and genitalia. Sometimes the lesions are herpetiform grouped and may require differential diagnosis with staphylococcal impetigo [1,25,47]. Above all, in adults, there are variants triggered by drugs (they usually disappear when withdrawn), such as vancomycin or beta-lactams, among others, and usually begin with the folds and roots of the limbs [69,70]. The mucosa can be affected, especially the oral one and to a lesser extent the ocular mucosa and are usually initially treated with dapsone, corticosteroids and even antibiotics such as cloxacillin [1,2,71].

## Dermatitis Herpetiformis (DH)

It could be given a role outside of subepidermal autoimmune bullous diseases. Its antigen is located at the level of the dermal papillae (epidermal transglutaminase) [1,2,47,72] and is usually associated with celiac disease in almost 100% of cases, although the digestive system may be asymptomatic. Today it is considered a cutaneous manifestation of gluten intolerance and it is considered that 5% of intolerant people will trigger it throughout their lives [73].

It usually presents with erythematous edematous papules or plaques (preferably on the surfaces of the limbs such as the elbows, knees, or buttocks) in which vesicles and / or abrasions settle that end in hemorrhagic crusts. Occasionally it can present with palmar purpura or with lesions in the mucous membranes. Integral blisters are rare [74–75].

Histologically there may be subepidermal vesicles, but the characteristic is neutrophil microabscesses in the upper part of the dermal papillae. It will be confirmed by a granular deposit of IgA (with or without C3) at the dermal-epidermal junction of healthy perilesional skin [76,77].

In its treatment, gluten should be avoided. You cannot eat wheat, barley or rye, but you can eat corn, rice and oats. It usually responds well to Dapsone at doses of 100-200mg / kg/day, so it should be the first choice [78-80].

## Treatment of Pemphigoids, Summary

**Treatment**

In all forms of pemphigoid, the objective must have three pillars: 1. Decrease the production of antibodies. 2. Decrease in inflammation. 3. Prevent sequelae. Attempts have been made to establish recommendations based on their severity [43,44, 45,46], but generically we can establish two large groups: Low risk (only oral and mild skin involvement) and High risk (ocular, nasopharyngeal involvement, genital and esophageal) [47]. We must also consider, in addition to the location of the injuries, the number of them. Thus, in the mild forms of the oral mucosa and skin, topical therapies can be effective. Topical steroids of moderate to high potency, in the form of a gel or ointment on the skin and as mouthwashes or formulated in orabase at the level of the oral mucosa, can be used initially 2 to 3 times per day. The frequency of topical steroid application can be slowly reduced depending on the patient's response. When topical preparations are applied to the oral mucosa, we should recommend that patients refrain from eating or drinking for 30 minutes after application to increase their absorption [48]. We can prescribe custom prosthetic devices, such as dental trays, if there are localized lesions, especially on the gingiva [49,50].

Remember that the long-term application of topical corticosteroids has few complications. A cutaneous application can cause hypopigmentation and atrophy. And the most frequent in the mouth is the risk of oral candidiasis (consider associating antifungals) and the reactivation of herpes simplex [1,2]. If the lesions are very localized, an intralesional injection may be useful [50]. In the most serious forms, we will use the systemic route. It can generally be started with prednisone 1 mg/kg/day orally. If there is no improvement, we should refer the patient to a specialist because it will be necessary to go through the intravenous route to administer boluses of cyclophosphamide (3

to 10 boluses) accompanied by oral cyclophosphamide. There are reports of improvement with mycophenolate, rituximab, and conjunctival mitomycin. In all cases, we must implement oral care: brushing the teeth with a soft bristle brush twice a day, flossing daily, and visiting the dentist every 3 to 6 months. If we observe injuries.

Based on the above, the lines of action would be:

-1st line. Only in low-risk cases [16,47]. Clobetasol propionate 0.05% topical (3v / day / 2-4 min, 3 months) or if we are familiar with this drug, topical tacrolimus, (calcineurin inhibitor) 1%, 3 / day / 15 minutes [ 51.52].

-2nd line. If topical treatment is not effective or the disease is considered moderate risk. Systemic corticosteroids (prednisone 1 to 2 mg/kg / day), associated or not with dapsone. We can also use Dapsone 100mg / day (from 50 to 200mg / day) [2,52].

-3rd line. High risk, that is, patients with mild or moderate ocular involvement [16,47]. Systemic corticosteroids (prednisone 1 to 2 mg / kg / day) alone or in combination with dapsone (50 to 200 mg / day).

-4th Line. For severe or rapidly progressive disease affecting the ocular, nasopharyngeal or anogenital mucosa. Systemic corticosteroids should be used (prednisone 1 to 2 mg / kg / day) + plus an additional immunosuppressive agent (2,53,54,55,56,57), which may be: azathioprine (1 to 2 mg / kg / day; up to 50 mg / 12 h) -mycophenolate (2 to 2.5 g / day) or cyclophosphamide (1 to 2 mg / kg / day).

Once control of the outbreak is established, the goal is to gradually decrease the administered dose over 6 to 12 months. If by reducing the dose, the disease regresses, we can try other treatment alternatives such as intravenous immunoglobulin [53,57], tumor necrosis factor-alpha inhibitors [53,58,59], or rituximab (alone or as associated therapy) [53.57.59.60]. Obviously, these treatments must be prescribed by specialists in these diseases.

Based on all the above, and based more specifically on the works of Suárez-Fernández et al (2), Schimdt & Zillikens (8), Amber et al (20) and Ludwig et al (57) we propose the following diagrams treatment (Figure 1 and 2; Table 3 and 4)

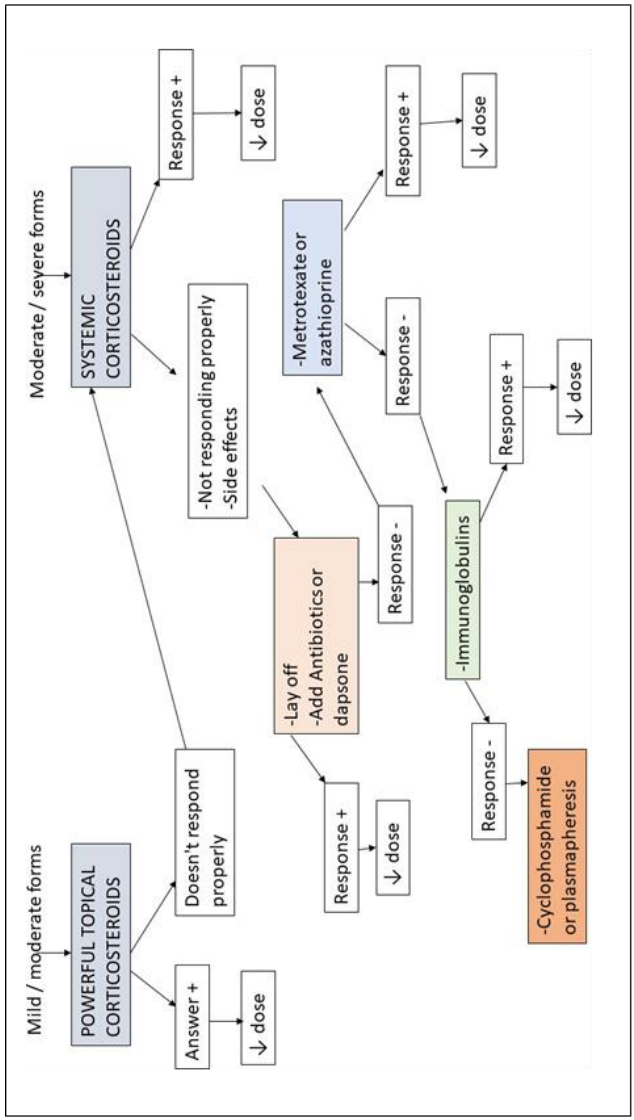


**Figure 1**: Treatment proposal for bullous pemphigoid, Based on Suárez-Fernandez et al [2].

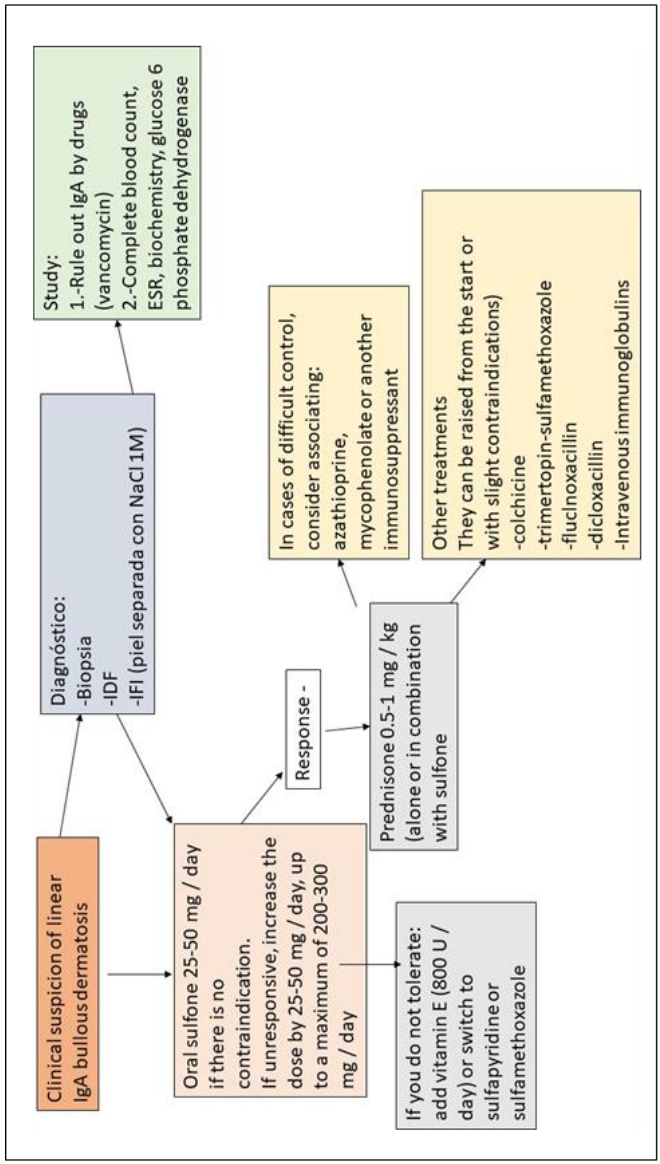


**Figura 2**: de tratamiento para la dermatosis ampollosa IgA lineal, Basado en Suárez-Fernández et al [2].

**Table 3**: Medical considerations in alternative treatments, based on Suárez Fernández et al [2].

| **Treatment with intravenous nonspecific immunoglobulins** |
|---|
| --Palliative use<br>-Does not respond to corticosteroids or ionmunosuppressants<br>-There is a risk of anaphylaxis, control IgA<br>-Do not combine preparations<br>-Recommended dose: 0.4g / Kg / day x 5 days (2g / Kg).<br>-Slow infusion: 6 hours, starting at 15ml / min 15 min<br>-Cycles every 21 days and distance if there are no injuries<br>-Premeditate 1 hour before with: deschlorferimain and paracetamol |
| **Intravenous cyclophosphamide (Genoxal)** |
| -Start oral cyclophosphamide 50mg / 12 h and assess analytical tolerance. If leukopenia appears <2,500 / mm3, discontinue<br>-INTRAVENOUS PAUTA<br>to. Dose every 15-30 days<br>b. 1-1.5 g / m2: infusion in 2 hours in 200 ml<br>c. Hydration with subsequent forced fluid therapy (500 ml in 3 hours). Drink abundantly 3 days (from the day of pre-infusion)<br>d. Ondasentron 1 ampoule before and another after 4 hours: if nausea continues, give 8 mg orally and. Mesna 1 previous ampoule and another at 4 hours<br>F. Cycles: from 3 to 10, depending on the evolution<br>-Vigilance blood count, urine, nausea-vomiting, infections<br>-The dose of corticosteroids will be regulated according to the clinical evolution |
| **Treatment with rituximab (Mabthera)** |
| -Resistant to other systemic therapies<br>-Compassionate use<br>-Pre-treatment:<br>a. HCV serology<br>b. Antibodies (IFI-ELISA)<br>- Dose: 375 mg / m2 (about 600-650 mg)<br>a. Once a week<br>b. Four weeks<br>c. Some use intravenous Ig 0.4 g / kg the day before (infection prophylaxis)<br>d. In case of relapses, single dose according to evolution<br>-Premedicate with 1 ampoule of dexchlorpheniramine and paracetamol 1 g intravenously 1 hour before<br>-Slow infusion rate: 6 hours, starting 15 ml / min 15 min<br>-The authors recommend: once a month intravenous Ig 0.4 g / kg in the day hospital for one year |
| **Sulfone (dapsone) treatment** |

| |
|---|
| -Request previously glucose 6 phosphate dehydrogenase, blood count, reticulocytes and biochemistry<br>-Start low doses: 50 mg / day, ascending according to tolerance up to 200 mg / day<br>-Associate vitamin E (800 IU / day) or optional cimetidine 1-2 g / day<br>-Dividing the dose of dapsone into 2 doses<br>-Request blood count, biochemistry every 15-30 days up to 3 months and then quarterly<br>a. Monitor methemoglobinemia (dizziness, dyspnea, fatigue): <20% does not need changes; > 30% consider methylene blue<br>b. Monitor hypersensitivity reaction, with hepatitis, erythroderma, <500 neutrophils, peripheral neuropathy<br>-Others: psychosis, nephrotic syndrome, blurred vision<br>-It interacts with trimethoprim, antimalarials such as chloroquine<br>-Do not use in pregnancy, lactation, kidney or liver failure |

**Table 4:** Management guide for bullous pemphigoid, based on Murrell et al. [43].

| **Datos evolutivos** | |
|---|---|
| Inicio | El día el diagnóstico |
| Control de la actividad de la enfermedad | El momento en que las nuevas lesiones inflamatorias dejan de formarse y las lesiones establecidas comienzan a curarse |
| Estabilización de la actividad de la enfermedad (control de la enfermedad; comienzo de la fase de consolidación) | El intervalo de tiempo desde el inicio hasta el control de la actividad de la enfermedad |
| Cicatrización | El tiempo necesario para controlar la progresión de la cicatrización |
| Fase de consolidación | No se desarrollan nuevas lesiones durante un mínimo de 4 semanas y aproximadamente el 80% de las lesiones inflamatorias han curado |
| **Datos intermedios de observación** | |
| Lesiones transitorias | Nuevas lesiones que se curan en 1 semana o que se eliminan sin tratamiento |
| Lesiones no transitorias | Nuevas lesiones que no se curan en 1 semana |
| Remisión completa con disminución gradual | La ausencia de lesiones no transitorias mientras el paciente recibe más terapia mínima |
| Terapia mínima | Dapsona ≤ 1.0 mg/kg /d; ≤ 0.1 mg/kg/d de prednisona (o su equivalente); minociclina ≤ 100 mg/d; doxiciclina 100 mg/d; Lymecycline 300 mg/d; corticosteroides tópicos una vez al día, incluida la suspensión de propionato de fluticasona 400 g/una vez al día; colchicina 500 g/d; Salazopirina 1 g/d; sulfapiridina 500 mg/d; |

| | |
|---|---|
| | sulfametoxipiridazina 500 mg/d; nicotinamida 500 mg/d |
| Tratamiento adyuvante mínimo (y / o tratamiento de mantenimiento) | Las siguientes dosis o menos: azatioprina (1 mg/Kg/d) con un nivel normal de tiopurina S-metiltransferasa; micofenolato mofetilo 500 mg/d; ácido micofenólico 360 mg/ ; metotrexato 5 mg/semana; Ciclosporina 1 mg/kg/d |
| Terapia biológica a largo plazo | Se refiere a las terapias administradas de manera intermitente, por ejemplo, cuando se usa rituximab para MMP, o IVIG mensualmente |
| **Seguimiento tardío** | |
| Remisión parcial en terapia mínima | La presencia de nuevas lesiones transitorias que sanan sin cicatrización dentro de 1 semana, mientras que el paciente recibe terapia mínima durante al menos 2 meses |
| Remisión completa en terapia mínima | La ausencia de lesiones nuevas o establecidas mientras que el paciente recibe terapia mínima para al menos 2 meses |
| Terapia de remisión parcial fuera de tratamiento | Presencia de nuevas lesiones transitorias que curan dentro de 1 semana sin tratamiento mientras el paciente no recibe tratamiento con MMP durante al menos 2 meses |
| Terapia de remisión completa sin tratamiento | Ausencia de lesiones nuevas o establecidas mientras el paciente está fuera de todo MMP terapia durante al menos 2 meses |
| **Recaída / brote** | |
| | Aparición de ≥ 3 nuevas lesiones al mes (ampollas, erosiones) que no se curan en 1 semana, o la extensión de lesiones establecidas en un paciente que ha logrado controlar la enfermedad |

IVIH: inmunoglobulina intravenosa; MMP: pénfigo de membranas mucosas

## Pemphigus

Pemphigus is a serious, life-threatening disease. It occurs with chronic intraepithelial autoimmune bullae produced by the phenomenon of acantholysis [a histological term that defines the separation of keratinocytes from each other]. It is diagnosed based on the clinical, but necessary, histopathology and

immunofluorescence. Its basic treatment is with systemic corticosteroids [81,82]. Two important forms are described: Pemphigus Vulgaris (PV), with significant mucosal involvement, and Pemphigus foliaceous (PF), with no mucosal involvement.

## Epidemiology

It is a rare disease affecting 0.3-3.2 x 100,000 inhabitants. Although there are more variants, PV and PF constitute 90–95% of all presentations and even though there are variations between populations of different countries, 70% are PV [83,84]. It usually manifests itself between the ages of 45 and 65 in most populations, but there are some populations in which the mean age is somewhat lower. It is very rare below 18 years. We also know that it is somewhat more common in Ashkenazi Jews and Japanese, and in most epidemiological studies, a slight female predominance (1.1 to 1.7) has been reported [85].

## Etiology

It is an autoimmune disease characterized by circulating IgG antibodies against desmoglein 3 (Des3) in the interstitial area of the epithelia. About half of the patients also have anti-desmoglein 1 (Des1) [82]. More susceptibility has also been described, coinciding with some immune disorders or neoplasms, but the strongest association is with the presence of some histocompatibility factors: HLA-A10, HLA-A26, DR4, and DR14, among others. These aspects have been analyzed by various reviews [86,87]. In addition to genetic susceptibility traits, environmental factors have been postulated that trigger the disease, among them are: drugs such as penicillamine and captopril, exposure to pesticides, metal fumes, ultraviolet light and ionizing radiation, sustained burns, surgeries and stressful life events [88,89]. In contrast, nicotine (a cholinergic agonist) has a protective effect on pemphigus, which could be explained by the observation that cholinergic agonists are capable of reducing IgG autoantibody-induced acantholysis in pemphigus vulgaris in vitro [ 90.91]

## Pathophysiology

We could summarize by saying that, in genetically susceptible individuals, the autoimmune reaction is driven by autoreactive T lymphocytes and B lymphocytes. Activated T cells mature by antigen-presenting cells that present specific desmoglein (Dsg) through their HLA class II molecules. These CD4 autoreactive T cells are specific for Dsg molecules and produce IL-10, and drive the generation of Dsg-specific antibodies by B cells [92]. This pathophysiological importance of T lymphocytes has also been demonstrated in vitro in transgenic mice. However, not all anti-Dsg antibodies are pathogenic, which could explain the finding that, in some patients with pemphigus vulgaris, serum anti-Dsg3 levels do not correlate with disease activity [93].

## Clinical Manifestations

### Pemphigus Vulgaris

If we briefly review the clinic of interest to the dentist, we can refer to the summary presented by Bagán Sebastián JV in chapter 7 of his book [82]. It summarizes that 60% begins in the oral cavity, and that the oral mucosa is affected in 90% of cases. Only 10- 15% are exclusively cutaneous. Other mucous membranes can also be affected and are serious forms, even affecting the larynx and pharynx [81]. Often, it begins with nonspecific lesions that take between 2 and 6 months to be diagnosed. The primary lesion is a blister and they are usually multiple, poorly defined, of variable size, with a thin roof that breaks very easily, leaving a very painful erosive-ulcerated area. At a certain moment, there may be blisters, erosions and ulcers, representing lesions in different evolution. Any area of the mucosa can be affected, but it is more evident in areas of pressure or friction. Other times it begins only as erosions. Pain is highly variable, ranging from mild discomfort when chewing hard food to severe pain that makes food difficult to eat, leading to rapid weight loss [81].

Many times it shows as desquamative gingivitis: erythematous, reddish and bright gums, sometimes with small blisters that can easily break. However, we should remember that this lesion can be attributed to pemphigoid, to liquen or to erythema multiforme [49,94].

In the mucocutaneous variant of pemphigus vulgaris, the skin lesions appear at the same time as the mucosal lesions or during the evolution of the disease (sometimes after months or years). The area of preference is the scalp, neck, armpits and upper part of the trunk, but any part of the body can be affected. Skin lesions typically present as flaccid blisters, erosions and scabs, and large denuded areas. Nail involvement can also be seen. When mechanical friction is applied to the perilesional skin, erosion can be induced, which is a characteristic but not pathognomonic effect of pemphigus called Nikolsky's sign. This phenomenon also occurs in the oral mucosa.

Both skin and mucosal lesions heal without scarring, but in patients with darker skin, residual hyperpigmentation may appear in the affected skin areas, which can persist for many months. Pemphigus vegetans, a clinical subtype of pemphigus vulgaris, appear with papillomatous vegetations located mainly in the intertriginous spaces and rarely affects the mouth [95].

The differential diagnosis of the mucosal variant of pemphigus vulgaris includes pemphigoid of the mucous membranes, as we have already discussed, herpes simplex virus infection, oral lichen planus, aphthous ulcers, Behçet's disease, erythema multiforme, and Stevens-Johnson syndrome. In the mucocutaneous variant, skin lesions may resemble those seen in pemphigoid, impetigo, varicella-zoster virus infection, Grover's disease, bullous drug eruptions, including toxic epidermal necrolysis, and artifactual dermatitis (factitious). When skin folds are affected, such as the armpits, groin, neck, under the breasts, and between the buttocks, Hailey-Hailey disease (benign chronic familial pemphigus) should be discarded [96].

**Pemphigus Foliaceus**

We only describe for didactic purposes as, contrary to pemphigus vulgaris, there are no mucous manifestations. It manifests predominantly as erythema, which shows as a peeling of the skin and later formation of crusts that remind of puff pastry.

Intact bullae are rarely seen because the affectation is very subcorneal. The Nikolsky sign is also positive and the lesions heal without scarring, but typically they tend to cause hyperpigmented areas. The mild forms resemble severe seborrheic dermatitis and Darier's disease. Unlike pemphigus vulgaris, even in severe forms there are no major erosions, but these can become superinfected and can be triggered by the sun [97].

c.- Paraneoplasic pemphigus

It is less common than pemphigus vulgaris, but it can have a special involvement in the oral cavity. It is defined by Sapadi & Anhalt [98] as an autoimmune disease caused by an underlying lymphoporliferative alteration, with clinical, histological and immunological criteria that define it.

Table 5. In the study by Ogawa et al, of 496 patients with internal neoplasia, 25 developed pemphigus (5%). The mean age of PNP patients was 64.7 years, and PNP development was correlated with increasing age [101]. It is usually associated preferentially with hematological neoplasms (84%), especially Hodking lymphoma (42%), chronic lymphocytic leukemias (29%), Castleman's disease (10%), and up to 18% with non-hematological neoplasms [81].

**Table 5:** Characteristics of paraneoplastic pemphigus. Based on data from Bagán Sebastián JV [82]. To find out more, the specific works of Kappius et al 99] and Wieczorek et al [100] can be reviewed.

| Paraneoplastic pemphigus | |
|---|---|
| Clinic | There are severe oral affectation and polymorphous lesions on the cutaneous level, especially on the trunk and extremities, as well as palms and soles. In a patient with confirmed (66%) or unknown (33%) neoplasia. |
| Histology | A lichenoid skin process is seen, frequently combined with intraepithelial detachment. |
| Direct Immunofluorescence [DFI] | It detects IgG and complement localized in the intercellular space with linear granular deposit of complement in the basal membrane. |

| | |
|---|---|
| Serum auotoantibodies | They bind not only to the surface of the skin and mucosal epithelium cells, but also to simple, columnar and transitional epithelium, determined by IFI [Indirect Immunofluorescence] and following the typical pattern of pemphigus. It is positive for antibodies to intercellular substance. |
| Immunoprecipitation | The presence of specific antigens of desmosomes and hemidesmosomes is recognized: desmoplakin 1, BPAg, envoplakin and desmoplakin II, periplakin, an indeterminate antigen of 170 KD and desmogellin 1 and 3 |
| Treatment and evolution | Controlling the underlying disease is important as early as possible, but it may persist beyond your control. Oral lesions are more difficult to control than skin lesions. Topical treatments are preferable to systemic ones whenever possible. |

## Diagnosis

There are three methods for diagnosing the disease: a.- Exfoliative cytology; b.- Hystopathology; and c.- Immunfluorescence studies: direct [IFD], indirect [IFI] and Immunoprecipitation [IP].

a.-Tzanck's acantholytic cells are non-pathognomonic, rounded cells, with deflected edges and large, hyperchromic nuclei.

b.-There is an intraepithelial blister with acantholysis.

c.-i) IFD is mainly for IgG in intercellular spaces, and to a lesser extent of IgM. Complement deposits can also be detected [especially fraction 3]. ii) IFI shows circulating antibodies against the surface of the epithelial cells [anti intercellular substance], especially for IgG4 and IgG1, and less for IgG3. Autoantibody titers are often a good marker of the level of disease activity. iii) IP, are considered today the most definitive for diagnosis. In fact, the severity of the lesions [at least of the cutaneous ones] is directly related to the level of anti-desmogliein antibodies 3 in PV and 1 in PF.

## Treatment

Treatment must be multidisciplinary and many of the aspects that we have discussed for pemphigoid can be applyed to pemphigus. We can summarize the different aspects in the scheme proposed by Schmidt et al, in their 2019 review [81] which is based on the recommendations of an international group of experts in 2018 (Figure 3) [102].

The aim of the treatment is to reduce circulating antibodies and therefore tissue damage. There are several aspects that we can review. The use of corticosteroids combined with other immunosuppressants have been a breatkthorough treatment option.

The new immunosuppressants allow to lower the dose of maintenance corticosteroids and, in this way, reduce the serious side effects triggered by high doses, for prolonged periods. Despite this, side effects are not always mitigated. Thus, until few years ago, 10% died [in the 1950s it reached 30-75%], 40% were cured and did not require treatment, 20% required low doses of corticosteroids and 30 had continuous recurrences. At present, despite the long-term complications of the treatments, mortality is below 5% for PV [103], but it could continue to reach 60% in 5 years in paraneoplastic.

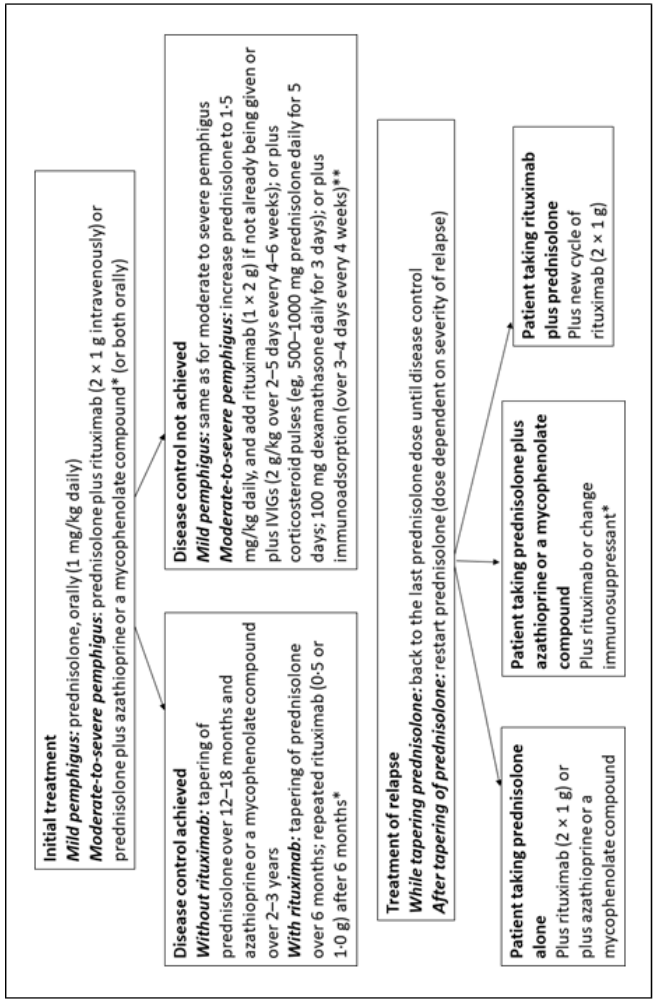


**Figura 3:** Treatment algorithm for pemphigus vulgaris and pemphigus foliaceus Based on recommendations of an international panel of experts (102) and revised guidelines of the European Academy of Dermatology and Venereology. Adaptado de Schmidt et al. (81).

VIGs: intravenous immunoglobulins; *If rituximab is not available or contraindicated; **In particular in patients with initially severe pemphigus and high serum concentrations of anti-desmoglein antibodies at month 3; additional rituximab infusions (0·5 g) after 12 months and 18 months might be considered.
****Might also be used as initial adjuvant therapy in patients with severe pemphigus**.**

# Case Reports

## Pemphigoid Case Report

A 68-year-old male farmer who presents because his mouth hurts and burns for weeks, even months. As a family history, it is only notable to mention one brother with colon cancer. Among the personal history, only "annoying" skin lesions that appear in outbreaks and that have not been diagnosed can be highlighted. He is not taking any medication and he has no known allergies.

The patient has a good oral hygiene. He brushes 3 times/day and occasionally uses an alcohol-free mouthwash. He does not refer to toxic habits. His water intake is low (<a liter of water a day) and he consumes a glass of red wine every day.

Current disease: For 6 months he has:

- Stinging and generalized burning in tongue, palate and gums.
- White lesions that disappear when brushing.
- Generalized gingival inflammation and erythema.
- Bullous type lesions (they swell and deflate).
- Heavy bleeding when brushing.

The patient has been treated with: Nystatin rinses: 3 weeks; Rhodogil® tablets: 7 days and scaling + RAR without expected results.

Clinical examination: Erythematous and edematous gums. Erosive and bleeding lesions on the upper and lower gingiva. Whitish blisters. Linear white lesions and gingival recessions, plaque and calculus (Figures 4 and 5). Bullous skin lesions are also seen.

Based on the examination and the clinical history, the following diagnostic options are established: Pemphigus vulgaris; Mucous membrane pemphigoid; Bullous pemphigoid; Bullous lichen planus; Bullous dermatosis (linear IgA); Bullous epidermolysis (acquired); Bullous systemic lupus erythematosus; Erythema multiforme and toxic epidermal necrolysis. Of all of them, we

think that special consideration should be given to the group of pemphigus and pemphigoids, whose main differences are presented in Table 6.

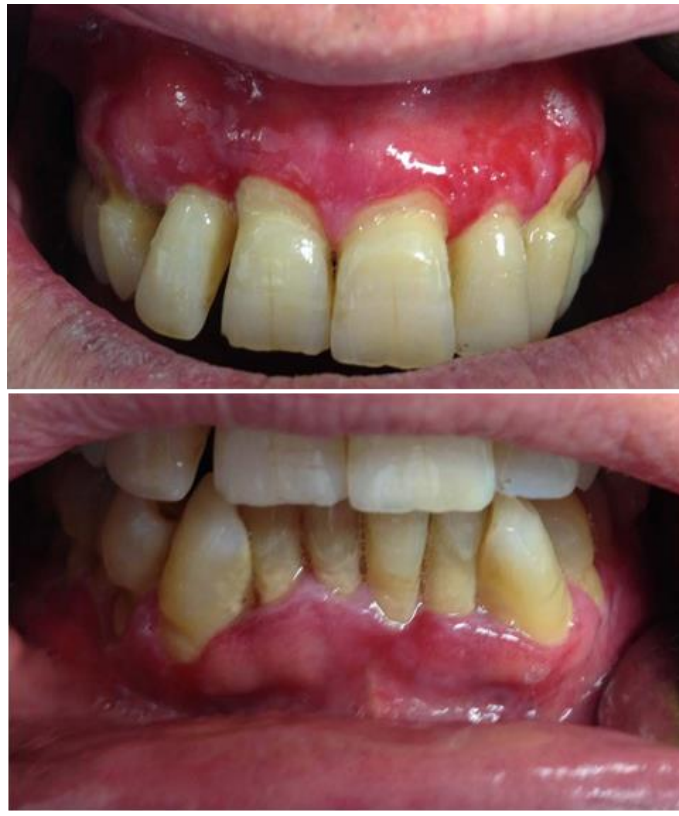

**Figure 4:** Appearance of the upper and lower gingiva, in the anterior sector on the day of the consultation.


**Figure 5:** Other areas of the oral mucosa showing extensive erosive areas, scaly lesions that resemble blister roofs and a clear blister per lingual tooth 45-46. In figure B, we present another case in which the blister is much more visible.

**Table 6:** Most notable aspects between pemphigus and pemphigoid. Adapted from Chimenos Küstner E & López López J. Oral Medicine Schemes. Barcelona: 2008 [104].

| **Pénfigo** | **Penifogoide** |
|---|---|
| -Menos frecuente<br>-Afecta mucosas (+oral) y luego la piel.<br>-Debuta en la 4ª -5ª década (raro en jóvenes)<br>-Ampollas de techo fino<br>-Signo de Nikolsky positivo | -Menos frecuente<br>-Afecta mucosas (+oral) y luego la piel.<br>-Debuta en la 4ª -5ª década (raro en jóvenes)<br>-Ampollas de techo fino<br>-Signo de Nikolsky positivo |
| *Anatomía patológica* | |
| -Ampolla intraepitelial suprabasal (acantolisis)<br>-Infiltrado Inflamatorio eosinófilos<br>-Células de Tzanck | -Ampolla subepitelial<br>-Con presencia o no de infiltrado inflamatorio Leucocitario<br>-Techo: todas las capas epitelio. |
| *Inmunofluorescencia directa* | |
| -Depósitos anticuerpos de Inmunoglobulina<br>G (IgG) en hemidesmosomas de unión de las élulas del epitelio | -Depósito lineal de IgG, IgA o C3, solos o<br>combinados en la membrana basal del epitelio |

With the presumed diagnosis of pemphigoid due to the oral and especially the skin lesions, given the difficulty of performing a previous scaling and due to the discomfort that the patient presents, we took two biopsy samples from the mouth (Figure 6 ), and the skin (Figure 7).

**Table 7:** Establishment of a diagnostic table in the case at hand.

| | LOCATION | DESCRIPTION OF INJURIES | EPIDEMIOLOGY | HISTOPATOLOGY |
|---|---|---|---|---|
| **PEMPHIGUS** | Skin and mucosa (rubbing areas) | Acantolysisi-induced intraepitlial blister | 40-60 years | Histology & immunofluorescence (intraepithelial bleb with acantholysis) |
| **PEMPHIGOID** | Oral, ocular and genital mucosa | Subepithelial blister | Women 40-80 years | Histology and immunofluorescence (subepithelial ampulla where the epithelium is detached from the connective tissue at the level of the basal layer) |
| **ERIYTHEMA MULTIFORME** | Skin and mucosa (bilateral and symmetric) non-keratinized areas | Polymorphic skin-mucous lesions. Vesicles, bullae, and serohomatic coasts | Young-adult males | Subepidermal or intraepidermal blisters, together with the presence of necrotic keratinocytes |
| **LINEAR IgA DERMATOSIS** | Skin (buttocks, thighs and genital area) | Bullous eruption of serous contents (subepithelial) and ulcers | Preschool | Presence in skin of linear IgA deposits in the basement membrane |
| **EPIDERMOLYSIS BULLA** | Skin (tongue, palate and yugal mucosa) | Vesicles blisters Scar formation | After the birth | Subepithelial ampulla with numerous neutrophils in the chorion |

**Figure 6:** Images of biopsy sampling.

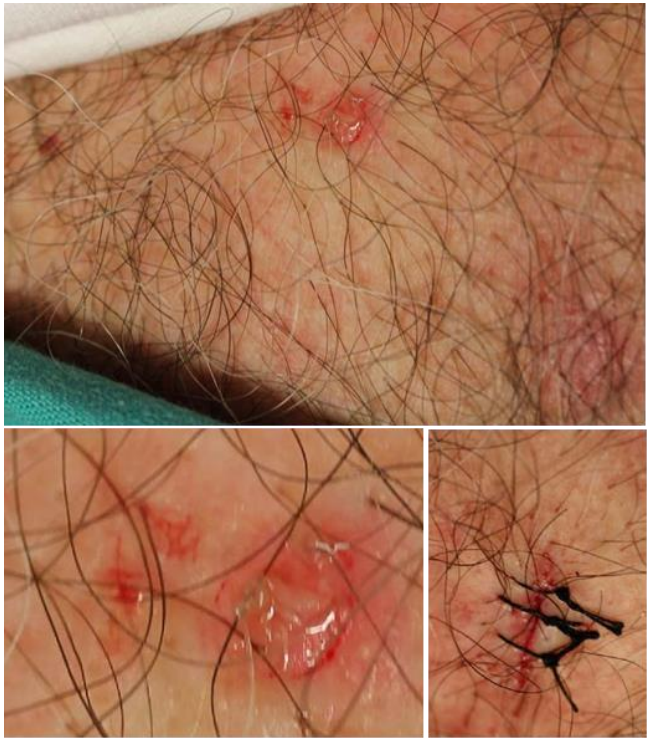

**Figure 7:** Images of the biopsy of skin lesions.

The histopathological report confirms the clinical suspicion of pemphigoid; both the eosin hematoxylin stain [shows a clear subepithelial bleb] and the immunofluorescence study shows linear positivity for IgG and C3 and negativity for IgA and IgM (Figure 8).

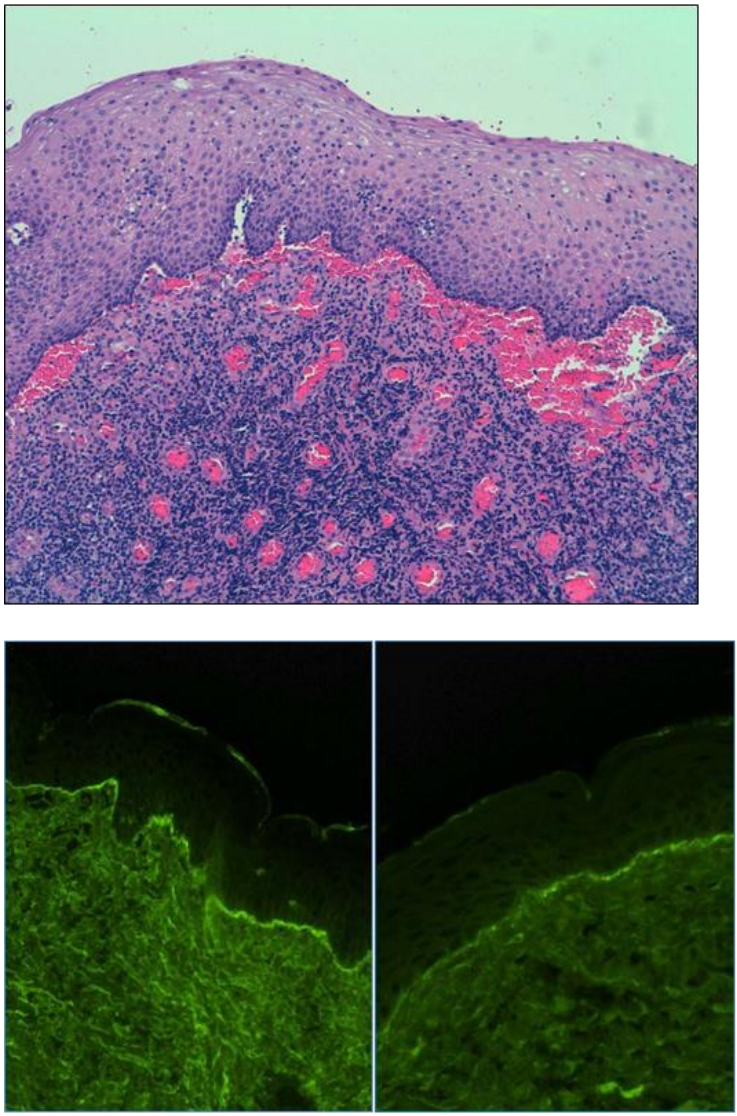

**Figure 8:** Subepithelial bleb and positivity for IgG and C3 in the basal layer.

Based on clinical and pathological data, we prescribed 0.2% triamcinolone acetonide mouthwash + 1% clotrimazole [prescribed from the day of the biopsy] for 3 minutes three times a day and we obtained a significant remission of the condition in 3 weeks, even though some lesions still remain (Figure 9).

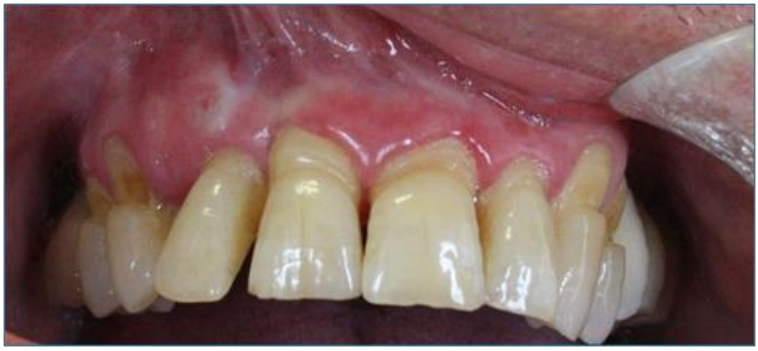

**Figure 9**: Follow-up after three weeks of treatment.

Given the diagnostic confirmation and the partial evolution of the lesions, we changed to a more potent corticosteroid and prescribed clobetasol propionate 0.1% + clotrimazole 1% in the same regimen for three more weeks.

In Figure 10 we show the evolution at one month, which remains stable and 6 months later with a regimen of 0.1% triamcinoilone acetonide at night. To control skin lesions, the patient is referred to a dermatologist.

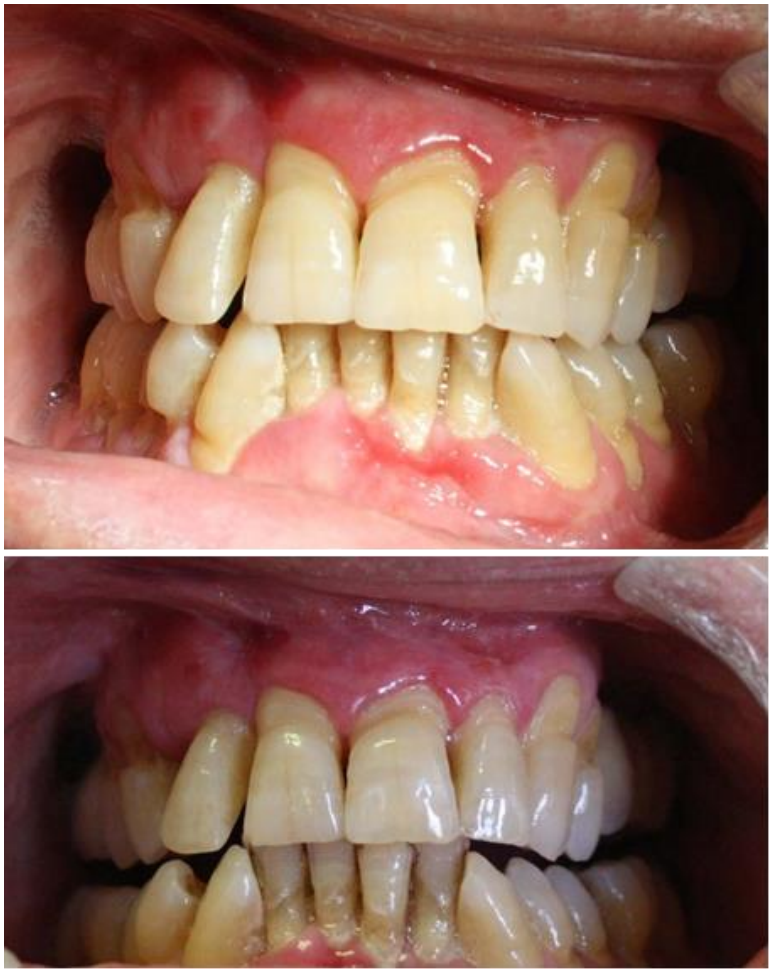

**Figure 10:** Control of lesions two months after presentation of the clinical picture.

## Case Discussion

From this case we can extrapolate that: pemphigoid frequently occurs in the form of chronic desquamative gingivitis in the oral cavity, its diagnosis is based on the clinic and is confirmed by the pathological study, and oral lesions are usually the first clinical sign. Even though in this case causes associated asymptomatic skin lesions, knowledge of this entity is essential for its correct

diagnosis and treatment, and above all for the correct and early diagnosis, which can facilitate the treatment.

## Pemphigus Case Report

We show the case of a 38-year-old male patient who presents with a lot of pain in an oral lesion, which prevents him from eating. He is not taking medications and he has no known allergies. The patient has no family history of any disease. He quit smoking 20 years ago.

He presents very painful oral lesions of several months of evolution. The patient tells us that he has “blister-like” lesions on his back from several years ago that they have not given importance. He tells us that they did a biopsy on his tongue with the diagnosis of herpetic infection and he was treated with Acyclovir.
We observed extensive erythematous lesions associated with bullous lesions on the jugal mucosa, palate and lips (Figures 11 and 12). Nikolski's sign is positive and the lesions bleed when touched. Residual back injuries are also seen (Figure 13).

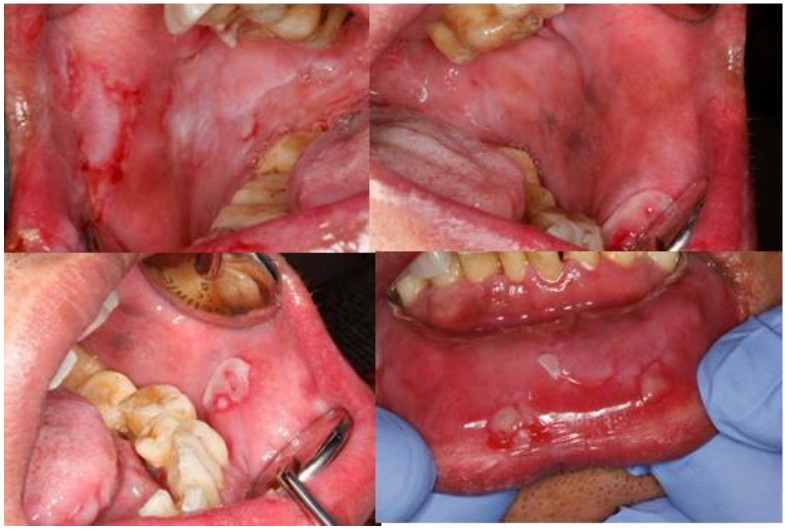

**Figure 11:** Erythematous lesions with blisters on the buccal mucosa and lips.

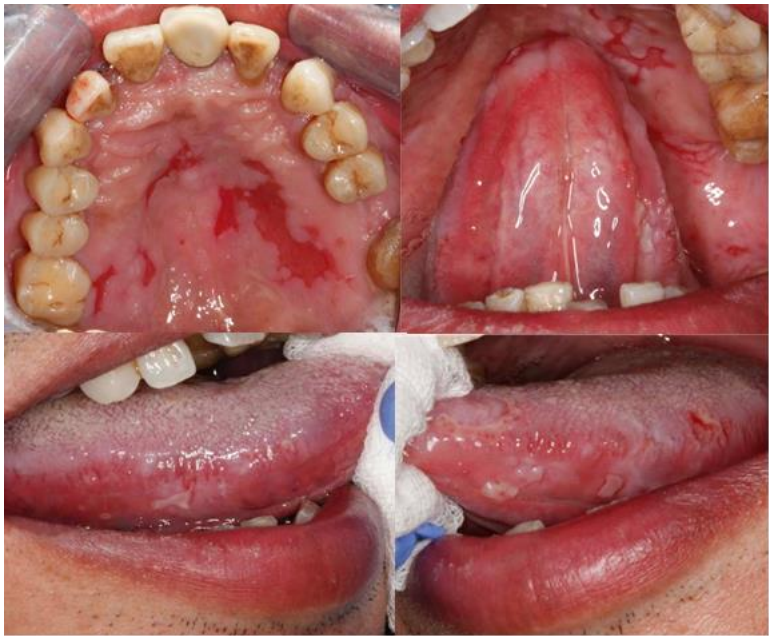

**Figure 12:** Same previous patient with lesions on the palate and tongue.

Based on this clinical history, several diagnostic possibilities can be established and an oral and skin biopsy is performed to confirm the diagnosis (Figures 14 and 15).

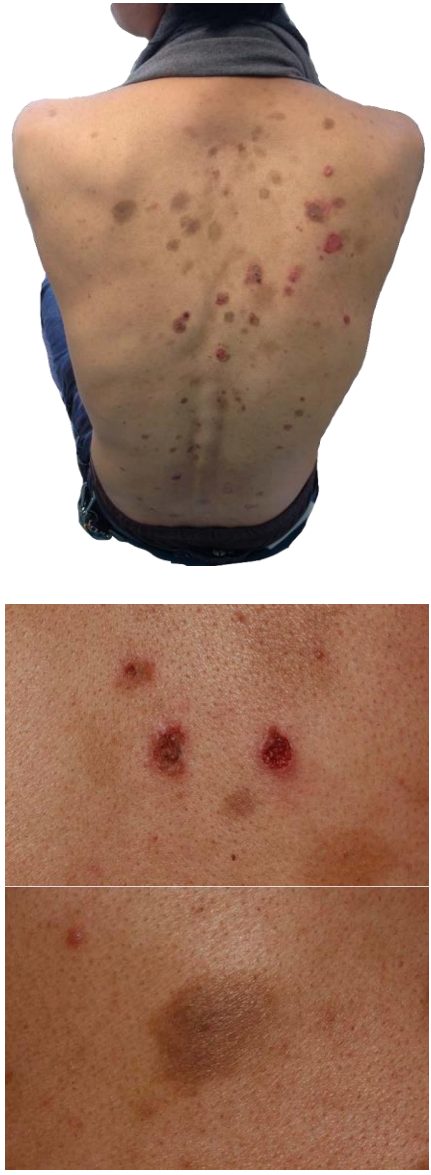

**Figure 13:** Scar Histological images related to oral biopsy.

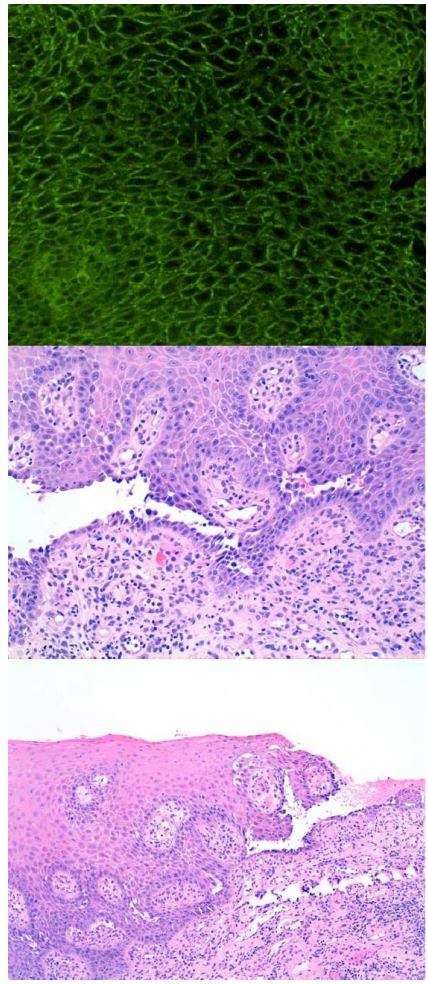

**Figure 14:** A 0.6 x 0.2 cm fragment of mucosa is received for fresh study (B) and a 0.8 x 0.5 fragment for Hematoxylin and eosin study. A: IFD: IgG and C3 deposits with an enveloping membrane pattern of suprabasal keratinocytes. IgA and IgM are negative. B: Suprabasal intraepithelial ampulla with moderate inflammatory infiltrate in the chorion. Images courtesy of Dr. August Vidal Bell.

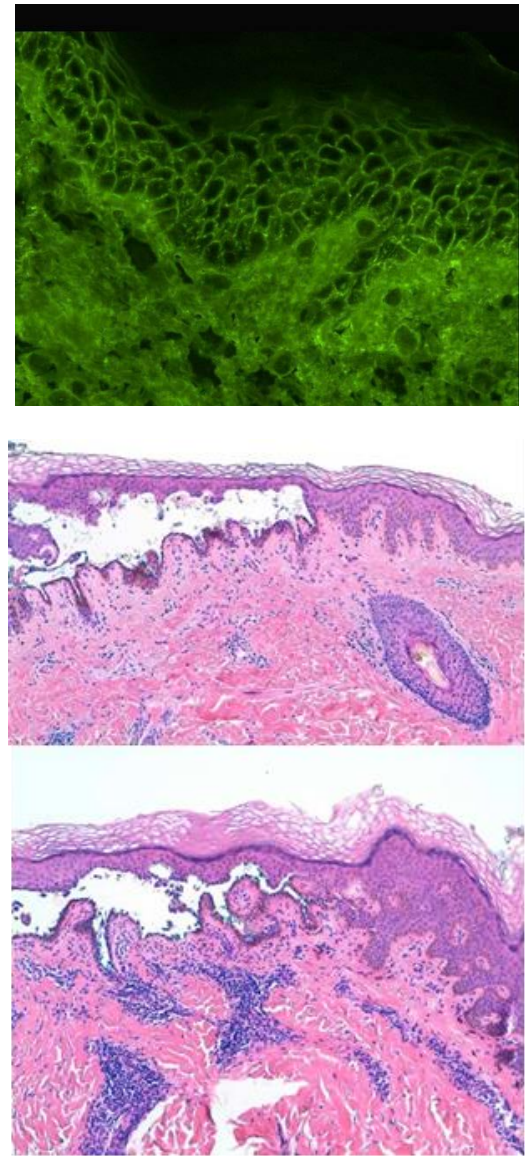

**Figure 15:** Histological images related to oral biopsy. Receive a 0.7 fragment for immunofluorescence study and another 0.7 for total inclusion. A: IDF has positive IgG and C in stratum spinosum cells and negative IgA and IgM. B: Intradermal blister compatible with pemphigus. Images courtesy of Dr. August Vidal Bell.

In the present case, the following treatment regimen was started: i.-Topical corticosteroid: Clobetasol Propionate 0.1% (3 times / day - 15 days); ii.-Systemic corticosteroid: Prednisone (Dacortin® 30mg) 1-1-0 for 30 days and iii.-Gastric protection: Omeprazole® 20mg - 1/24 hours, this guideline was agreed with the dermatologist. In the one-month follow-up, a significant improvement in the lesions was observed, which was maintained with a dose of 5mg of Dacortin® per day and occasional treatment with 0.1% triamcinolone acetonide at night, in the oral lesions (Figure 16 and 17). With this treatment it is possible to reduce the symptoms but not to cure completely the lesions.

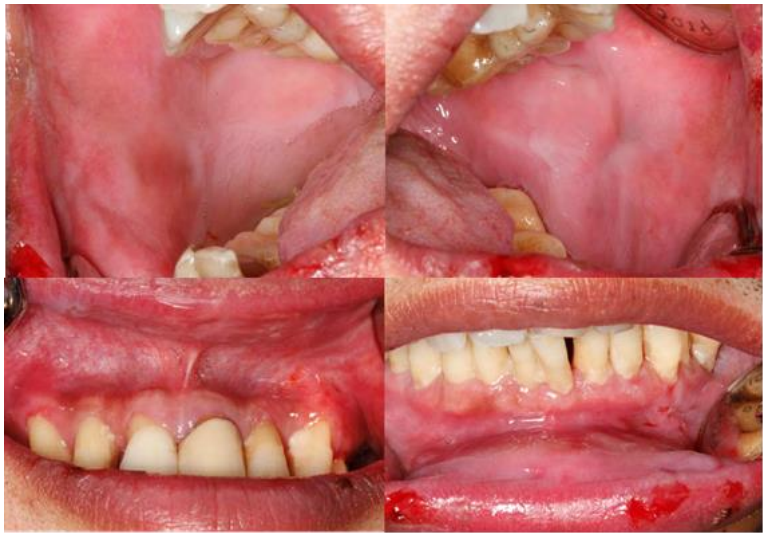

**Figure 16:** Evolution of the lesions of the jugal mucosa and lips.

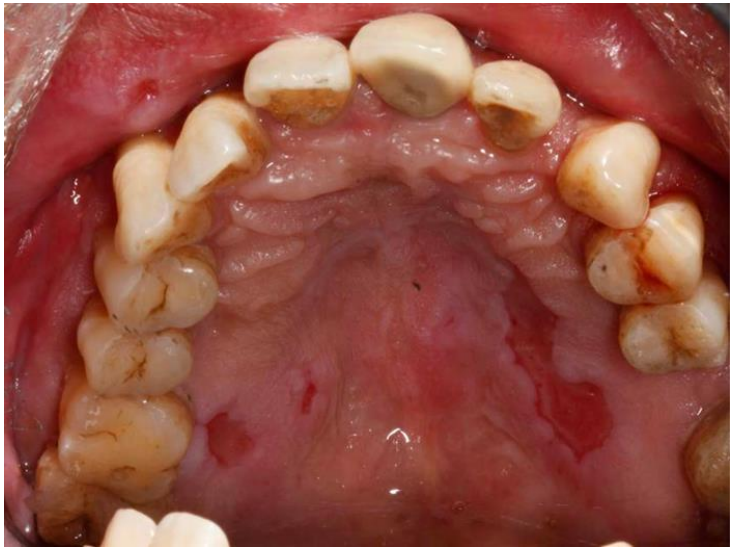

**Figure 17:** Evolution of palate lesions.

### Case Discussion

Since the skin lesions have been controlled, we are faced with a pemphigus of low aggressiveness. However, oral lesions are difficult to fully control.

## Conclusions

Due to the different prognosis they have and therefore the different therapeutic approach, it is important to distinguish between the two entities: pemphigus and pemphigoid.

Dentists play an important role in the diagnosis and chronic control of oral lesions in the case of pemphigoids that affect the mouth.

In pemphigus, in addition to the possible control of mucosal lesions, early diagnosis play a fundamental role, especially if we take into account that the prognosis of this serious disease is related, among other factors, to its treatment in the early stages of the disease .

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## Case Report

# Oral Lichen Planus: Case Report

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## Abstract

Oral lichen planus (OLP) is a chronic mucocutaneous disease that affects 0.5-1% of the population. Although there is a marked controversy over its etiopathogenesis, most authors defend OLP as a T-cell mediated autoimmune disorder. Within its clinical variants, bullous OLP is usually characterized by the presence of subepithelial blisters and it is usually accompanied by lesions in nails, scalp and skin. The diagnosis of autoimmune bullous diseases, which is mainly based on clinical and laboratory findings. poses a diagnostic challenge, due to their rarity and

heterogeneous clinical characteristics. Diagnosis cannot just be based on clinical signs and histopathological findings, but also on the detection of circulating autoantibodies which continues being the gold standard for its diagnosis. It is important to make a correct differential diagnosis between the different autoimmune bullous diseases, when we see the presence of chronic oral blisters.

We present a clinical case, and on its basis, we will review all the concepts related to OLP. Furthermore, we will show what the literature says about the management of a specially resistant variant of the disease, which is the erosive form.

## Key Points

- Description of the disease, classification and its main clinical features
- Review of the diagnostic criteria and its process
- Show how to manage and treat the oral manifestations of the disease, based on the current literature

## Introduction

Lichen planus (LP) is a chronic inflammatory disease which can involve the skin and the mucosal surfaces, among them, oral mucosa. It is frequently found it on the buccal mucosa and on the dorsal surface of the tongue. It is not uncommon that oral lesions precede the cutaneous lesions, actually, there have been reported some cases in which the oral lesions are the only manifestation of the disease (Figure 1).

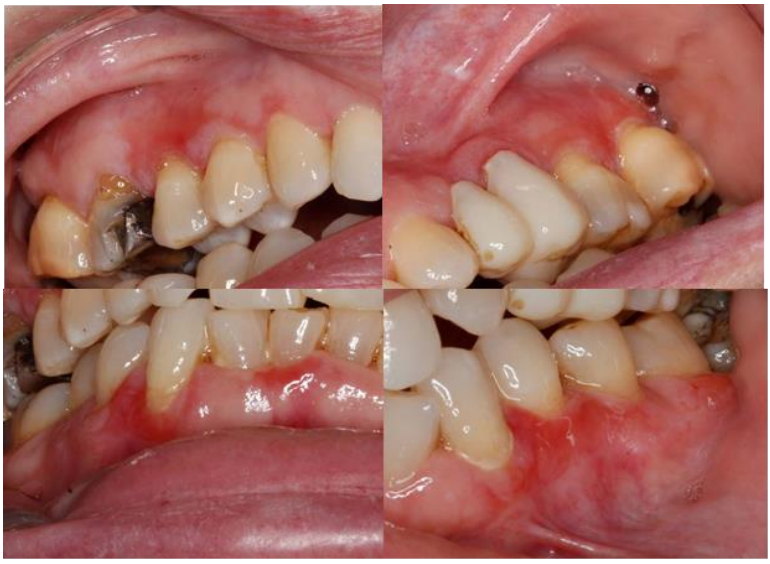

**Figure 1:** Typical erosive LP lesion in a patient without skin affectation, manifesting with desquamative gingivitis.

Although it is currently considered that it has an idiopathic etiology, it is known that it has an autoimmune background and it has a recurrent course. Its clinical course generally presents a benign prognose, however it can suffer a malignant degeneration, which is why the World Health Organization (WHO) refers to it as a precancerous lesion.

In the ancient times, Hippocrates and Celsus made some descriptions of the disease which they referred as a papulous lesion [1]. It is not until 1868 when Von Hebra and Kaposi [2] described, a group of papulous lesions which they called "lichen" among a variety of skin diseases.

In 1968 Erasmus Wilson reported "an eruption with remarkable pustules because of their color, configuration, structure, their isolated and aggregated development, their location, their localized and chronic nature, and because of the melanic pigmentation it leaves when it disappears" [3] which he called lichen planus.

Some years after that, in 1895, Wickham described "some white-greyish thin lines that can be seen over the cutaneous papules of the disease" [4] which later would be called "Wickham striae", that in fact is a pathognomonic sign of lichen planus.

At the beginning of the 20th century Dubrevilh and Darier, in 1906 and in 1909 respectively, described the histological features of this disease, emphasizing the need to perform biopsies on these patients to confirm the lichen planus diagnosis [1].

Several authors as Little, Safronn, Grinspan, Andreasen, Bagán, Scully, etc., have undertaken serious researches about the disease over the years, providing knowledge and important data about its manifestations, epidemiology and histopathology. Current studies are trying to clarify some aspects related with its etiology.

## Epidemiology

Oral Lichen Planus (OLP) is regarded as the most frequent non-infectious disorder in the oral mucosa [5]. Although its real prevalence remains unknown, several epidemiologic studies on large case reports gave it a value between 0,1% and 0,4% [6]. These ranges vary between the different populations which are chosen in every study. In table 1 we can see a summary of the prevalence rates found in different papers between 1972 and 2001.

Nowadays, the existence of a higher prevalence in women is well known. An investigation conducted in Egypt, concluded that a 68,75% of patients diagnosed with OLP were females and 31,25% were males, establishing a 2,2:1 ratio [13].

Regarding patients age, it has been noticed that most of the lesions appear on middle- aged, between 40 and 60 years old [8,13,14].

It has not been reported any correlation between human races and a higher lesions prevalence.

**Table 1:** Prevalence of OLP according to seven studies on different populations.

| **Prevalence %** | | | | | |
|---|---|---|---|---|---|
| **Study** | ***Year*** | ***Country*** | ***General*** | ***Males*** | ***Females*** |
| Pindborg et al. [7] | 1972 | India | 1,5 | 1,5 | 1,6 |
| Axéll and Rundquist [8] | 1987 | Sweden | 1,9 | 1,6 | 2,2 |
| Axéll et al .[9] | 1990 | Thailand | 3,8 | 1,9 | 5,4 |
| Axéll et al. [9] | 1990 | Malaysia | 2,1 | 0,7 | 4,2 |
| Ikeda et al. [10] | 1995 | Cambodia | 1,8 | 0 | 2,5 |
| Kova-Kavcic and Skaleric [11] | 2000 | Slovenia | 2,3 | 1,5 | 3,0 |
| Bokor-Bratic and Picuric [12] | 2001 | Yugoslavia | 1,6 | 0,8 | 2,6 |

## Etiopathogenesis

Although LP etiology is currently considered to be idiopathic, some autoimmune factors have been related to the onset of the disorder. In this sense, there is a general belief that there is an interaction between: predisposing, triggering and aggravating factors, listed on Figure 2.

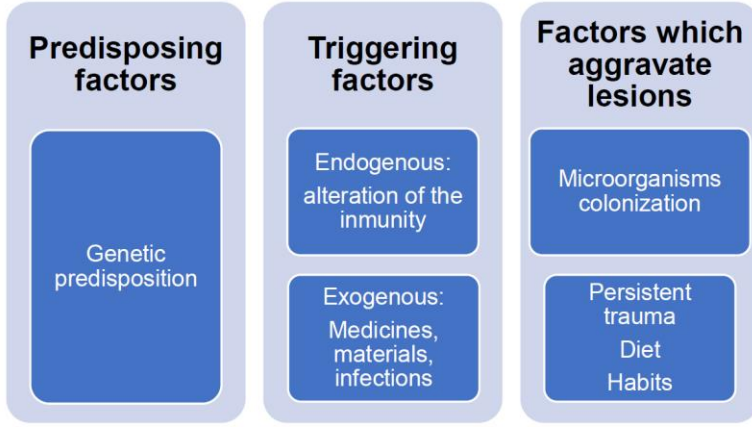


**Figure 2:** Factors associated with the onset of OLP lesions.

Antigens which trigger the epithelial inflammatory reaction that gives rise to OLP, are still unknown. The lymphocytes which accumulate in these lesions are mainly T cells, both CD4+ and

CD8+ [15], closely linked to autoimmune diseases.

The destruction of the keratinocytes that form the basal layer is attributed to the presence of cytotoxic CD8+. Those cells increase with the progress of the disease, resulting in a greater destruction of the epithelium. Likewise, it has been noted an increased frequency of antibodies SMA (smooth muscle antibodies) in patients presenting OLP compared to healthy ones. Moreover, erosive forms also feature a high concentration of circulating antibodies against Desmoglein 1 and 3 [15].

## Clinical Appearance

Taking into account that LP is a mucocutaneous disorder, it can present skin, scalp, nails and mucosal lesions, either oral and genital [16,17]. It is considered that the oral cavity is its main location, as it may appear independently of skin lesions [18], since the disease may not have dermatological manifestations.

LP lesions can appear in any spot of the oral cavity. The location changes depending on the clinical presentation. Among the most frequent we have: buccal mucosa, back of the tongue, gums, lips and palate [14].

OLP can have different clinical manifestations. Eventually, different authors have proposed different classifications. One of them was Andreasen [19] who, in 1968, divided them into 6 clinical forms:

- Reticular form: characterized by the presence of intertwined whitish lines that give a reticular appearance. These lines are called “Whickham striae”. These striae are slightly raised and cannot be rubbed off. This manifestation can be associated with papular and atrophic lesions.
- Papular form: in this case we can see isolated or grouped little raised lesions of 1mm in diameter. Moreover, they can appear on the periphery of reticular elements or individually.
- Patch-like form: it has a similar appearance to leucoplakia. They are raised lesions, frequently located on the tongue, producing a lingual papillae loss. Sometimes, we can see reticular elements on the periphery of the lesions.

- Atrophic form: red and atrophic areas. It can show erythematous and inflammatory regions. That is why a differential diagnosis with erythroplakia is necessary.
- Erosive form: it is not uncommon that atrophic lesions present solutions of continuity on the mucosa, generating painful ulcerations.
- Blistering form: it is an infrequent form which can range from little vesicles to big blisters.

Afterward, other authors simplified this classification, reducing it to three presentations [17]:

- Reticular form: white lesion which appears more frequently on the buccal mucosa. It has a ramified shape because of the presentation of the so-called "Wickham striae". They usually do not produce any symptoms and have a bilateral pattern.
- Patch-like form: its favorite location is the dorsal face of the tongue. It is a whitish plaque, similar to homogenous leucoplakia, characterize by its bilateral and symmetrical appearance on both sides of the tongue and it is called "butterfly´s wings" lesion.
- Atrophic-erosive form: it features a combination of reticular and erythematous forms in which a mucosal continuity solution has taken place, giving way to ulcerations. It can have symptoms such as burning sensation, pain and even functional impairment.

In addition to these classifications, there are others like the one from Silverman [20], in which he explains the reticular, atrophic and erosive forms; and Bagán et al. [21] which divides OLP into two forms: white lichen planus and red lichen planus. This variety of classifications let us conclude that there may be different clinical appearances in just one patient.

## Diagnose

If we suspect an OLP lesion, we need to emphasize the clinical features, as well as consider a differential diagnosis with other lesions listed on Figure 3. Through this protocol we will be able to stablish a presumptive diagnosis which needs to be confirmed with a histopathological examination.

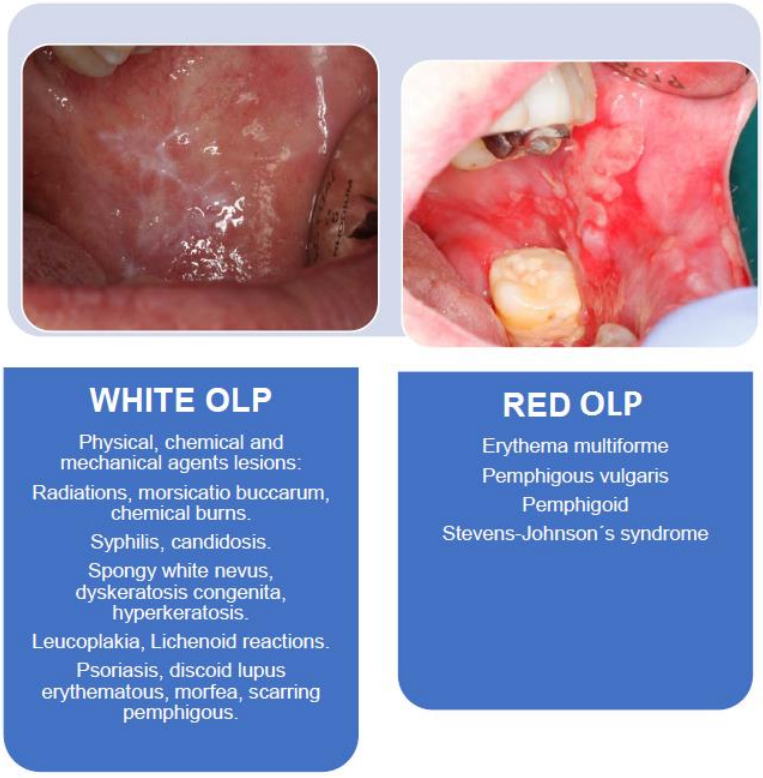


**Figure 3**: Differential diagnosis of OLP.

A great deal of professionals follow clinical and pathological criteria proposed by WHO for OLP diagnosis [22]:

- **Clinical criteria**
- Mainly symmetric bilateral lesions
- Presence of white striae with a reticular-papular appearance
- Erosive, atrophic, blistering and patch-like lesions, whenever there are white striae on other locations of the oral mucosa.

- **Histopathological criteria**
- Band-like juxtaepithelial inflammatory infiltration
- Dropsical degeneration of the basal layer

- Absence of epithelial dysplasias

In order to achieve the diagnosis, the biopsy of the lesions is necessary. It must be preferably performed on areas with white striae and an intact mucosa. Furthermore, in those cases with ulcerations we need, as far as possible, to extend the sample to the healthy mucosa, and include white and erythematous areas [17,23].

For the purpose of a better conservation of the sample it is convenient to use a fixative agent as 10% formalin. On the other hand, in those cases in which an Immunofluorescence analysis is indicated, mainly to discard other kind of pathologies, the sample must be kept in fresh, and needs to be processed by the pathologist in a maximum time of one hour [23].

When we examine an OLP lesion under the microscope, we can see a hyperkeratosis and an acanthosis [17], there is a thickening of the corneal layer and the granular cells surface will be widened, showing a globular appearance and an irregular acanthosis with saw pattern papillae. On the other side, areas with Wickham striae seem to correspond to a significative expansion of granular layer. We can see that there is an early formation of fibrine deposits in the basal layer which, in the majority of cases, doubles the basal layer size. Afterwards there is a formation of basilar gaps between keratinocytes, resulting in the dropsical degeneration of the basal layer and the formation of colloidal inclusions. There is a vacuolization of the basal layer and a liquid accumulation in the form of clefts, rifts or blisters. At dermis level we can see a band-like juxtaepithelial inflammatory infiltration, which is parallel to the epithelium, that seems to embrace the basal layer. This infiltration is mainly composed by T-lymphocytes and macrophages [23].

Direct Immunofluorescence (DIF) is mainly used to stablish a differential diagnosis with other disorders such as pemphigus and Lupus Erythematosus (LE). In LP cases we can see a fibrinogen accumulation in the basal layer and Immunoglobulin (Ig)M in the colloidal inclusions. Additionally, in some cases we can also see the presence of C3 [24]. In LE cases we can

distinguish IgG, IgA, IgM and complement deposits in the basal layer area [25], being the accumulation of IgG the feature which stablish the differential diagnosis between LE and OLP. Likewise, the accumulation of fluorescent substance in the colloidal inclusions and fibrinogen in the basal layer, are more common in OLP than in LE [24].

We want to highlight the convenience of requesting a blood test in these patients in order to discard systemic conditions.

## Treatment

It is important to emphasize the lack of a curative treatment for LP. That is why the main goal of our treatment will be the control of the symptoms and the remission of the lesions.

We will start controlling the local factors which could exacerbate the symptoms: polish cutting surfaces, dental edges or any other element which could traumatize the lesions. Dentures need to have a correct adjustment and patients need to hold an appropriate oral hygiene. Likewise, patients need to quit smoking and alcohol drinking or at least reduce them [26].

Patients with erosive lesions need to avoid eating food which could aggravate the symptoms: acid products such as lemon, oranges, vinegar and spicy meals. Furthermore, it is important to control psychosomatic conditions such as stress. The control of these factors is summarized on Figure 4.

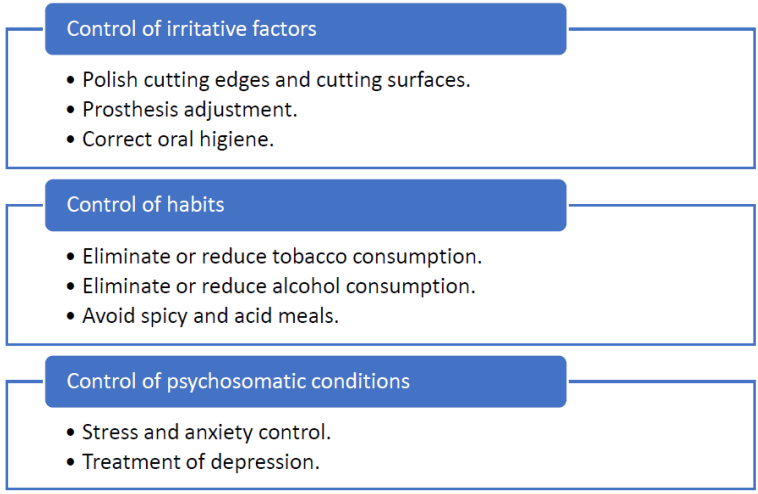


**Figure 4:** Initial treatment of OLP.

Pharmacological treatment will only be indicated in those patients presenting erosive forms. Since it is a disease with an autoimmune background, the treatment is based on topical corticoids, in order to control the inflammatory activity [17,26]:

- 0,1-0,3% Triamcinolone acetonide
- 0,05-0,1% Fluocinolone acetonide
- 0,025-0,05% Clobetasol propionate

The drug, its dosage and its posology will depend on the severity of the lesions. Similarly, the lesions extension will determine if the medicine need to be administered in orabase, for little and localized lesions, or in an aqueous solution in multiple and large lesions [17,26]. In patients presenting chronic desquamative gingivitis, the administration of the drug can be improved by the use of a night splint [26].

In those cases presenting a persistent form of the disease, in which the topical treatment has been unsuccessful or with lesions in other mucous membranes (genitals, esophagus) we can use systemic corticoids or intralesional injections (for oral lesions), whether there is not any contraindication [17,26].

In this last case, the use of 1-1,5mg/kg/daily of a single dose of Prednisone is recommended. It will be administered in the morning for 2 or 3 weeks, afterwards, the dosage will be reduced gradually. Intralesional treatment consists on the application of injections around the lesions with a preparation of Triamcinolone acetonid (30mg) or Betamethasone acetate (6mg) once a week for 2-4 weeks [26], as it is summarized on Figure 5.

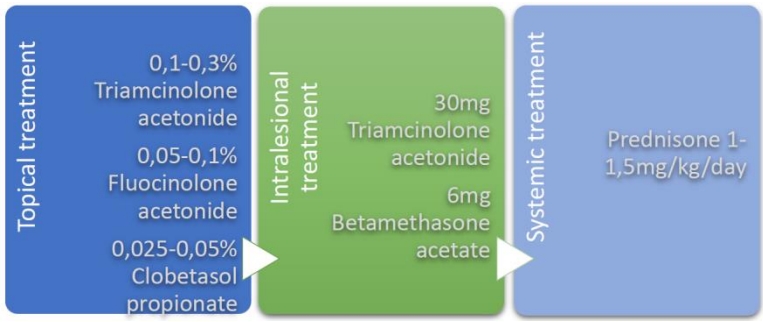


**Figure 5:** Pharmacological treatment of OLP lesions.

Giving information about the exacerbations of the disease to the patient is of great importance. Patients cannot expect a complete recovery from it. Cases with reticular or patch-like lesions need periodic revisions, at least every 6 months, because of the possibility of a cancerous degeneration of them.

## Clinical Case

i.-84 years old female patient, without surplus significant medical history, who occasionally takes Diazepam for sleeping. No surgical history and her motive of consultation is that she suffers from generalized pain in the mouth during the last 5 months.

In the clinical examination we see an erythematous left buccal mucosa with whitish patches and ulcerations, 2 pedicle nodules on the mesial keratinized gum of 3.7 which bleed on contact. The right buccal mucosa has a normal appearance. Moreover, a blister on the lower left hemilip, an atrophic, erythematous and irregular lesion on right hemipalate which spreads to the tonsil

pillar, a white patch-like lesion on the tip and the right side of the back of the tongue and some ulcerations on the right and left side of the floor of the mouth. Nikolsky´s sign is negative (Figure 6).

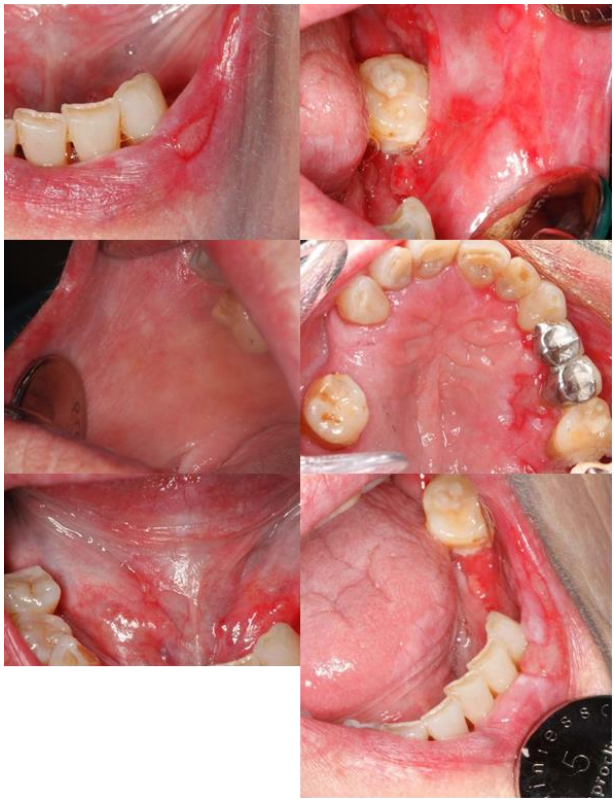

**Figure 6:** Intraoral examination on the day of the visit.

Extraoral examination reveals atrophic nails on both hands which according to the patient, correspond to the beginning of the discomfort in the mouth. Sometimes, she presents crusty and plaque-like skin lesions, such as the ones on right ear (Figure 7).

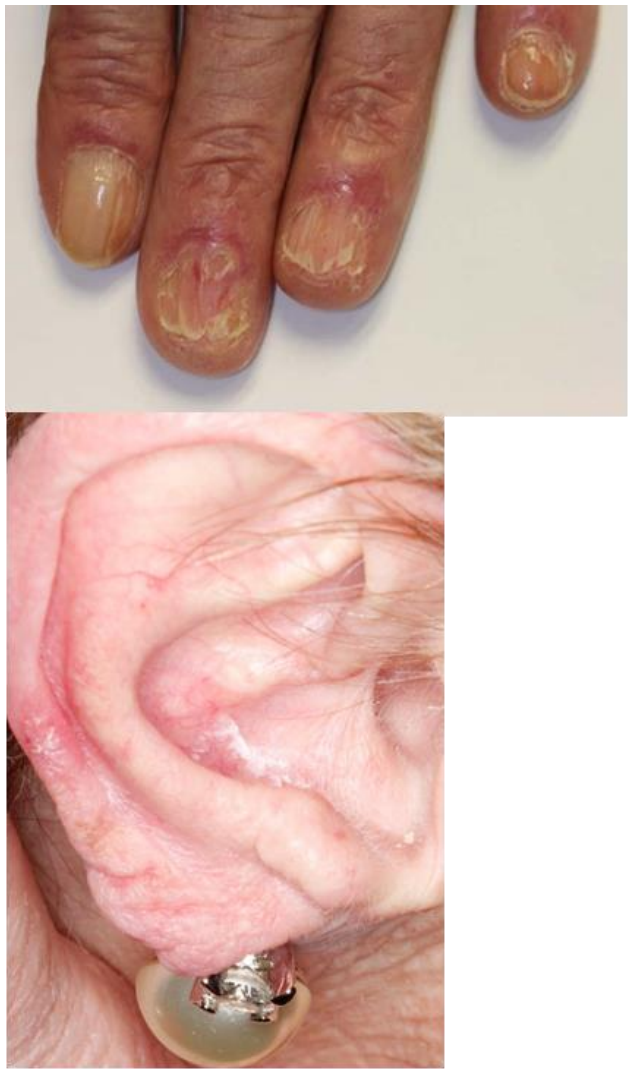

**Figure 7:** Lesions on the nails of the right hand and right ear.

Blood test with blood count, iron, Zn, ANA, Anti Sa, Anti SB, was requested. The results were anodyne.

Among the possible differential diagnose we find: pemphigus vulgaris, bullous OLP, Lupus erythematous, IgA lineal dermatosis.

ii.-We took a biopsy sample of left buccal mucosa. One sample is fixed with formalin for histopathological analysis and another one is kept in fresh for direct Inmunofluorescence in which we see an interphase stomatitis with negative IgG, IgA, IgM, and C3 (Figure 8).

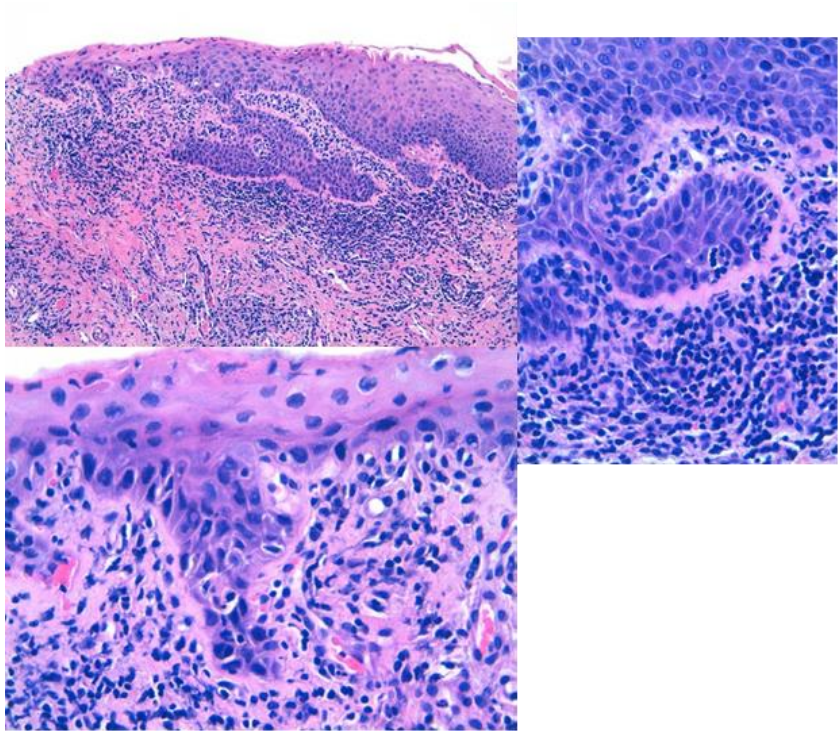

**Figure 8:** Histopathological images.

iii.-After 7 days we controlled the biopsy area with an exacerbation of the process (Figure 9)

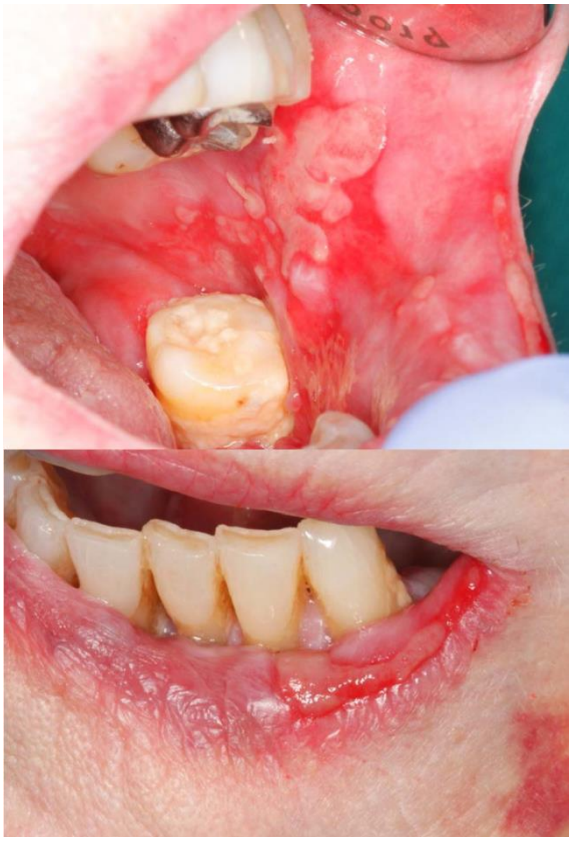

**Figure 9:** Control 7 days after the biopsy. We did not indicate any medication, resulting in an exacerbation of the lesions.

iv.-The lesion resulted to be and atrophic-erosive OLP clinical and histological diagnosis and we prescribe a topical treatment with 0,1% Triamcinolone acetonid 3 times a day during 3 weeks (Figure 10). In the next visit we observed an improvement of the lesions, though there was a persistence of them. We decided to change the treatment to 0,05% Clobetasol propionate twice a day (Figure 11).

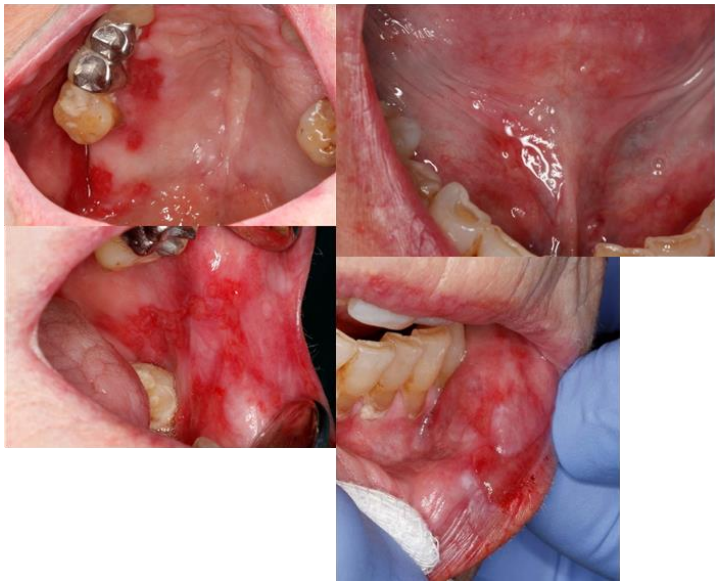

**Figure 10:** Control after three weeks post-treatment.

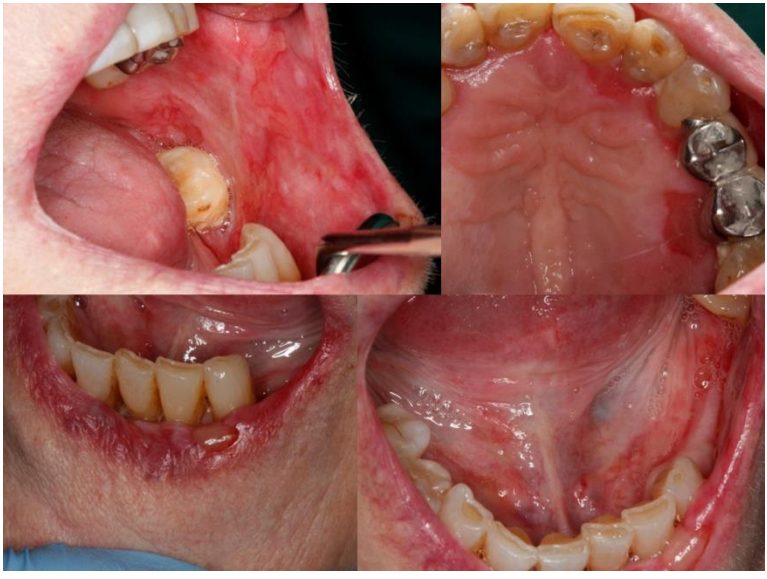

**Figure 11:** Control after 5 weeks, there is a clear improvement but lesions still persist.

v.- After 2 years of surveillance, there was a recurrent progression of the disease, with a persistent erosive palatal lesion (Figure 12), we administered a perilesional infiltration of 1ml of Trigon depot® (Triamcinolone acetonide 40mg/ml), producing an improvement after 7 days (Figure 13).

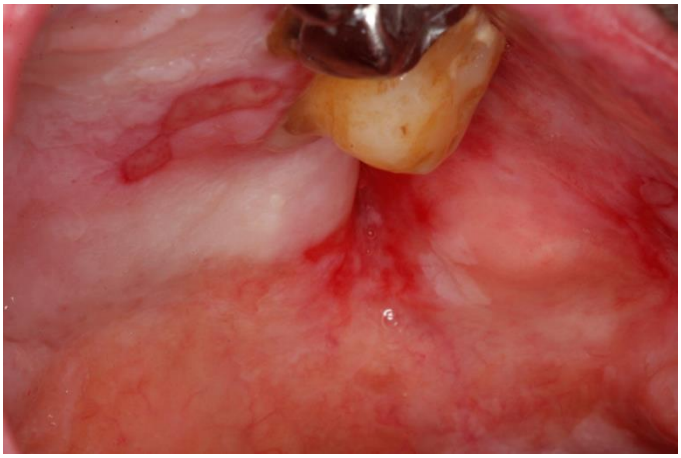

**Figure 12:** Control after 2 years, there is a persistence of the palatal lesion which could not be controlled with topical corticoids.

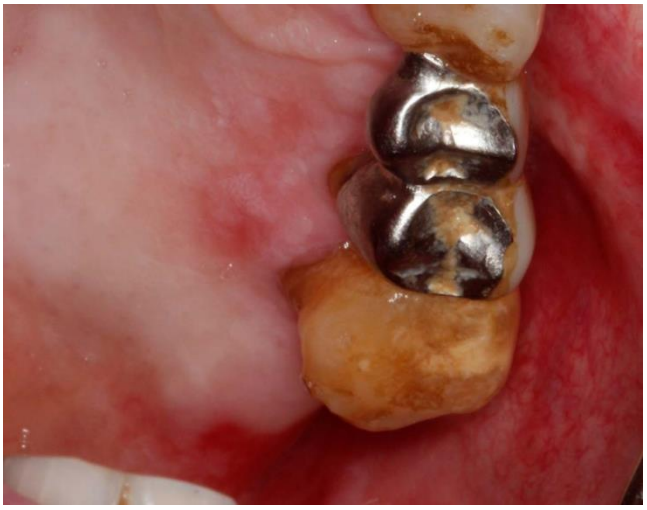

**Figure 13:** Control after 7 days of the perilesional infiltration, there is an almost total disappearance of the lesion.

vi.- After 3 years of surveillance the patient developed a lesion consistent with squamous cell oral carcinoma (Figure 14).

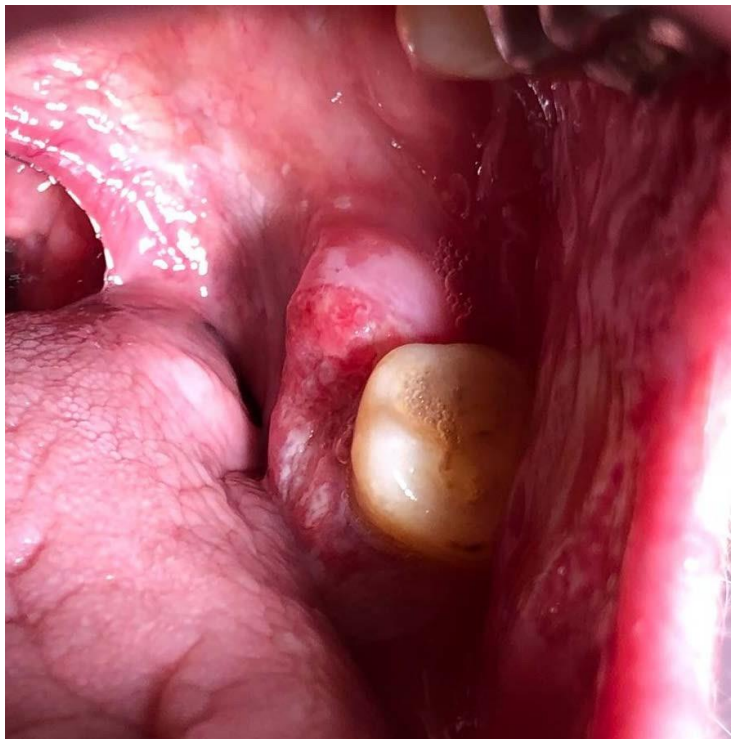

**Figure 14:** Control after 3 years, we observe a lesion consistent with squamous cell oral carcinoma on retromolar trigone and gingival lingual area of 3.8.

## Conclusions

OLP is an autoimmune disease which can show a blistering and ulcerative formation. Although classically OLP is not included in the blistering autoimmune conditions, it may be considered into the differential diagnosis since its clinical presentation can emulate a pemphigus vulgaris or a pemphigoid. A biopsy, together with the observation of the disease clinical manifestations, will allow us to reach a right diagnosis of the condition.

Knowing and managing the appropriate drugs for the treatment of these illnesses is necessary, since these conditions may bring discomfort and have a negative influence in the patient´s quality of life, specially in cases of rebel recurrences.

Periodic monitoring will enable us to detect changes in the lesions and will lead to an early diagnosis of a possible oral carcinoma.

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## Case Report

# Update and Malignancy of Oral Lichen Planus

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## Abstract

Lichen Planus (LP) is a chronic mucocutaneous inflammatory disease with a systemic impact and an unknown etiology. It is considered that its prevalence rates are around 5% and presents a preference for females. It is characterized for episodes of remission and reactivation.

The clinical manifestation includes reticular pattern lesions, as well as raised, erosive, atrophic, bullous and plaque-like lesions.

Its diagnosis is based on clinic and histopathologic criteria and it has to fulfill all of them to be diagnosed as LP, otherwise we will identify it as lichenoid reaction (LR).

One of the major complications involving the progress and prognosis of Oral Lichen Planus (OLP) is the onset of an oral squamous cells carcinoma (OSCC). The risk of a malignant disruption is stablished between 0% and 5% of cases, being a controversial issue. Females are more likely to present an OLP, specially in their 5$^{th}$ decade of life.

In terms of malignancy, the tongue is its more frequent localization and erosive lesions are more prone to it.

There are a number of risks factors related with its malignant transformation. Namely smoking, alcohol, viral infections (hepatitis C and human papilloma virus), systemic diseases as diabetes mellitus and hypertension, candidiasis and its location.

## Key Points

- OLP is a chronic inflammatory mucocutaneous disease, which in most cases affects the oral cavity.
- OLP is classified as a "potentially malignant disorder" with a nonspecific malignancy risk, however it is estimated to be around 1% of cases.
- Some authors agree that all subtypes of OLP present the same range of malignancy, nevertheless some researchers claim that atrophic-erosive patterns have a higher malignant potential.
- Since there are multiple cases reported in the literature, it´s extremely important to perform regular examinations every 6-12 months of patients presenting OLP.

## Introduction

LP is a chronic inflammatory mucocutaneous condition with a systemic involvement and an unknown etiology that can affect skin, hair, nails and mucous linings. Pathogenesis is still unclear, but it is accepted that arises from the immune system response, involving lymphocytes T CD4+ and CD8+ which produce cytokines, interleukine-2 and tumoral necrosis factor inside oral epithelium which induce a chronic inflammatory response and keratinocytes apoptosis. Therefore, this disease is related to other

illnesses with which shares an immunological basis. LP has a familial aggregation, meaning a genetic predisposition [1,2]. The presence of different histocompatibility antigens (HLA) and the involvement of subjects of the same family confirm that hypothesis [3].

It is estimated that OLP prevalence ranges are around 5% and present a predilection for females in a 2:1 proportion [4]. Its highest prevalence was documented in Europe and the lowest in India [5]. Lesions usually are bilateral and symmetric. Although, there is a wide variability in its clinical features, skin and oral cavity are its favorite surfaces. OLP affects 1-4% of populations, preferring women older than 40 years old. [6]. It is connected to different systemic conditions which make the patient more susceptible to develop an OLP because of the inherent disruptions which those diseases carry (diabetes and hepatitis C) or conditions that are immunologically very similar to OLP (same autoimmune basis), basically chronic liver diseases and others like myasthenia gravis, lupus erythematosus, ulcerative colitis or thymoma. It is also associated with biochemical- enzymatic disorders, essentially high cholesterol levels [7].

LP is characterized by episodes of reactivation and remission which apparently have a psychosomatic influence [7]. Patients presenting this condition seem to have higher sleepless degree and that lack of sleep leads to psychiatric disorders as depression and anxiety. The development of LP and especially its aggravation is related to stress, anxiety, depression and eventually detriment of patient´s life quality. It was proved by an increased salivation and/or cortisol urinary levels corresponding to anxiety and depressive states.

Clinical presentation of OLP comprises reticular pattern, raised lesions, erosive, atrophic, bullous and plaque-like lesions [8], being the reticular pattern the most frequent presentation [9]. Occasionally, it can develop OLP-like lesions in patients taking specific medicines as antidiabetics, antihypertensive and anti-inflammatory drugs, as well as patients with dental restorations such as amalgam, toxic habits or patients experiencing graft-versus-host disease; calling it lichenoid reactions (LR) [10].
More recently, a new classification has been proposed that, in

order to clarify diagnosis, grouping all similar lesions to OLP in a new one, called Oral Lichenoid Disease (OLD) [11,12].

## Diagnosis

The diagnosis is based on clinic and histopathologic criteria [8]. Some standards to diagnose it based on World Health Organization (WHO) have been proposed (Table 1). Classically there are some histological and clinical points that need to be fulfilled to be diagnosed with OLP. Otherwise, it will be called LR in case it doesn't satisfy these criteria.

**Table 1**: Clinical and histological criteria.

| | |
|---|---|
| **Clinical Criteria** | Presence of symmetric bilateral lesions |
| | Presence of white reticular lesions, there can be erosive, blistering or plaque-like concomitant lesions |
| **Histologic Criteria** | Presence of a defined band of inflammatory lymphocytic infiltration |
| | Signs of dropsical degeneration of basal layer |
| | Absence of epithelial dysplasia signs |

Immunofluorescence is important to confirm the diagnosis. Nevertheless, a complete anamnesis facilitates the diagnosis [2]. Direct immunofluorescence can show fibrinogen deposits along basal membrane or deposits one or more immunoglobulins, or both elements to considerate a compatible diagnosis with OLP. In the quality checks for its diagnosis, it has been proved that the presence of fibrinogen in the basal membrane is the best indicator. Regarding immunoglobulins deposits, the ones with more possibilities are IgM, being these as well as IgG, highly specific. The combination with higher diagnosis quality (sensibility/specifity) is the one which detects fibrinogen and IgM [7].

## Histology

Histological features of OLP include epithelial hyperkeratosis (orthokeratosis or parakeratosis), basal membrane degeneration, and classically a band-like lymphocytic infiltration on lamina propria surface, which contains degenerated colloidal particles

and keratinocytes in the interface between epithelium and mucosa. A serrated epithelial combs pattern is more common in the dermis of LP than in the mucosa. The histopathological evaluation is essential for a precise determination for the establishment of a correct OLP diagnosis, specially to discard a malignant transformation [2].

## Clinical Variants

One of the first classifications which boasted of more popularity was the one proposed by Andreasen (13) in which it was included six clinical forms of LP: papular, reticular, plaque-like, atrophic, erosive and blistering. On the other hand, Bagán et al. [3], divided OLP into two clinical forms: *white lichen planus* in those situations in which only appeared reticular lesions (or plaque-like lesions) and *red lichen planus* when it presented atrophic or erosive lesions, regardless of having reticular lesions surrounding it or in other locations.

The reticular variant is the most prevalent. It is presented as a white lesion, lineal and starry, reticular, branch-like, annular, slightly raised, palpable (Wickham´s striae) and does not peel off when scaling. It usually appears on buccal mucosa areas, they are usually bilateral, symmetric and asymptomatic [14].

The atrophic-erosive version features an epithelium thinning with a generalized and diffuse redness which exposes underlying chorion blood vessels. The tongue is the most typically affected part, however gums are also a frequent location in which it manifests as a chronic desquamative gingivitis. This clinical expression is characterized by the presence of ulcerations of the epithelium over an atrophic mucosa, nevertheless it can also have a blistering presentation [14].

## Symptomatic Aspects

Symptomatology varies depending on the clinical features. In the case of white LP, lesions are classically asymptomatic, actually, they are incidental findings and they are not a reason for consultation. Patients can feel a roughness sensation on the area in which striae are located. On the other side, red lichen planus is

accompanied by an evident symptomatology which ranges between a burning sensation to an intense pain exacerbated by rubbing. Patients refer a swelling sensation, specially when it takes place on the buccal mucosa (genial swelling). The burning feeling worsens when taking some acid and sour drinks or foods, as well as tooth pastes and mouth washes. Those discomforting sensations result in a functional incapacity, sometimes of huge relevance. Occasionally, we find xerostomia, specially in those patients taking plenty of psychoactive drugs, halitosis and bacterial superinfection of erosive areas with submaxillary lymphadenopathies. Superimposed candidiasis can arise during the pathological process, mainly when we prescript a topical or systemic treatment with corticoids during a long period. We have to take into account these issues when treating these patients. In cases of desquamative gingivitis, the main clinical manifestation is a profuse bleeding from the gums, with discomfort or pain which makes the toothbrushing difficult. It goes together with dentin sensitivity and gingival retraction with deposits of bacterial plaque and tartar [2,7].

## Differential Diagnosis

Differential diagnosis will depend on the type of lichen planus we find: white one in which reticular variety is the most frequent but we may find papular or plaque-like lesions. On the other side, in a predominantly red OLP, we may find atrophic, erosive or blistering lesions (Table 2) [14,15].

**Table 2:** Differential diagnosis [14,15].

| | |
|---|---|
| **Predominantly white forms** | Mechanical, physical and chemical agents lesions |
| | Microbial agents lesions: syphilis, fungal diseases |
| | Inmunologic disorders: scar-like pemphigoid, lupus, scleroderma |
| | Hyperplasias and benign tumors: white nevus, dyskeratosis, psoriasis |
| | Precancer and cancer: leucoplakia, OSCC |
| **Predominantly red forms** | Erythema multiforme |
| | Pemphigus vulgaris |
| | Pemphigoid |

**Table 3:** OLP treatment [14].

| | | |
|---|---|---|
| **Corticoesteroids** | Topical | Betametasone Fosfate, Betametasone Valerate, Clobetasol Propionate, Fluocinolone Acetonid, Fluocinonide, Hydrocortisone Hemisuccinate and Triamcinolone Acetonid |
| | Systemical | Prednisone and Methylprednisone |
| **Retinoids** | Topical | Fenretinidide, Isotretinoine, Tretinoine and Tezarotene |
| | Systemical | Acitracine Etretinate, Isotretinoine, Tretinoine and Temarotene |
| **Immunosupressive agents** | Cyclosporine, Azathioprina and Tacrolimus | |
| **Others** | Amphotericine A, Diethildithiocarbamate, Dapsone, Doxicycline, Hydroxichloroquine Sulfate, Levamisole, Glycyrrhizin, Griseofulvin, Eticol and Enoxaparin | |

## Treatment

The chronicity of these diseases with periods of activity and others of remission makes these patients difficult to manage. However, the treatment focus on removing ulcerations, relieving symptoms and reducing the possibility of a malignant transformation. The first of the measures should be to eliminate the traumatic factors in the proximity of the lesion, namely root remains, cutting edges, prosthetic attachments, etc. It is mandatory to suppress local irritative factors such as smoking, alcohol and spices. Patients should maintain an exquisite oral hygiene, removing tartar deposits and treating the patient´s psychological imbalance [14].
OLP and LR can inflict a significative pain, particularly in the erosive and ulcerative forms. Pain is an indication to treat OLP and LR. Corticosteroids have classically been the first line of the treatment of OLP, and they show effectivity when they are used topically as adhesive gels or similar preparations [16].

The medical drugs more used in these cases are 0,1% triamcinolone acetonide in orabase or perilesional infiltration of a dosage of 30mg/ml, 0,05% clobetasol propionate in orabase, 0,025% fluocinolone acetonide in orabase, betamethasone valerate in a spray presentation and 0,05% fluocinocide in

orabase. Their use needs to be 3-5 times a day after meals, during 4-6 weeks depending on the evolution of the lesions. The main side effect is Candida superinfection, that is why some authors recommend to add fungicides to the corticoid compound [14].

In severe cases, with intense atrophic erosive lesions, we prefer the systemic administration with 40-80mg a day of prednisone, reducing the dosage when the patient presents an improvement of the clinical picture [14].

Calcineurin inhibitors, specifically topical application of 0,1% tacrolimus, could be more effective in reducing pain than corticoids, nevertheless there is some uncertainty about its side effects [16].

Therefore, in most cases, initially topic corticoids are the election for symptomatic OLP, and if they do not work, we consider systemic treatment. However, in refractory cases calcineurin inhibitors suppose a second line of therapy. These medicines should be used cautiously by experts and preferably in short term treatments due to the risk of developing OSCC after their use. Nonetheless, given the chronic nature of this disease, full recovery is difficult to reach. There is not a full agreement about how to treat it [2].

## Malignancy

In 2005, WHO coined the term “oral potentially malignant disorders” (OPMD). An oral premalignant lesion is defined as any lesion or disorder of oral mucosa which has a potential of malignant transformation (MT). A new term, “potentially premalignant oral epithelial lesion”, has been recently used as a wide concept to define clinical and histological lesions with a malignant potential. This expression includes lesions such as leucoplakia, erythroplakia, palatine lesions of reverse smokers, oral submucous fibrosis, actinic keratosis, lichen planus and discoid lupus erythematous. The knowledge about them and their progression to a malignant disruption will minimize their morbidity and mortality, will help to decide the best treatment and will have a direct effect on patient´s survival [1,17,18].

As we said before one of the most important complications regarding to its progress and OLP prognosis is the onset of an OSCC [19]. We can claim that the molecular pathways which control the growing, proliferation, maturity and apoptosis in the attacked epithelial cells can play a major role in the process of malignant transformation. (14) The first case of OSCC over an LP was documented in 1910 and since then countless studies have been published in order to clarify the OLP malignancy rate, concluding it was between 0 and 5% being always controversial [19]. Its predilection for malignancy is unclear due to its common features with LR and the lack of universal diagnosis criteria [6,8,11,12,19]. There are authors who state that LR is the only condition which becomes malignant, and not OLP [19].

The most common clinical presentation is an ulcerative-excrescent lesion which infiltrates the tissues, with round and raised edges, irregular contour, rough surface, with an indurated bottom area when palpated and with a tendency to spontaneous bleeding or when rubbing [20].

The typical demographic presentation of OLP is the female sex on the fifth decade of life. The tongue is the first location of malignant transformation, followed by the oral mucosa, gums, floor of the mouth, palate and lips [21,22]. The majority of the lesions which become malignant are erosive ones [6,23]. Some authors found differences between LR and OLP with lower malignant degeneration rates for OLP than for LR [12].

There are some risk factors associated with malignity in cases of OLP, named smoking, alcohol, viral infections (hepatitis C and human papilloma virus), systemic diseases as diabetes mellitus and hypertension [15,24], candidiasis [25] and its location [25,26], being tobacco and alcohol the most related ones with the onset of an oral cancer according to the literature [25,26]. OLP has a benign nature, however his association with human papilloma virus suggests a causative role in its malignant progression which is of major significance and it supposes a potential risk, although it may not happen in all cases. Furthermore, it has been associated with thymoma and Good´s syndrome [2].

Regarding its mortality rate, OSCC developed from OLP, show a most favorable prognosis [27].

The transition between a normal mucosa and a premalignant or a dysplastic one and the final malignant transformation is a complex interaction between environment and host. As professionals, implementing primary prevention for reducing prevalence and incidence of premalignant diseases which have known causes which could be prevented, is mandatory. We can do that by educating and giving information to our patients against the exposure to those environmental carcinogens. If primary prevention fails, then detection and early intervention are the key in case of OPMD, in which diagnosis and treatment are based on histopathology. Early identification of these lesions may allow interventions which minimize or remove that risk.

## Clinical Case

i.-58-year old male who came to Bellvitge dental hospital in February 2018. He smokes 40 cigarettes and is an alcohol consumer of 1 SDU (standard drink unit) per day. He has not a medical history of interest, nor known allergies.

The reason of consultation was “last lower left molar has a huge mobility. However it does not cause a remarkable discomfort to me”.

We performed a complete oral exploration in which we found a generalized periodontal disease, numerous caries lesions and poor hygiene (Figure 1).

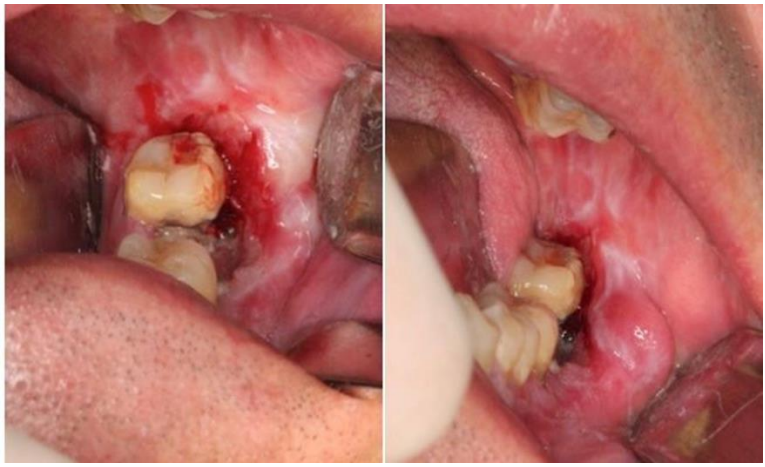

**Figure 1:** Intraoral photographies on the day of the consultation.

We saw a mobility type 2 of the tooth 3.8, and ulcerations on the area of retromolar trigone and left buccal mucosa, with bleeding, surrounded by a white reticular area and erythematous macules.

ii.-We take an orthopantomograph in which we see radicular remains of 3.7 with a poorly delimited radiolucent image on the area of 3.7 and 3.8 (Figure 2).

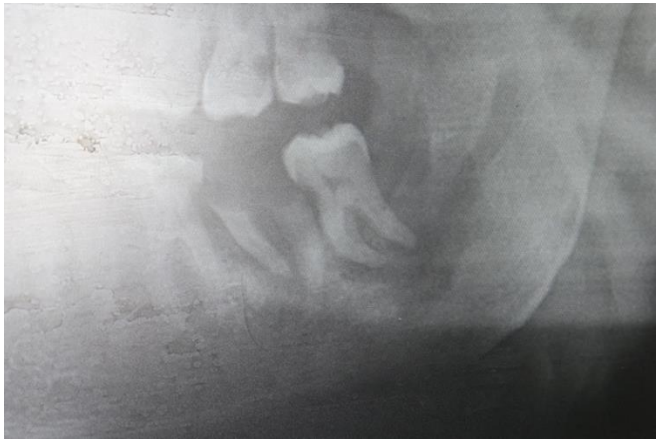

**Figure 2**: Detail from the orthopantomograph.

iii.- Patient relates that he was diagnosed of OLP in 2017 and they performed a biopsy in which they saw a defined band of lymphocytary inflammatory infiltration on the connective tissue, signs of dropsical degeneration of basal layer and absence of signs of epithelial dysplasia (Figure 3).

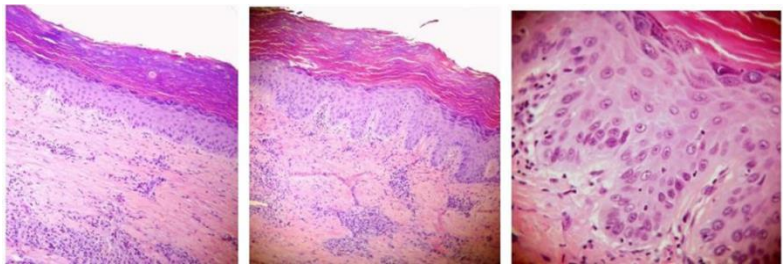

**Figure 3:** Histology 2017.

iv.-We decided to perform an incisional biopsy of the area during that first visit (Figure 4)

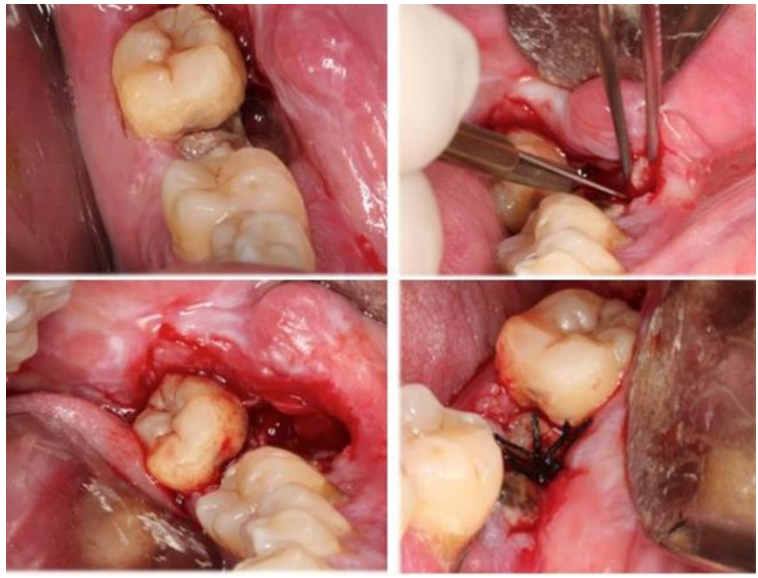

**Figure 4:** Sampling of the biopsy.

v.- We receive the results of pathological anatomy in which the parts analyzed showed a focally infiltrative neoplastic squamous epithelial proliferation. It showed an epithelial disestablishment, cellular atypia and formation of epithelial nests with a slight keratisis. We noticed an intense mixed inflammatory lymphoplasmocytic and polymorphonuclear infiltrate, with a high number of eosinophils. The marginal epithelium shows alterations which are suggestive of moderated epithelial dysplasia. The final diagnosis was moderately differentiated oral squamous cells carcinoma (Figure 5)

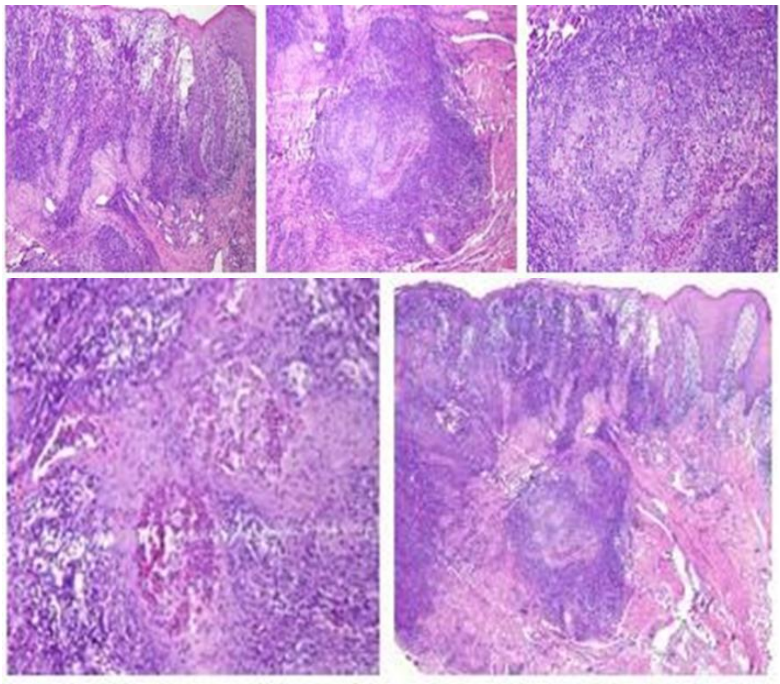

**Figure 5:** Histology which shows numerous corneal corpuscles.

vi.- We order a cervical computerized tomography and refer the case to the Maxillofacial Surgery Service of Bellvitge Hospital (Figure 6)

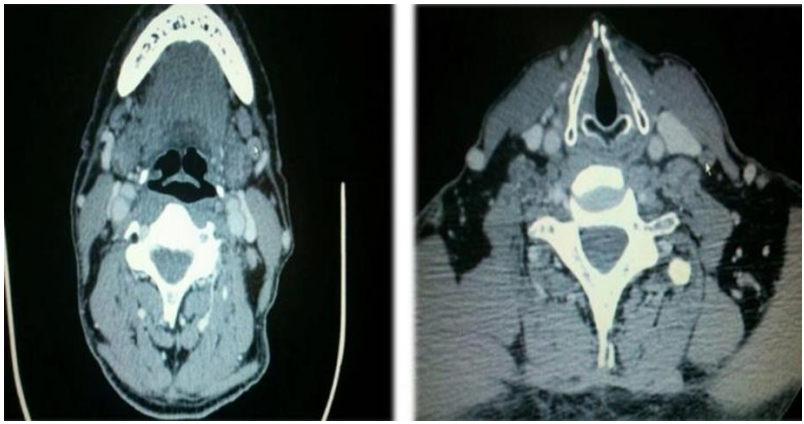

**Figure 6:** Cervical tomography.

vii.- The next treatment was planned (Figure 7 and 8):

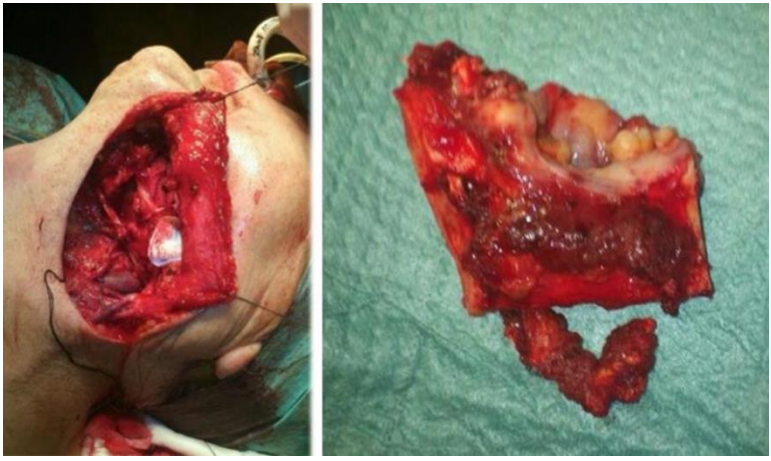

**Figure 7:** Intraoperative pictures.

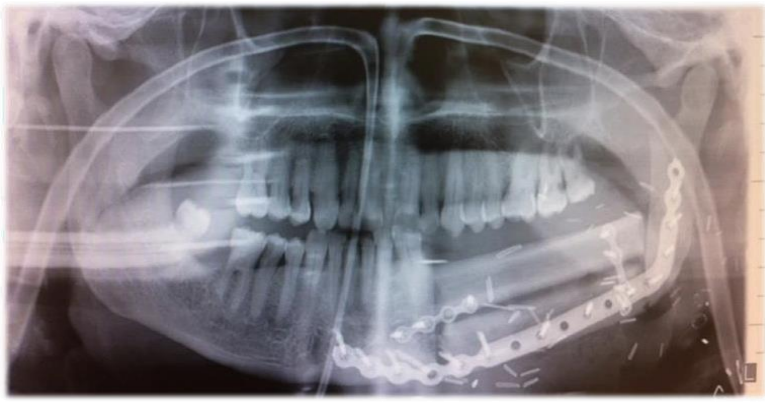

**Figure 8:** Postoperative orthopantomograph.

- Homolateral lymphadenectomy
- Mandibular body hemimandibulectomy
- Reconstruction of the defect created with a microvascularized graft from fibula, double bar bone technique.

viii.- We got confirmation of OSCC diagnosis in stage: T4 N2b M0

After the treatment, the patient had a positive evolution and we do not see any sign of recurrence after 5 months (Figure 9 and 10),

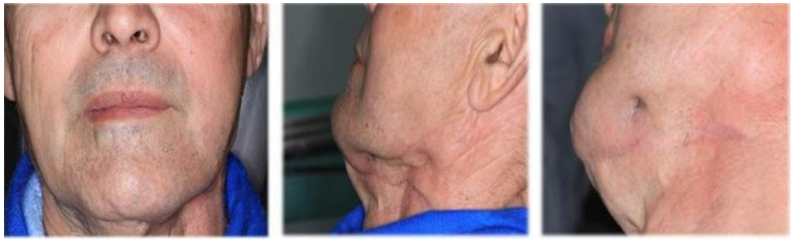

**Figure 9:** Postoperative extraoral images after 5 months.

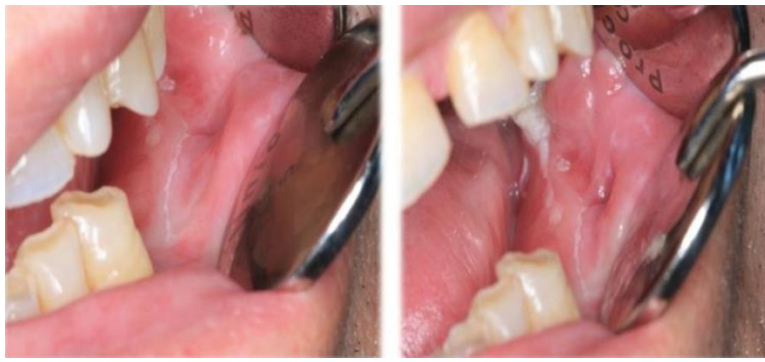

**Figure 10:** Postoperative intraoral images after 5 months.

After 2 years of surveillance, patient has no recurrence and do not feel the need to rehabilitate the area.

## Conclusions

Malignant disruption after a diagnosis of OLP is a cause of controversy. There are few well documented cases that can endorse this fact and we as mentioned before, the fact that it has common features with LR provides even more uncertainty. Therefore, for a number of authors, the only one which presents a risk of malignant transformation is LR. It is important to do a correct diagnosis of OLP and a subsequent surveillance because of its malignant degeneration capacity.

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## Case Report

# Herpes Virus: Case Report

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## Summary

Herpetic infections commonly affect oral region. Primary infection goes asymptomatic in most of the cases, sometimes can cause an acute herpetic gingivostomatitis. It commonly presents in children before the age of 6 it can also occur in adult. The clinical manifestations are characterized by a prodrome of fever followed by painful ulcerative lesions in gingiva and oral mucosa. HSV-1 is usually spread from direct contact or via droplets of oral secretions or lesions from an asymptomatic or symptomatic individual. Herpes simplex virus can recur in the form of herpes labialis with intermittent re- activation occurring throughout life. The treatment is usually with antiretrovirals, pain medication and local care to avoid infections

In the present clinical case, we can review different types of herpes viruses that can affect oral cavity, main diagnostic characteristics and treatment.

## Key Points

- Describe the oral manifestations of human herpes virus.
- Learn the importance of a proper clinical history for the diagnosis.
- Review the treatment available.

## Introduction

The family of Herpesviridae viruses is one of the most widespread families in nature, with 8 known species that affect humans. They are made up of four components: two DNA strands in the nucleus, a protein capsid, the integument, and a lipid envelope that contains glycoproteins derived from the nuclear membrane of the infected host cells [1]. This family is characterized (more markedly by some members than others) by being able to infect its hosts in a primary way and then remain latent, being able to reactivate itself in the face of certain stimulus (Trauma, ultraviolet light, stress, etc ...) giving clinical manifestations involving the oral mucosa [2].

The site of latency depends on the type of herpes virus. Types 1 and 2 do so in the ganglia of the sensory nerve surplus. The Epstein-Barr virus occurs in the oropharyngeal epithelial cells and in the tissues of the salivary glands, also occurring in B lymphocytes as does Kaposi's sarcoma. We can find Cytomegalovirus in monocytes, in hematopoietic, epithelial and endothelial progenitor cells and possibly in salivary gland tissues. Viruses 6 and 7 will be latent in CD4 lymphocytes (Table 1). When the virus undergoes reactivation it can affect both locally and systemically, as well as being involved in other important pathologies such as carcinomas or lymphomas [2].

**Table 1:** Types of human herpesviruses, target cells and oral manifestations.

| HUMAN HERPES VIRUS | VIRUS | TARGET CELLS | ORAL MANIFESTATION |
|---|---|---|---|
| **HHV1 AND HHV2** | Herpes simplex virus Type 1 and 2 (HSV-1 and HSV2) | Mucoepithelial | Herpetic gingivostomatitis, recurrent herpes |
| **HHV3** | Varicella Zoster Virus (VZV) | Mucoepithelial | Chickenpox, herpoes zoster or "shingles" |
| **HHV4** | Epstein-Barr virus (EBV) | Epithelial cells and B cells | Mononucleosis Hairy leukoplakia |
| **HHV5** | Cytomegalovirus (CMV) | Monocytes, lymphocytes and epithelial cells | Mononucleosis |
| **HHV6** | Roseolovirus | T cells | Roseola in infants |
| **HHV7** | Roseolovirus | T cells | Roseola in infants |
| **HHV8** | Kaposi sarcoma associated virus | Lymphocites and epithelial cells | Kaposi's sarcoma |

## Herpes simplex virus (HSV)

There are two types of herpes simplex virus: herpes simplex virus type 1 (HSV-1), usually related to recurrent labial herpes, and herpes simplex virus type 2 (HSV-2) associated with genital and neonatal herpes. These two types are the most common and both can cause oral and pharyngeal lesions, meningoencephalitis, genital and skin lesions [2].

It is a disease that is normally transmitted in early childhood with the maximum peak between 2-3 years, but even so, it may still occur throughout life. When primary infection occurs, it goes asymptomatically in most cases [1]. When this is not the case, the patient presents a condition known as primary herpetic gingivostomatitis.

The recurrence of herpes occurs more in adults in situations such as cold, exposure to UV radiation, stress, immunosuppression or trauma (including dental treatments or simple dental visit), being herpes simplex type 1 the one that most frequently recurs [2,3], with a higher prevalence in women than in men [4].

It is transmitted through direct contact with the contents of the vesicles, saliva, or genital secretions that contain viral particles [1]. The incubation period can vary between 1 and 26 days, with an average of 7 days.

The most frequent manifestations are:

## Herpetic Gingivostomatitis

The case of primary herpetic gingivostomatitis is the most frequent clinical manifestation of the primary infection. Presents a period known as prodromal, in which the patient may present nonspecific symptoms such as fever, malaise, pharyngitis, lymphadenopathy and headache, later the gums begin to swell, suffer bleeding and reddening and in a short time vesicles appear that can affect any location of the oral mucosa (yugal mucosa, free and attached gingiva, tongue, etc.). These vesicles usually break, leaving erosions in the mucosa and that are solved without a scar. It is a self-limited pathology in immunocompetent patients [2,5].

## Recurrent Labial Herpes

It is the most frequent oral lesion produced by viruses in the oral cavity. The lesions appear in the area of the mucocutaneous junction of the lip and present prodromes, where the patient may notice stinging, itching, paresthesia and pain in the area. After a few days, small vesicles grouped in clusters with a yellowish liquid content and variable in number and size can be observed (Figure 1). These vesicles rupture and dry out, appearing crusty lesions that in most cases heal without a scar in 8 to 15 days [2,3].

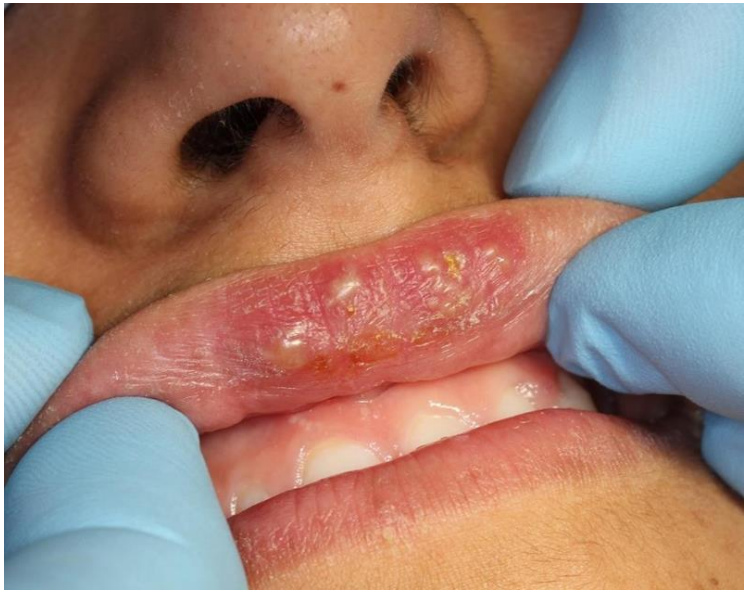

**Figure 1:** Recurrent cold sores.

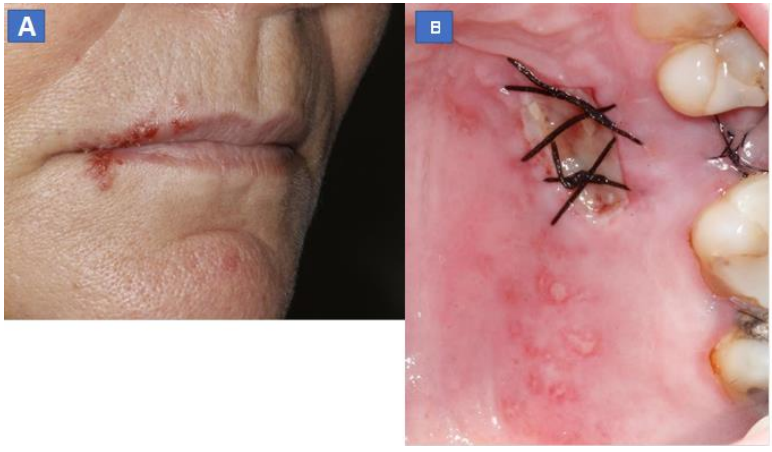


**Figure 2:** Herpes labialis (A) and intraoral rrecurence (B) possibly triggered by dental treatment (A).

### Recurrent Intraoral Herpes

Similar to labial herpes, the clinical manifestation is the appearance of vesicles grouped in attached gum, very common on the palate, which rapidly ulcerate, leaving painful erythematous erosions that disappear between 8 and 10 days [6]. The appearance of intraoral herpes can be triggered by dental treatment, especially in treatments where mucosal trauma occurs [3].

### Diagnosis

The diagnosis of these entities is based mainly on clinical examination, however, it is important to establish a good differential diagnosis with other vesicular-bullous diseases such as the coxakie virus, erythema multiforme and recurrent oral aphthosis, among others [1,7].

Laboratory tests such as exfoliative cytology, virus isolation and cultivation, viral antigen detection, PCR, and serological studies can be performed.

### Treatment

As it is a viral process, we must take into consideration that they remit spontaneously after 10-15 days. In the case of immunocompromised patients or severe clinical manifestations, such as herpetic gingivostomatitis, antiviral treatment with Acyclovir 200mg 5 times/day can be considered. It is important to include symptomatic treatment with oral analgesics, and if necessary, mouthwash with topical anesthetics such as 2% lidocaine can be used [8].

In the case of labial recurrences, the use of 5% acyclovir cream 5 times a day and its administration should begin in the prodromal phase, prior to the appearance of the vesicles [8].

## Varicella Zoster Virus (VZV)

The primary infection by VZV manifests itself as varicella. It mainly affects children and it is a highly contagious disease that is transmitted through nasopharyngeal secretions or with direct

contact of the lesions. It has an incubation period of 1 to 3 weeks and manifests as an itchy rash, fever, malaise, and cervical lymphadenitis [8,9].

After primary infection, the virus remains latent in the dorsal root of ganglion cells and its reactivation produces herpes zoster, or commonly called "shingles" [8]. It is common in older adults and immunocompromised patients [9]. Clinically it presents with the appearance of vesicles that erode rapidly, of unilateral appearance and that follow the nervous path of the affected ganglion. These are lesions that present constant, burning pain [8,9].

In the facial territory, it can affect the trigeminal ganglion, with preference for the maxillary and mandibular nerve, with lesions on the palate, lips and jugal mucosa [9]. When it affects the geniculate ganglion, Ramsay-Hunt Syndrome occurs, characterized by the presence of unilateral facial paralysis, pain and the appearance or not of vesicles in the ear of the affected side [8,11].

Diagnosis is mainly based on clinical examination, although the same laboratory methods as for herpes simplex can be used [8].

Treatment is carried out by administering antiviral drugs such as acyclovir (800mg 5 times a day for 15 days), famciclovir (500mg 3 times a day), valaciclovir (1g 3 times a day). [8,10] Treatment with valaciclovir or famcicyclovir allows a reduction in frequency and dose, in addition to achieving better antiviral effects [10]. In the case of Ramsay-hunt syndrome, the association of antivirals and corticosteroids is frequent [11].

Different drugs can be administered for pain control. The use of paracetamol associated with opiates or tramadol (50mg once or twice a day) and antidepressants such as amitriptyline are very common [8,10].

A possible sequel is the appearance of sensory and taste alterations, including post- herpetic neuralgia, whose management can be a challenge for the professional, especially in elderly patients. Some authors advise treatment as anticonvulsants such as gabapentin or opioids [10, 11].

## Epstein-Barr Virus

This herpesvirus has been associated with important diseases such as infectious mononucleosis, nasopharyngeal carcinoma, Burkitt's lymphoma, B-cell lymphoma, and oral carcinoma [12].

It is transmitted through saliva and blood and its primary infection occurs frequently in adolescence presenting fever, lymphadenopathy, asthenia and pharyngitis. Occasionally the presence of palatal ulcers or petechiae can be found in the oral cavity, although its most frequent oral manifestation is hairy leukoplakia [8].

Hairy leukoplakia clinically presents as raised white lesions located on the lateral border of the tongue. They are usually asymptomatic and do not require treatment.

The diagnosis of this entity is fundamentally clinical. Although there are documented cases in HIV-negative patients, due to its high association with immunocompromised and HIV-positive patients, it is prudent to request a control test [8,13]

## Cytomegalovirus

Cytomegalovirus infection is more common in childhood and usually goes unnoted, except in cases where it can present as a non-specific viral condition (pharyngitis, malaise, fever, and lymphadenopathy) [8].

It is an opportunistic pathogen that affects immunocompromised patients and can trigger a syndrome similar to mononucleosis. In the oral cavity it mainly causes ulcerations with very diverse clinical characteristics and located in any region. Other possible manifestations include gingival hyperplasia, gingivitis, oral mucosal hyperplasia, and recurrent aphthous stomatitis [8,14]

## Kaposi's Sarcoma

It is a multifocal mesenchymal neoplasm characterized by neoangiogenesis, inflammatory infiltration, and spindle tumor

cells derived from the endothelium [15]. From the 1980s onwards, Kaposi's sarcoma is a predominantly AIDS-defining malignant neoplasm, but other clinical subtypes such as classic, posttransplant (iatrogenic or immunodeficient), and African (endemic) Kaposi's sarcoma [16, 17].

The global incidence of Kaposi Sarcoma is currently 481.54 per-100.000 person/year. HIV-infected men who have sex with men have the highest incidence 1,397.11 per-100.000 person/year. The incidence is significantly lower in women than in men, and in people receiving highly active antiretroviral therapy (HAART) compared to people who have never received HAART [15].

Kaposi's Sarcoma is associated with Human Herpes virus type 8 (HHV-8). Virus infection induces a dynamic alteration of gene expression in endothelial cells, affecting the expression of cellular proteins such as LANA-1 for the establishment and maintenance of virus latency and lytic proteins such as IL-6 that form lesions [17].

## Clinical Features

Kaposi's sarcoma typically presents with painless, dark brown, purple, or reddish-blue plaques/macules or nodules that may bleed, ulcerate, and become verrucous and hyperkeratotic. Lymphedema is common and may precede maculopapular lesions. It mainly affects mucocutaneous areas, although they can have nodal and visceral involvement such as the lung, gastrointestinal, bone or liver involvement [18].

## Diagnosis

It is performed by the Immunohistochemical study using a monoclonal antibody against LANA. The detection of HHV-8 by PCR has high sensitivity and specificity, although in clinical practice they are intended for monitoring and follow-up of the disease. Serological tests with Western blot are discussed by specialists [18].

## Treatment

The most widely used local therapies are radiotherapy and surgical excision. Radiation therapy (30-36 Gy) is the most efficient treatment for treating all localized forms of Kaposi's sarcoma; whereas surgical excision presents high recurrence and cannot be performed in extensive lesions. Other types of treatment have been reported, such as cryosurgery, laser, and intralesional injections with immunomodulators. Systemic therapies will depend on the type of carcinoma [18].

## Clinical Case

i.- A 55-year-old male patient, laboratory technician in a hospital, allergic to penicillin and with a medical history of hiatal hernia, does not refer any type of pharmacological treatment. As a surgical history of interest, a tonsillectomy was performed in childhood and did not report toxic habits. The patient reports pain and stinging that he describes as unbearable, in addition to fatigue, muscle pain and earache.

The clinical examination shows the presence of vesicular and erosive lesions that affect the attached gingiva, even in edentulous areas and palate, and that do not come off when scraping. On the palate we can see necrotic tissue predominantly in the papillae and the cervical area of the teeth, it also presents an accumulation of plaque. In addition, vesicular lesions are observed that are grouped in clusters on the left border, tip of the tongue and left jugal mucosa (Figure 3). The patient had marked halitosis.

ii.- We performed an extraoral examination and found soft cervical and submandibular lymphadenopathy, rolling and painful on palpation. When taking a correct anamnesis, the patient reports muscle fatigue, musculoskeletal pain and chills. The temperature measurement indicates that the patient had a fever (38.6ºC).

We inquired about the antecedents prior to the condition, to which the patient refers that his spouse had a recurrent outbreak of cold sores approximately one week before the onset of the

condition. A few days later, he started with a fever and general malaise that the next day progressed to a sensation of oral discomfort without apparent lesions. As the days passed, the discomfort increased and after 4 days of the fever, the first lesions appeared on the tongue and yugal mucosa.

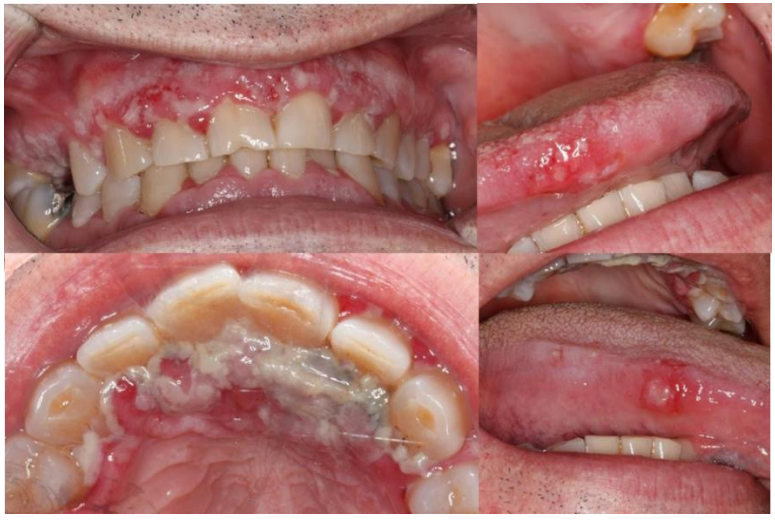

**Figure 3:** Initial state of the patient. We can observe vesicular and erosive lesions that affects keratinized gingiva, tongue and jugal mucosa.

iii.- A blood test is requested where there was only significant alteration of C-reactive protein and ESR test, non-specific indicators of the inflammatory process. A differential diagnosis is established between: herpetic gingivostomatitis, erythema multiforme, plasma cell gingivitis, leukemia, recurrent aphthosis stomatitis and necrotizing gingivostomatitis.

iv.- Symptomatic treatment is prescribed with 600mg ibuprofen every 8 hours, 2% lidocaine rinses and 200mg acyclovir 5 times a day. We request a serological study for the herpes viridae family, HIV, HBV and HCV where IgM antibodies to HSV-1 are detected.

vi.- At 15 days we can observe the complete remission (Figure 4).

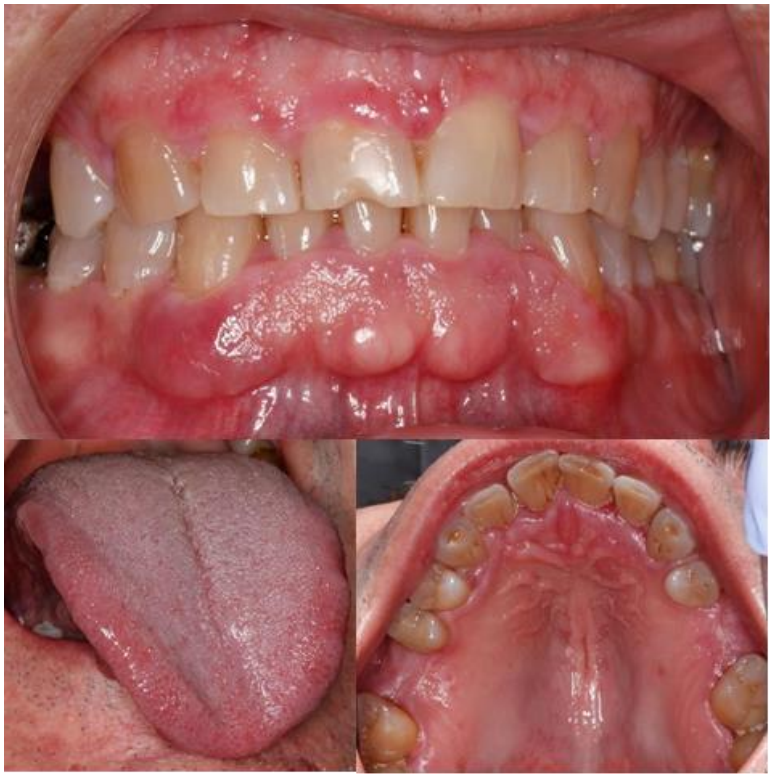

**Figure 4:** Control at 15 days. Complete remission of the disease

## Conclusions

Viral infections in the oral cavity manifest mainly in the form of self-limited vesicles, erosions and ulcers that heal spontaneously after 10-15 days.

They tend to affect mostly immunocompromised patients, however, it is not uncommon to find them in immunocompetent patients.

It is vitally important to carry out a good clinical examination, an exhaustive anamnesis, and a history prior to the condition in order to reach a certain diagnosis.

In these cases, the treatment will be predominantly symptomatic, except in those patients where serious systemic complications may arise.

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## Case Report

# Oral Candidosis: Review and Case Report

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## Summary

Oral candidosis is undoubtedly the most common infection that affects the oral mucosa. All professionals must be familiar with this entity and with its different clinical variants. Its diagnosis is usually straightforward but is sometimes overestimated. In the present work, we review the predisposing factors related to this pathology in a broad way and the therapeutic alternatives. In the clinical case we present, we focus on these factors and review the need to make a good diagnosis to achieve a good therapeutic result.

## Points of Interest

- The oral candidosis is very frequent in the oral cavity with different clinical forms of presentation.
- It is a disease "of sick man."
- To be successful in its treatment, predisposing factors must be controlled.

## Introduction

Among the different oral infections, candidiasis or oral candidosis plays a very important role, especially if we are talking about elderly people [1], or if we relate it to local treatment with corticosteroids; treatment, on the other hand, very common in multiple diseases of the oral mucosa [2]. This disease is caused by the growth of candida and their penetration into oral tissues, for this to occur, it is necessary that the host's defenses are weakened, since it is an opportunistic disease. Among the different species of candida, the most frequent is *Candida albicans* [3].

We know that the presence of species of the genus *Candida* in the oral cavity is a frequent finding, but few carriers are infected. On the other hand, the concentration of *C. albicans* in asymptomatic people is usually found in 300-800 colony-forming units per milliliter of saliva (CFU / ml), compared to counts higher than 20,000 CFU / ml, in patients with symptoms. However, these aspects are not always fulfilled [4,5].

Based on the above, it is usually called the sick man's disease [6] and it is a frequent process, with a prevalence of compatible symptoms of more than 4 / 1,000 patients in a general consultation. And if we take into account that most of the time it is almost asymptomatic, surely the prevalence is much higher; Furthermore, it is known that this prevalence increases in certain situations: extreme ages (newborns and the elderly), in the presence of mucosal-supported prostheses, xerostomia or in associated pathologies [6,7].

Although, as we have mentioned, *C. albicans* is the most prevalent oral species and the one that most frequently becomes pathogenic, about 20 genus and almost 90 species of yeast have been isolated from humans [6]. Most authors agree that colonization of the oral cavity by fungi, and more specifically by *C. albicans*, is very common among healthy people, and even more so in the elderly (between 7% and 65%). The factors that affect the carrier state are age, sex, quantitative and qualitative salivary alterations, the use of mucosal-supported prostheses, tobacco, health status, mainly immunological or endocrine alterations, certain pharmacological treatments, etc. It has even been possible to verify that there are variations in the carrier state throughout the day and a special affinity for colonizing the lingual dorsum, the palate and the buccal mucosa [4,6]. Regarding age, the mean prevalence values vary. In neonates, the numbers are relatively low (16%); they increase during the first 18 months of life (44%), decrease during childhood (6%) to, again, rise in adulthood and, especially, in senescence. Due to this and many other factors [already mentioned]: hyposalivation, the existence of removable prostheses, alterations of the immune and or endocrine system and polypharmacy, the elderly are frequently carriers of *C. albicans* [5].

## Etiopathogenesis

For *C. albicans* to go from commensal to pathogenic, three elements are required:
i.- virulence factors of the fungus,
ii.- alteration of defense mechanisms against candida infection, there is a host- microorganism interaction and
iii.-the participation of some predisposing factors essential for the infection to occur.

In fact, there are studies that show that the inoculation of *Candida* organisms to healthy individuals is not enough to cause disease; thus, there must be a series of factors that cause the microorganism to become infective. These factors can be divided into local, systemic and iatrogenic [8] (Table 1) [9].

**Table 1:** Predisposing factors for candida infection. Adapted from Otero Rey et al [9].

| **LOCAL PREDISPOSING FACTORS** |
|---|
| **They act on the mucous barrier:**<br>- Loss of continuity or integrity of the mucosa. Especially mucosal supported prostheses, which are common in elderly patients, simple epithelial fissuring even in well-fitted prostheses may be sufficient. Prostheses are an important reservoir, and this means that between 11 and 77% of prosthetic stomatitis result in a positive culture. Another chronic form related to age and repeated trauma is angular cheilitis.<br>- Changes in the thickness of the mucosa. As the epithelium atrophies, an element associated with aging, the penetration of candida is facilitated and *C. albicans* itself is capable of inducing changes, especially increased mitotic activity.<br>• **Salivary changes.** The decrease in quality and quantity is directly related to superinfection and in a very special way its acidification.<br>**Commensal flora.** The role is dual as shown by different in vitro studies.<br>• **Diet rich in carbohydrates.** Apart from the systemic effect, it also acts locally, its metabolism causes a decrease in local pH and high glucose concentrations increase the iC3b receptors in *C. albicans*, increasing its resistance to phagocytosis.<br>• **Tobacco.** Its influence is controversial, tobacco smoke has some anticandidal factor in saliva; However, smoking can favor the appearance of lesions in the mucosa that facilitate colonization. Smoke contains nutrients for *C. albicans*, and even some *Candida* species can convert aromatic hydrocarbons in smoke to carcinogenic metabolites. |
| **SYSTEMIC PREDISPOSING FACTORS** |
| • **Age.** Oral candidiasis, especially chronic candidal palatitis and angular cheilitis, is a common disease in the elderly, with a prevalence of 38% and 26% respectively. However, the elderly should not be considered a predisposing factor in itself, but they are more polymedicated patients and with more systemic pathology.<br>• **Endocrine disorders.** Diabetes is the most related, a fact not accepted by all scholars. The mechanism is not clear, the glucose concentration, the improvement in the ease of fungus adhesion or the associated use of prostheses and tobacco. Also, hyper and hypothyroidism, as well as pregnancy favor the development of the disease. In the latter case, hormonal changes are the main responsible.<br>• **Nutritional alterations.** Iron deficiency anemia is the most frequently involved, but not everyone shares this idea, the etiopathogenesis may be in the affectation that this deficiency causes in the epithelium.<br>• **Alterations of the immune system.** In patients with AIDS, elderly or not, it is the most frequent opportunistic infection, between 11 and 96%. Its appearance is directly related to CD4 levels. It is also a common finding in certain severe immunodeficiency syndromes (Di George syndrome, Glanzmann-Rinker syndrome). Mucocutaneous candidiasis pictures are also related to |

immunological and / or endocrine disorders.

• **Systemic diseases.** As discussed above, iron deficiency anemia is frequently associated with oral candidiasis in its various clinical presentations (chronic mucocutaneous candidiasis, chronic atrophic candidiasis, atrophic glossitis and angular cheilitis). In certain malignant diseases, the prevalence is also higher. Acute forms of oral candidiasis are common in patients with myeloproliferative syndromes.

**Blood groups.** The relationship between blood groups and vulnerability to infectious diseases, including fungal infections, is known. The H antigen functions as a receptor for C. albicans; therefore, people with group O are more susceptible to colonization and subsequent infection.

**IATROGENIC FACTORS**

• **Treatment with antibiotics.** The clearest example is that of acute atrophic candida glossitis or antibiotic painful tongue. It may happen that, under normal conditions, there is competition between *Candida* and bacteria for essential nutrients and / or for receptors on the surface of epithelial cells. On the other hand, some antibiotics can act systemically on the oral fungal flora. Antibiotics such as erythromycin, cotrimoxazole, and some aminoglycosides reduce the anticardia activity of neutrophils in vitro, while others such as penicillin and tetracycline increase the immune response against *Candida.* Likewise, the excessive use of antibacterial rinses can also promote oral fungal infection.

• **Treatment with corticosteroids.** Several studies have described that corticosteroids systemically favor the growth of *C. albicans*. However, the role of the underlying disease for which they are administered should be added to the effect of corticosteroids. The increasing use of inhaled corticosteroids, widely used in older patients, for the treatment of mild forms or as an adjunct in the most severe forms of asthma is accompanied by an increase in the oral prevalence of *Candida* and a greater predisposition to it. infection by this, but the incidence of oral candidiasis due to this cause is low and lacks clinical importance.

• **Contraceptives and replacement therapy.** There is a general belief that hormonal contraceptives predispose to vaginal candidiasis, but we do not have studies on oral prevalence.

• **Treatment with chemo and / or radiotherapy.** In some centers, fungal infections, particularly candidiasis, are the leading cause of death in leukemic patients undergoing chemotherapy. Neutropenia associated with medication and the direct toxicity of the products on the mucosa appear to be the causes most directly related to superinfection. Thus, the frequency of oral candidiasis in patients undergoing chemotherapy treatment has
been estimated at 16% for cases of leukemia and 7% for patients with solid tumors.

## Clinic

Classically, there are acute forms, of short evolution and that remit with treatment, and chronic forms, of long evolution and generally resistant to treatment, probably due to the persistence

of predisposing factors. The clinical forms of oral candidiasis in the elderly [those that we will most frequently find in the dental clinic] are: pseudomembranous candidiasis, erythematous candidiasis, both acute and chronic, chronic hyperplastic candidiasis, oral alterations commonly associated with candidiasis (subplaque palatitis, commissural cheilitis, rhomboid glossitis and hairy tongue) chronic mucocutaneous forms of candidiasis in the elderly.

## Pseudomembranous Candidiasis (acute)

It is a typical form in infants (Muguet), but it can appear in debilitated elderly or in elderly people after treatment with antibiotics and / or corticosteroids, with malignant diseases or in situations of alteration of immune mechanisms (Figure 1). They can present in an acute form, less than 15 days of evolution, or in a chronic form, persisting over time due to the persistence of predisposing factors. It manifests itself in the form of whitish or yellowish, soft and creamy, semi-adherent plaques, located in any part of the oral mucosa. They are described as "snowflake-like or milk- clot-like" and are easily rubbed off and leave areas of normal or slightly erythematous mucosa. Whereas, in infants, the plaques often cover large areas of mucosa, in the elderly, they are interposed between erythematous lesions. Symptoms are usually very scarce, although on occasions they may report loss of taste, bad taste in the mouth and burning, or even pain [1].

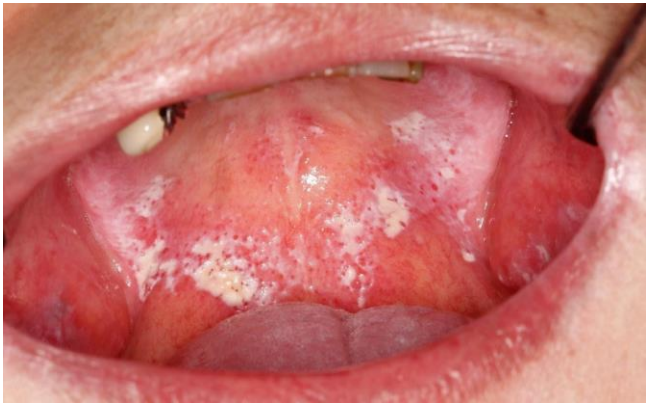

**Figure 1**: Pseudomembranous candidiasis in an immunocompromised patient.

## Acute Erythematous Candidiasis

The lesions appear as areas of erythema, larger or smaller and any part of the oral mucosa can be affected, but it has a certain affinity for being located on the lingual dorsum. Some authors consider that it may appear primarily or be secondary to the acute pseudomembranous form.

Others, however, only recognize the existence of a primary form of it that would affect the back of the tongue after indiscriminate administration of broad-spectrum antibiotics and / or corticosteroids [1,10]. When it affects the back of the tongue, it causes a depapilation of the lingual mucosa accompanied by pain and stinging, with difficulty in ingesting acidic, spicy or hot foods; in fact, it is the only variety of oral candidosis that causes real pain. Some authors call it a "candida tongue" or an "antibiotic painful tongue", since many of it are related to the use of broad- spectrum or long-acting antibiotics (especially amoxicillin with clavulanic acid) [7,10] (Figure 2).

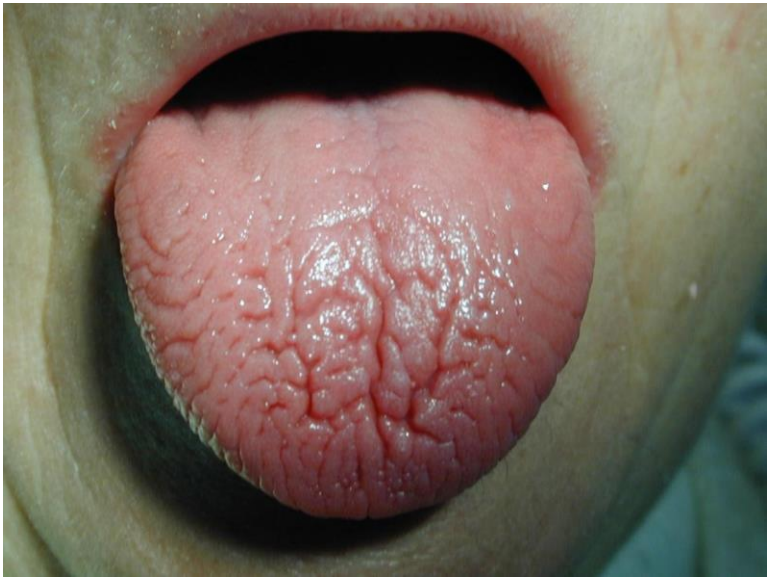

**Figure 2:** Acute candidiasis on the tongue five days after Augmentin 875-125® 3 times / day.

## Chronic Erythematous Candidiasis

It includes two clinical forms: chronic erythematous candida palatitis and chronic erythematous candida glossitis:

### Chronic Erythematous Candidal Palatitis

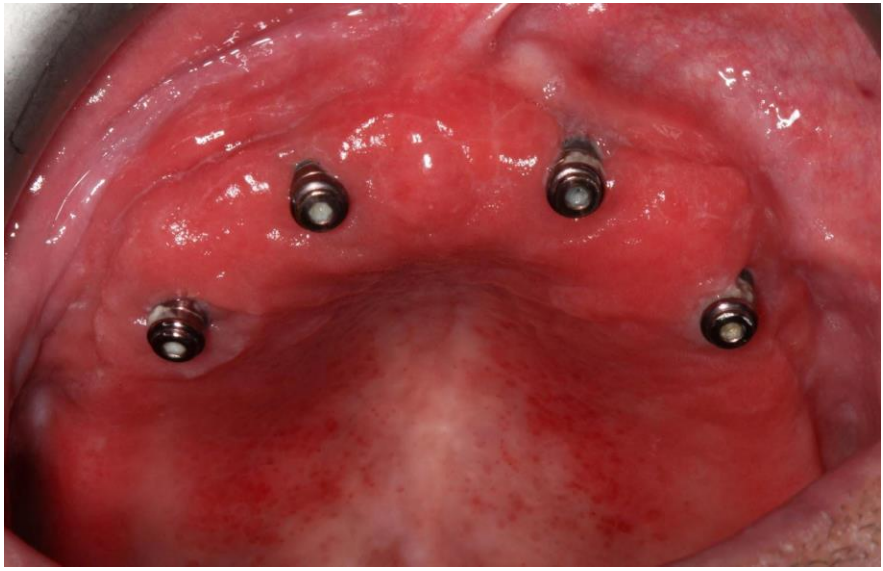

**Figure 3:** Chronic erythematous candidiasis in an elderly patient with a prosthesis on implants.

Related to three situations in a special way with immunosuppression, HIV infection, and above all, and in the case of the elderly, chronic lung diseases that cause dry mouth and the use of aerosols and / or sprays (COPD, asthma, etc. ) and above all, the candidal superinfection of a prosthetic stomatitis, in which case we speak of prosthetic stomatitis or prosthetic stomatitis associated with Candida [see later]. From the clinical point of view, the palatal mucosa appears reddened, with atrophy of the affected mucosa, either partially or the entire palate. It is asymptomatic and may present taste alterations or a bad taste in the mouth, but it is usually a reason for consultation.

### Chronic Erythematous Candida Glossitis

It is often difficult to distinguish from acute except for the duration of the lesions. It manifests as more or less extensive areas on the dorsal surface of the tongue, in which the filiform papillae have disappeared, giving rise to a smooth reddish surface. It is related to two fundamental situations, sometimes coincident, with xerostomia and associated with chronic erythematous candidal palatitis. In the latter case you can find a classic mirror image. The symptoms are scarce and at most, there is an alteration of taste that is not accompanied by pain, or at most a slight stinging.

## Chronic Hyperplastic Candidiasis or Leukoplakia-Candidiasis

It is a rare form. It is characterized by the presence of white plaques that do not come off with scraping, persistent over time and are located in order of frequency in the yugal mucosa (especially in the retrocommissural area), tongue, lips and palate. Sometimes the lesions are bilateral, retrocommissural with a triangular shape with an anterior base and posterior vertex. We differentiate between the homogeneous form, which appears as a white, uniform, adherent and asymptomatic plaque; and on the other hand, the nodular, painful form, characterized by the presence of multiple whitish nodules in an erythematous mucosa. It is important to keep in mind that the only form of candidiasis in which biopsy is practically always indicated to differentiate it from other processes. Clinically and histologically it is indistinguishable from leukoplakia. Only a good response to antifungal treatment confirms the diagnosis [7,9].

## Oral Lesions Commonly associated with Candidiasis

### Prosthetic Stomatitis

Prosthetic stomatitis, also called subprosthesis stomatitis or subplate palatitis, is a clinical entity that appears in patients who use full or partial mucosa-supported prostheses. It is characterized by erythematous changes in the mucosa on which

the prosthesis sits. It is more frequent in the palatal mucosa and usually affects patients over 50 years of age and it seems to be more common in women [11,12]. We could consider it a traumatic injury in which different factors intervene: poor hygiene, non-stop use of the prosthesis, continuous microtrauma on the mucosa, due to a mismatch or poor adaptation of the prosthesis, etc. Its prevalence among removable prosthesis wearers is highly variable (11-77.4%); and more frequently in the wearers of complete prostheses than in the wearers of partial prostheses [12]. However, we must not forget that the presence of candida in patients with prosthetic stomatitis and in prosthetic wearers without clinical evidence of stomatitis is similar (86-93%). However, in patients with prosthetic stomatitis, there is a higher density of yeast (CFU / ml) on the surface of the prosthesis in contact with the palatal mucosa and on that mucosa. In fact, fungal colony counts are 100 times higher in patients with stomatitis (0.3%) compared to those obtained in patients with intact palatal mucosa (0.002%) [11], that is why it is recommended to confirm the diagnosis, by the demonstration of yeasts in large quantities, mainly through a smear, taken from the underlying mucosa and even from the prosthesis. However, even when few yeasts are isolated from dental plaque, it usually improves greatly with antifungal treatment. Although there are many treatments, some of them alternative [13], for some authors it can be improved simply by combining the prosthesis [14]. Ceballos et al [15], based on the initial criteria of Newton [16], classify them as: Grade I: reddish stippling on the palatal mucosa; Grade II: hyperemia of the mucosa with smoothing and atrophy of the same; and Grade III: hyperemia of the mucosa with a nodular or granular appearance. In this degree, the mucosa resembles a paving of small nodules, which do not disappear once the *Candida* have been removed.

## Commissural or Angular Cheilitis due to Candida

Also called "mouthpiece" or in Spanish "perleche", they affect the angles of the mouth. They are generally bilateral lesions in the commissures, characterized by small erosions, fissures and cracks with crusty formations around them. Symptoms vary from intense pain, even with bleeding to a nonexistent clinic. Yeasts

and staphylococci are usually isolated and may disappear after treatment with antimicrobials, but the fact that the lesions recur after cessation of medical treatment indicates that there are local or systemic predisposing factors to which the infection is secondary. These factors include the loss of vertical dimension (a circumstance that frequently occurs in prosthesis wearers) and vitamin deficiencies, especially riboflavin, iron and folic acid. Angular cheilitis is sometimes observed together with prosthetic stomatitis associated with Candida, often indicating the progression of Candida infection from the mucosa covered by the prosthesis towards the corners of the mouth [11]. Ohman et al [17] (1985) classified it into four groups: Type I: Localized, with minimal skin lesion; Type II: Fissured, with stripes, more extensive in length and depth; Type III: With intense fissures radially from the angle to the skin and Type IV: Erythematous, without fissures. It extends to the edge of the lips. While type I is common in dentate patients, the other three are characteristic of patients with dental prostheses [9].

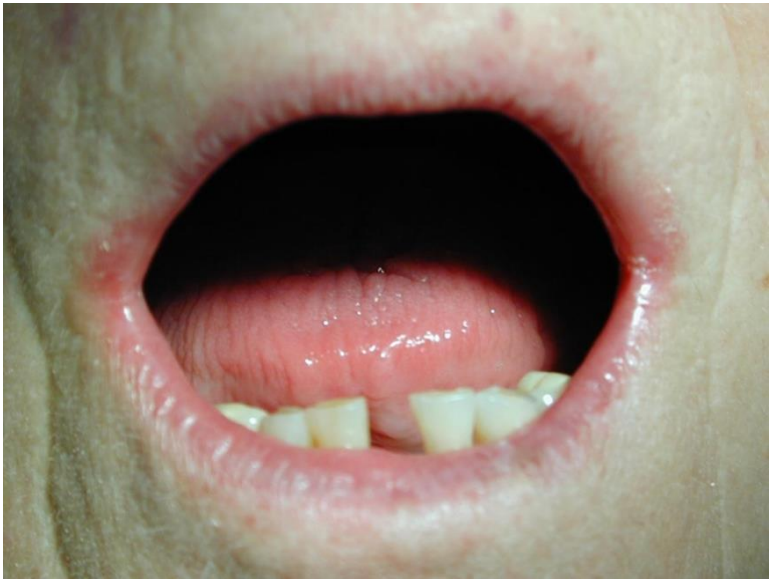

**Figure 4:** Angular cheilitis in a patient with loss of vertical dimension, anemia, and candidal superinfection.

## Median Rhomboid Glossitis

This lesion, described by Brocq (1907) with the name of median leangic glossitis [9] and one of the first references of which is from Breiner [18], is a relatively rare alteration of the tongue (0.2-3.0%); more common in males. There are characteristic histopathological changes. Diagnosis is usually clinical: it appears in the midline of the tongue dorsum, in front of the circumvallated papillae, in the form of a reddish, rhomboid, flat and sometimes mameloned area, which can protrude 2 to 5 mm from the surface and in the filiform papillae are not observed, in some series it is more prevalent in older people [19]. Classically, it has been considered a congenital anomaly due to the persistence of the odd tuber, but the low frequency of lesions at childhood ages and the absence of a family history of median rhomboid glossitis played down this theory. Later, it was postulated that it could be the consequence of a chronic infection by *C. albicans*, favored by smoking, minor trauma or prosthetics, and many authors supported the theory that, in fact, it was a chronic form of oral candidiasis [7]. Histologically, it is characterized by the absence of filiform papillae, an inflammatory infiltrate, predominantly of lymphocyte lineage, and hyperplasia of the spinous layer. Hyphae can be seen in the lingual parakeratinized area and in the superficial spinous layer of the epithelium [10].

## Hairy Black Tongue

It is frequently related to infection with *C. albicans.* It is common in the elderly [but also occurs in young people], especially males (Figure 5). It is due to an increase in the size of the filiform papillae at the end of which villi are formed that take on a dark color, due to the oxidation of the keratin. It usually affects the middle third of the tongue, but it can spread over its entire surface. The use of antibiotics and antiseptics (chlorhexidine) alters the ecology of the oral environment, contributing to the considerable proliferation of saprophytic microorganisms, including *Candida*, as well as bacteria with pigmentary capacity. The hairy black tongue can also be a complication of chemo and / or radiotherapy, where the decrease

in the host's defensive capacity allows the development of fungi and other unusual bacteria [20].

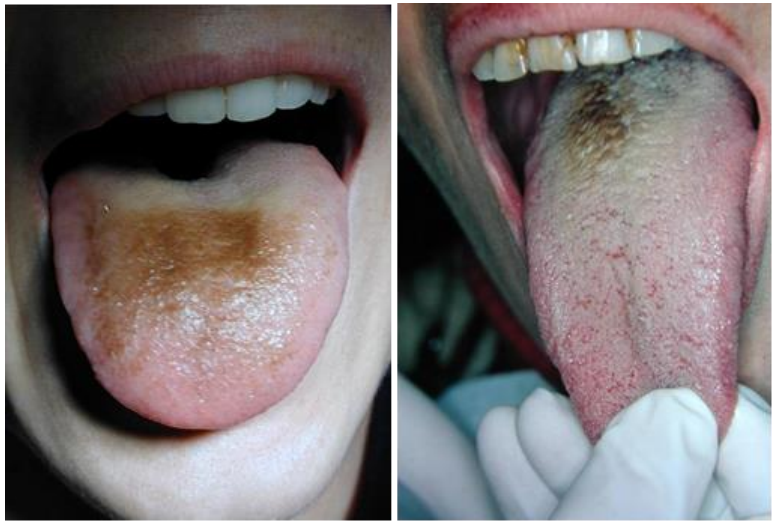

**Figure 5:** Hairy black tongue, unrelated to candidiasis in a young patient (A) with poor dietary habits and abundant coating, and the same in an elderly heavy smoker (B).

## Chronic Mucocutaneous Candidiasis

Just two words about chronic mucocutaneous candidiasis, the only one that can appear in older people is the diffuse form. It starts late (from the age of 55) and is the least frequent of all. It is not hereditary, and candidiasis is the only manifestation of the disease, which manifests itself occupying large areas of skin, oral mucosa and nails.

### Diagnosis

The clinic of this entity is fundamental, and the laboratory diagnosis is based on the demonstration and identification of the fungus in clinical samples (smear or culture) and / or serological diagnosis. But if we think that *Candida* is a common commensal in the oral cavity, its microbiological demonstration is not significant in the absence of symptoms suggestive of candidiasis;

It is therefore necessary to establish the clinical significance of the isolation of the microorganism. Neither has a definitive "critical" value been established for the colony count, which allows differentiating between commensalism and disease. For this reason, there is a need to reach a consensus between the clinic and the laboratory to reach a diagnosis of oral candidiasis [21]. Otero Rey et al [9] propose two guidelines for action (Table 2).

**Table 2:** Diagnosis of oral candidiasis. Adapted from Otero Rey et al [9].

| |
|---|
| **Clinical suspicion**<br>It's fundamental |
| **Microbiology**<br>The cytological smear (by scraping or swab) is usually useful.<br><br>[*The material obtained is spread on a slide, they can be treated with a 20% KOH (potassium hydroxide) solution and subsequent microscopic observation. Other times, observation is done after smear material is stained with PAS, GRAM, Hematoxylin-Eosin, or Pap. In this way, C. albicans is identified by observation of fungal cells (blastopores with or without hyphae or pseudohyphae)]*.<br><br>*[Identification is based on culture. A widely used medium is that of peptone-glucose (dextrose) or peptone-maltose agar which, when described in 1896 by Sabouraud, adopted its name. There are specific means that make it possible to colorimetrically differentiate specific species of Candida (Microstix-Candida®, Oricult_N®). Recently, the CROMagar medium has been introduced; this contains a chromogenic substrate that allows differentiating the colonies of C. albicans, C. krusei*<br>*and C. tropicalis, which grow green, pale pink and blue gray, respectively]*. |
| **Histology**<br>A biopsy should only be performed in those lesions in which there is a difficult differential diagnosis, in cases of hyperplastic candidiasis, when there are obvious doubts in the diagnosis and when the process does not respond to the correct treatment.<br><br>*[They may go unnoticed on a routine Hematoxylin-Eosin stain. Therefore, staining with PAS, methenamine silver, GRAM or Gomori is recommended to identify fungal elements. However, it does not allow to differentiate the species]*.<br><br>The demonstration of tissue invasion by fungal elements constitutes a diagnostic criterion; It is important to consider it because *Candida* is a common commensal of the oral cavity, both in humans and in animal research. |

| |
|---|
| Immunology<br>Lehner et al [23] was probably the first to use immunofluorescence techniques to detect the presence of *C. albicans*. Today, serum antibodies (IgM, IgA, IgE) can be detected by indirect immunofluorescence and ELISA test. However, the usefulness of this type of technique, being able to use other simpler and more reliable ones, remains in doubt. But the reality is that they are practically not used for the laboratory diagnosis of oral candidiasis [22]. |
| Proposal |
| In pseudomembranous candidiasis, the technique of choice will be a smear. A culture can be done, but it will not be final. |
| In erythematous candidiasis, to confirm the diagnosis the presence of the fungus must be determined microbiologically. For this, a smear must be made. With the culture we can have false positives. |
| In hyperplastic candidiasis, smears may show abundant fungal and inflammatory cells. A biopsy is always recommended, since the existence of dysplastic phenomena in the epithelium must be ruled out. |
| In patients with prosthetic stomatitis, the diagnosis is also clinical. Complementary tests (smears) have to confirm the possible participation of Candida in the process to be able to define it as candidiasis. |
| Angular cheilitis has a clinical diagnosis. Candida superinfection must be demonstrated by smear. |
| In rhombic glossitis, the diagnosis will be eminently clinical. A biopsy should only be performed in situations in which the presence of a tumor process is suspected. |
| In the hairy black tongue, a clinical diagnosis will be made. The presence of candida will be confirmed by smear. |

## Treatment

First of all, we have to ask ourselves: 1. Are we sure it is a yeast infection? The answer is in the diagnosis, where there must be a clinical and microbiological or histological confirmation. 2. What clinical type is it? According to the clinical data presented. 3. Why? We will look for the predisposing factors related to the appearance of candidiasis.

Second, the elimination or attenuation of the predisposing factors detected is essential for the success of the treatment; being this the fundamental aspect in the therapy of this infection in the elderly; and without which, a recurrence of the lesions will probably occur after cessation of the applied antifungal therapy [1,7,9,24].

Third, a series of hygienic measures must be implemented previously to drug treatment. We will use mild antiseptic alkaline solutions (bicarbonate, sodium borate, magnesium hydroxide) to wash the oral cavity and that hinder the colonization and growth of fungi. Other coloring substances, such as gentian violet 0.5-1%, there are different natural substances that also act on gram + germs.

In the case of stomatitis due to prosthesis, in addition to night rest without prosthesis, disinfection of the prosthesis is recommended; the antiseptic of choice is 0.2-0.12% chlorhexidine and / or sodium hypochlorite, without it being a resin prosthesis [1,25-27].

Finally, treatment is started with antifungal therapy, locally or topically as well as a systemically, if deemed appropriate. The decision to treat superficial infections with a topical or systemic agent depends on the fungus, its location, and the extent of the lesion. In general, the simplest cases are treated topically, while the more severe forms of the disease are treated systemically. Topical treatment requires sufficient contact time between the drug and the oral mucosa. In order to avoid recurrences, it is recommended to continue therapy 2-3 weeks beyond the cessation of signs and symptoms. Treatment with topical antifungal agents after elimination [7] or control of predisposing factors is the most effective way to treat oral candidiasis in the elderly. Topical agents are available in the form of oral rinses, oral tablets, vaginal tablets, and creams. The different forms of application can be combined to increase the topical effect. In general, oral rinses provide less drug contact time and therefore less efficacy. They are preferably used in patients with oral dryness, who have difficulty dissolving the tablet forms. Tablets could be the most effective form of medication since they dissolve slowly in the mouth and provide a longer contact time with the oral environment and pharynx, but they are complex to use in dry mouth and are also usually sweetened to improve taste [9]. To improve contact, we can use different adhesives or thickeners, such as orabase, chitosan, zilactin or guar gum. It has been experimentally proven that the association of nystatin with orabase or chitosan produces a significant improvement, both at a

clinical, microbiological and histological level, of the lesions caused by *C. albicans* compared to nystatin alone [28,29].

When topical agents are not sufficient to control the infection, one must resort to systemic agents. The concomitant use of a topical agent facilitates a faster cure of the infection and allows to reduce the dose and duration of systemic therapy. Oral systemic drugs are frequently used in outpatient treatment; systemic candidiasis in immunosuppressed patients generally require intravenous medication (in hospitals).

In Table 3 we present the topical antifungals [nystatin, amphotericin B, and azole derivatives (miconazole, clotrimazole, econazole and ketoconazole)] and systemic [ketoconazole, fluconazole, itraconazole, miconazole, amphotericin B, flucytosine and griseofulvin] most frequently used and some of its most significant characteristics [9,28-32].

**Table 3:** Characteristics of only significant antifungals for systemic use.

| **Ketoconazole** |
|---|
| It is used in tablets of 200 mg, 1 or 2 daily for 3-4 weeks, being even more effective in genital candidiasis than oral. Noteworthy is its hepatotoxicity with elevated transaminases and sometimes abdominal pain and itching. On the other hand, absorption depends on adequate gastric secretion, therefore the simultaneous administration of drugs that inhibit gastric secretion or its acidity (anticholinergics, antacids, H2 antagonists) as well as other drugs whose effectiveness may be reduced<br>(tuberculosis, theophylline, etc.) |
| **Fluconazole and Itraconazole** |
| Fluconazole is possibly the systemic antifungal of choice. They inhibit the enzymes associated with cytochrome P 450 and block the synthesis of ergosterol. They are used in tablets with doses of 50-200 mg / day for 1 to 4 weeks. They have low toxicity, sometimes nausea, vomiting, diarrhea and headache. They are more powerful than ketoconazole but significantly more expensive. On occasions, fluconazole has been used preventively in cases of immunosuppression to avoid recurrences, but we consider that this could be the reason for the appearance of resistance |
| **Miconazole** |
| In situations of systemic candidiasis, miconazole can be used orally or intravenously.<br>It is little used systematically |
| **Amphotericin B** |
| All and that it has topical absorption, it will be used in severe candidiasis and will be |

| |
|---|
| administered intravenously |
| **Flucytosine** |
| Fluoracil analog that is incorporated into fungal RNA, resulting in poor protein synthesis; blocks fungal DNA synthesis. Its antifungal power has been known for years. It develops resistance when used as the sole antifungal, hence it is frequently<br>used in combination with amphotericin B. |
| **Griseofulvin**<br>Fungistatic action. It interferes with mitosis and the synthesis of the cell wall and nucleic acids. It has quite a few side effects. Contraindicated during pregnancy. It binds to the keratin of developmental tissues. It is not currently a commonly used antifungal. |

## Case Report

38-year-old female RGH patient with oral candidiasis. She is a patient with immunosuppression (HIV +) with antiviral therapy, antidepressants, with hyposialia and xerostomia. Smoker of 5-10 cigarettes / day.

On clinical examination, he presented erythematous lesions on the oral mucosa, more marked on the palate (Figure 6), and white lesions that were removed by scraping through different areas of the mucosa (Figure 7). They are asymptomatic and have been evolving for 10 days. She is not a prosthesis wearer.

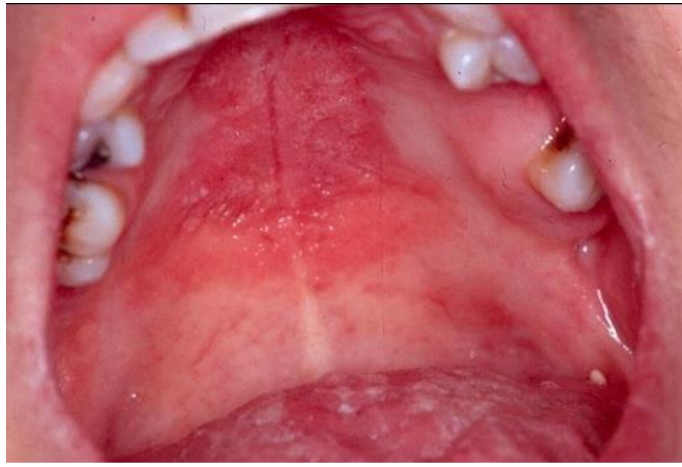

**Figure 6:** Erythematous lesions in palatal mucosa not related to prosthesis.

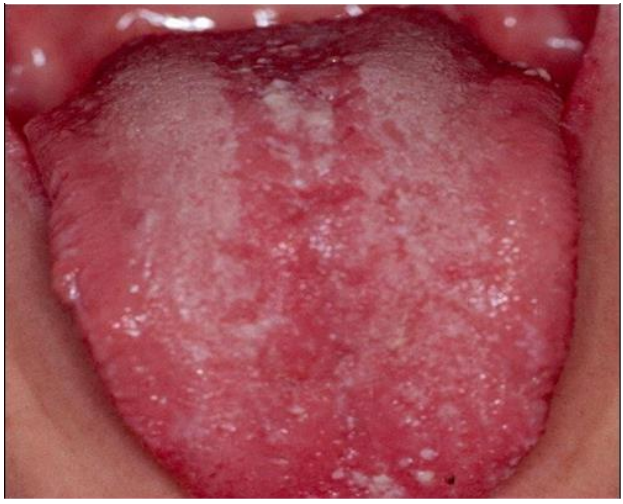

**Figure 7**: Erythematous and white lesions (detached by scraping) on the lingual mucosa, asymptomatic with 10 days of evolution.

With clinical suspicion of oral candidiasis, a smear is made on the palatal mucosa and the back of the tongue resulting in the presence of candidal pseudohyphae between the epithelial cells (Figure 8). In the culture it is confirmed that it is *Candida albicans* (Figure 9).

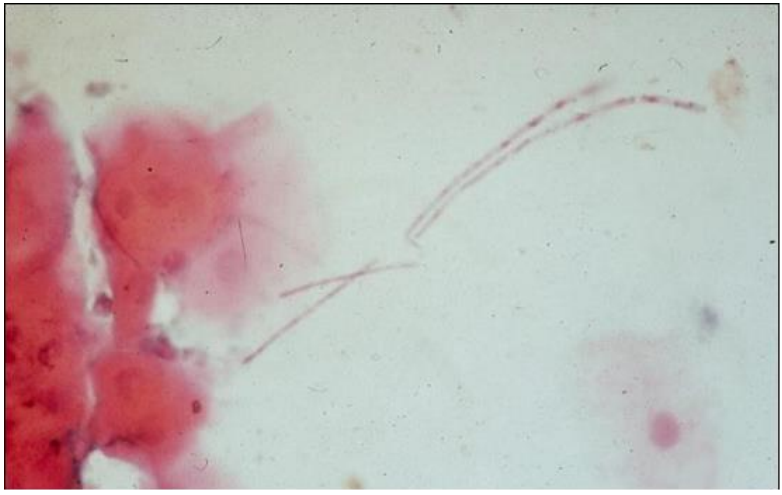

**Figure 8:** Smear of the oral mucosa stained with eosin-hematoxylin showing pseudohyphae of candida between the epithelial cells.

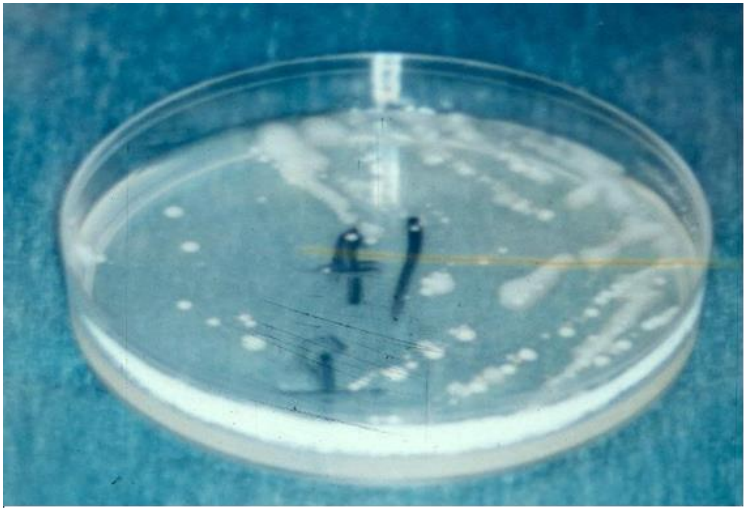

**Figure 9:** Culture in Sabouraud with growth at 48h of Candida albicans colonies.

The patient is treated with topical antifungals, specifically Nystatin oral suspension 3 times a day, 3 minutes each time for 2 weeks. The patient is checked, and the lesions are checked for disappearance (Figure 10). The patient is recommended hydration guidelines by increasing water intake and frequently "sucking" sugar-free candies.

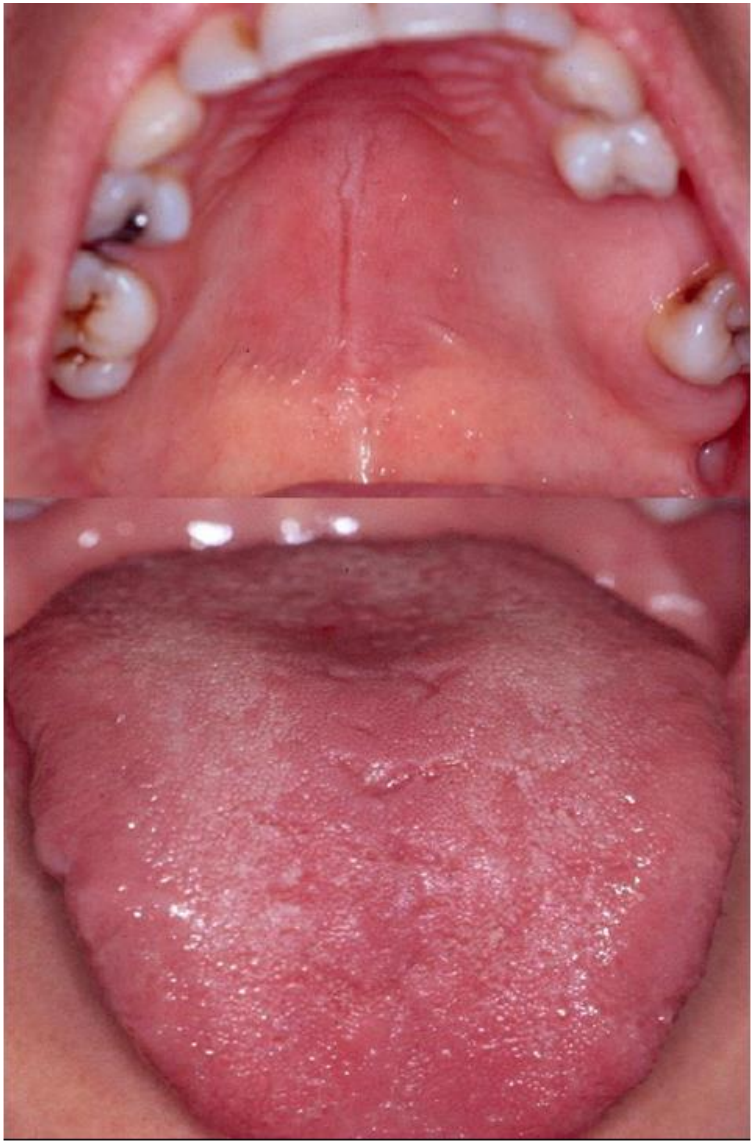

**Figure 10:** Appearance of the palate of the patient with oral candidiasis treated with Nystatin in oral suspension for 2 weeks. The disappearance of the yeast lesions is observed.

## Discussion

Being an opportunistic pathogen, oral candidosis is related to predisposing factors that modify the host's response and favor infection. In this case the situation of immunosuppression to which is added a situation of xerostomia with hyposialia.

Although sometimes the culture may not be done, especially if the symptoms are clear and the patient responds well to treatment, in others it may be necessary to do so.

We believe that the clinic is essential for the diagnosis, which must be confirmed with a smear. The culture, with less diagnostic value, helps us to identify the species and if necessary, to know the antifungal of choice by means of an antibiogram. Based on this statement, it may not be shared, we present two clinical cases, incorrectly treated as candidosis for weeks (Figures 11 and 12).

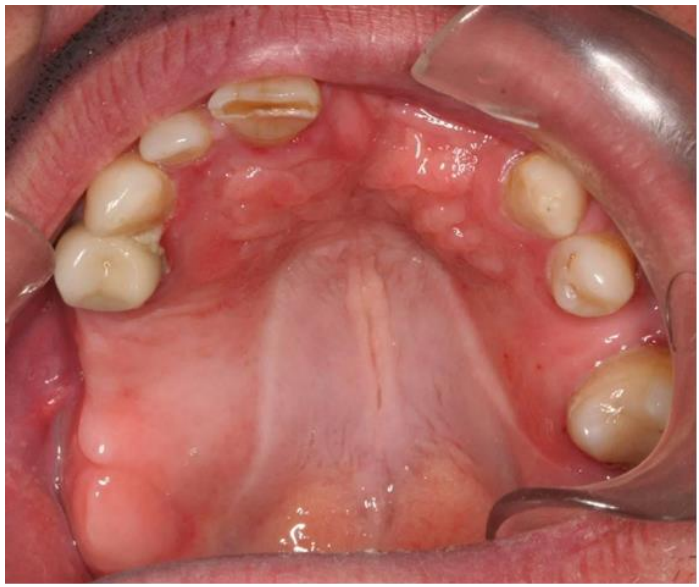

**Figure 11:** A 68-year-old male with chronic, asymptomatic erythematous lesion on the palate. Metal upper removable prosthesis holder.
*[The patient goes to his family doctor, he takes an oral culture and tests positive for candida, which diagnoses him with candidiasis. He treats it with nystatin in aqueous solution (Mycostatin R) for 3 weeks without appreciating improvement.*

*If we look precisely, the situation corresponds to a subplaque palatitis related to the use of his prosthesis, which, as we have seen, consists of a traumatic injury and which can sometimes be superinfected with candida. You do not need drug treatment, or it will be sufficient. The fundamental thing is to act on the prosthesis, with adequate hygiene and resting its use, not sleeping with it]*

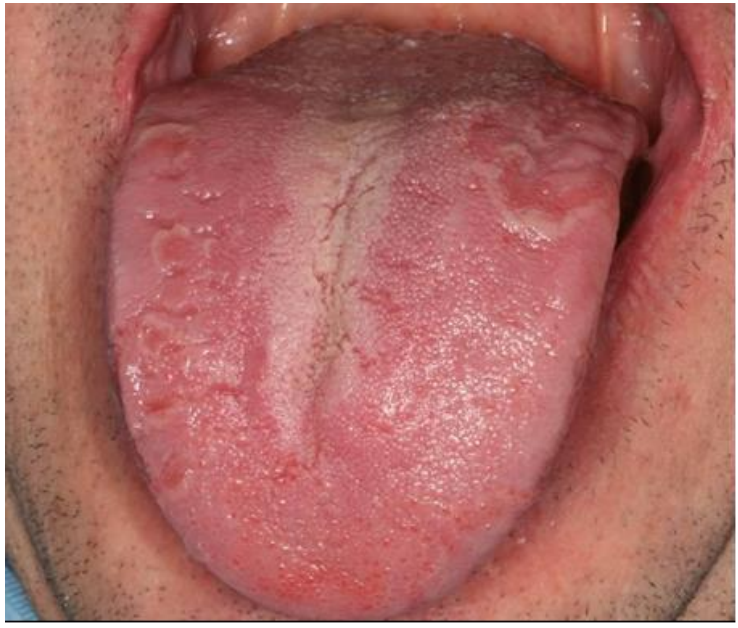

**Figure 12:** 44-year-old male patient diagnosed with candidiasis by his family doctor by culture and treated with oral antifungals (Mycostatin oral suspension R) for 3 weeks.
*[During the visit it is explained that it is not an oral yeast infection. Presents alterations in the tongue compatible with geographic tongue or benign migratory glossitis. It does not need pharmacological treatment].*

Antifungal drugs and elimination, whenever possible, of predisposing factors are used in the treatment. In the case we have described, as immunosuppression cannot be cured, we recommend hydration to improve this dry mouth situation and frequent reviews of your immune status. This will cause possible recurrences throughout your evolution as an immunosuppressed patient.

## Conclusions

Candidosis is a very common entity that is not always diagnosed in the correct way. It is an opportunistic infection in which it is fundamentally to control the associated risk factors, both local and systemic.

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## Case Report

# HIV-AIDS Update: Frequent Oral Lesions. About a Case

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## Abstract

The Human Immunodeficiency Virus (HIV) has been the biggest pandemic of our time, and there is expanded around the planet. Until now, there is no treatment for this disease, although it has been achieved that infected people can enjoy a good quality of life. Oral manifestations are frequent in seropositive and in AIDS patients, being the most common lesions oral candidiasis and non-specifics ulcers. We have to be able to know these oral

lesions and control oral health of these patients, to take an optimal immune state.

## Points of Interest

- We have to know what is HIV and AIDS and that involve for our patients
- Maintain a good oral health state, can recover immunologic state of patients
- To help at diagnosis, evolution and develop of these disease we have to know oral lesions associated with them.

## Introduction

Infection by Human Immunodeficiency Virus (HIV) can be defined like the biggest pandemic of our time with human, social and economic serious implications. It is a chronic infection. In the first time, these disease is characterized by asymptomatic phase (these can last for years), until appeared the first symptoms because of immunosuppression that involve manifestation of Acquired Immune Deficiency Syndrome (AIDS) [1].

The 2020 Joint United Nations Programme of HIV/AIDS (UNAIDS), reported at the end of 2019 that 38 million people were HIV positive, which 7'1 million (approximated 19%) did not know they were infected [2]. In 2018 in Spain were diagnosed 3244 new cases of HIV, which 85'3% was men and 47'6% of these were late diagnosis [3]. It is estimated that 25-30% seropositive patients did not know that they were infected by HIV. It seems that they were responsible about 50-70% of new infections [4].

HIV is a RNA retrovirus that complicate the body defense mechanisms, causing a decrease in CD4 cells [5]. The CD4 T lymphocytes are the main target for HIV due to the affinity of this virus for the surface markers of CD4+. CD4 lymphocytes coordinate various immunological functions and the progressive loss of these functions leads to a deficiency in the immune response [6].

This virus attacks immunological system, causing suppress immunity of the infected people. This fact weakens host defenses and the human body becomes prone to opportunistic infections and cancers [7-12]. Some studies shown an association between the development of opportunistic diseases and absolute number (per µL of blood) or CD4 T lymphocytes percentage. Whenever decrease the number of CD4, increase the risk and severity of the opportunistic diseases [13-15].

The total CD4 lymphocytes count is a laboratory marker to value the immune suppression in HIV infections. Nowadays, it is use like parameter/important criteria for HIV/AIDS, together with clinic manifestations and viral load [16-19].

At present be use the 1993 classification of control disease center (CDC) (Table 1) [20].

**Table 1:** Mixed classification (clinical and immunological) of patients by HIV/AIDS [20].

| Clinical categories | | | |
|---|---|---|---|
| Immunological categories | A | B | C |
| 1. > 500 CD4 o CD4 > 29% | A1 | B1 | **C1** |
| 2. 200-499 CD4 o CD4 14-28% | A2 | B2 | **C2** |
| 3. < 200 CD4 o CD4 < 14% | A3 | B3 | **C3** |
| All categories are exclusive and the patient should be classified in the most advanced possible. In bold the categories considered with AIDS in Europe. In the USA, in addition to these, categories A3 and B3 are considered AIDS | | | |

These 3 categories correspond to the number of CD4 T lymphocytes per microliter of blood or the absolute percentage; and it serves to management clinically and therapeutically of HIV infected people [21,22].

Category A applies to primary infection and to patients who are asymptomatic with or without persistent generalized lymphadenopathy. Category B applies to patients who present or have presented illnesses related to HIV (not belonging to category C) or whose management or treatment may be complicated due to the presence of HIV infection. Finally,

category C is applied to patients who present or have presented any of the complications already included in the definition of AIDS when the patient has a clinical diagnosed by HIV infection and there are no other causes of immunodeficiency that can explain it [6,20]. Table 2 shown the pathologies included in category C.

**Table 2**: Pathologies included in category C, of 1993 CDC [6].

| |
|---|
| Candidiasis of bonchi, trachea, lungs or esophageal |
| Invasive cervical cancer |
| Coccidiodomycosis, diseminated or extrapulmonary |
| Cryptococcosis, extrapulmonary |
| Cryptosporidiosis, chronic intestinal (greater tan 1 month duration) |
| Cytomegalovirus disease (other tan liver, spleen, or nodes) |
| Cytomegalovirus retinitis (with loss of visión) |
| Encephalopathy, HIV-related |
| Herpes Simplex: chronic ulcer(s) (greater than 1 month duration); or bronchitis, pneumonitis or esophagitis |
| Histoplasmosis, disseminated or extrapulmonary |
| Isosporiasis, chronic intestinal (greater than 1 month duration) |
| Kaposi's sarcoma |
| Burkitt's lymphoma (or equivalent term) |
| Inmunoblastic lymphoma (or equivalent term) |
| Primary lymphoma of brain |
| Mycobacterium avium complexo r M. Kansasii, disseminated or extrapulmonary |
| Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary) |
| Mycobacterium, other species or unidentified species, disseminated or extrapulmonary |
| Pneumocystis carinii pneumonia |
| Recurrent pneumonia |
| Progresive multifocal leukoencephalopathy |
| Recurrent salmonella septicemia |
| Toxoplasmosis of brain |
| Wasting syndomre due to HIV |

In recent years, the most common via of transmission is in men who have sex with men, followed by heteroxexual transmission and later by injecting drug users [23].

In addition to systemic pathologies, oral lesions are frequently found in seropositive subjects due to dysregulation of the oral microbiota and the consequent development of opportunistic infections [24].

Today, the 1993 classification of oral lesions in HIV / AIDS patients is still valid (Table 3) [25].

**Table 3:** Oral lesions associated with HIV infection [25].

| **Group 1. Lesions strongly associated with HIV infection** | **Group 2. Lesions less commonly associated with HIV infection** | **Group 2. Lesions seen in HIV infection** |
|---|---|---|
| Candidiosis:<br>-Erythematous<br>-Pseudomembranous | Bacterial infections:<br>-Mycobacterium avium-intracellulare<br>-Mycobacterium tuberculosis | Bacterial infections:<br>-Actinomyces israelii<br>-Escherichia coli<br>-Klebsiella pneumonia |
| Hairy leukoplakia | Melanotic hyperpigmentation | Cat-scratch disease |
| Kaposi's sarcoma | Necotrizing (ulcerative) stomatitis | Epitheloid (bacillary) angiomatosis |
| Non-Hodgkin's lymphoma | Salivary gland disease:<br>-Dry mouth due to decrease salivary flow rate<br>-Uni or bilateral swelling of major salivary gland | Drug-reactions:<br>-Ulcerative<br>-Erythema multiforme<br>-Lichenoid<br>-Toxic epidermolysis |
| Periodontal disease:<br>-Linear gingival erythema<br>-Necrotizing gingivitis<br>-Necrotizing periodontits | Thrombocytopenic purpura | Funal infections other than candida:<br>-Cryptococcus neoformans<br>-Geotrichum candidum<br>-Histoplasma capsulatum<br>-Mucocraceae<br>-Aspergillus flavus |
| | Ulceration NOS (nor otherwise specified) | Neurological disturbances:<br>-Facial palsy |

| | | |
|---|---|---|
| | | -Trigeminal flavus |
| | Viral infections:<br>-Herpes sumplex virus<br>-Human papillomavirus lesions:<br>-Condyloma acuminatum<br>-Focal epitelial hiperplasia<br>-Verruca vulgarias<br>-Varicella zoster virus:<br>-Herpes zoster<br>-Varicella | Viral infections<br>-Cytomegalovirus<br>-Molluscum contagiosum |

## Clinic Case

A 30-year-old man attends at the University of Barcelona Dental Hospital. The reason is generalized pain and stinging throughout the mouth. The patient tells us that he is HIV positive and that he is under treatment with antiretrovirals. Although he has not attended his doctor visits control for about 6 months and that he does not take the medication in the correct way. Finally, he smokes about 20 cigars a day.

We are request for his last blood test, which he tells us is approximately two months ago. The most striking data from the analytics were:

- CD3 lymphocytes: 76% → reference values (68-80)
- CD4 lymphocytes: 26% → reference values (39-52) → total CD4 442
- CD8 lymphocytes: 47% → reference values (24-37) → total CD8 799
- CD4 lymphocytes / CD8 lymphocytes: 0.55 → reference values (1.05-2.15)
- Plasma viral load (CVP) → 126554

Intraoral examination revealed bilaterally eroded-looking and erythematous lesions at the corner of the mouth (Figure 1, 2 and 3). Both of them have fissures in their central part and whitish-looking crust areas in the spaces in contact with the skin. The

patient tells us that they are also very painful when he opens and closes his mouth. In the retrocommissural mucosa on the left side (Figure 2), there is an erythematous macule with some whitish areas, which is poorly defined. Some areas of the lesion are desquamated with the absence of epithelium, which confirms the itching and discomfort of the patient. Clinically, these bilateral lesions are diagnosed as angular cheilitis.

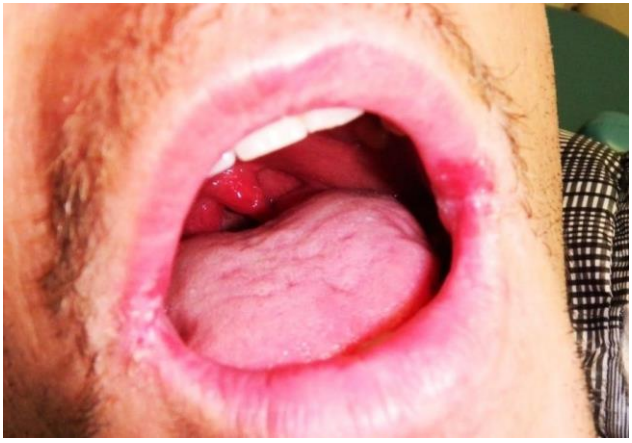

**Figure 1:** Erythematous lesions with fissured and desquamate areas of the patient in the corner mouth of clinical case 1. Clinically diagnosed as bilateral angular cheilitis.

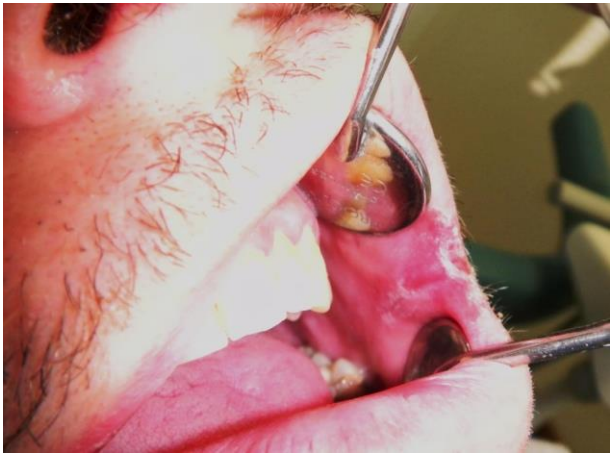

**Figure 2:** Lesion in the left retrocommissural area. As a whole it belongs to an angular cheilitis that extends towards the retrocommissural mucosa.

Angular cheilitis is an inflammatory process of the skin of multifactorial etiology that occurs at the corner of the mouth. Angular refers to the area where the infection is located and cheilitis refers to an inflamed lip. The commissures of the mouth are interface points between the squamous epithelium of the oral mucosa and the skin. In addition, these are areas subjected to repetitive movements and are therefore susceptible to stress. These lesions could appear because of environmental, mechanical, chemical, inflammatory or infectious causes; or a set of them. In addition, they can also reflect the systemic condition of the patient. Another colloquial name that is given to this lesion is rhagades [26].

The palate area (Figure 3) is reddened area with erythematous spotted. It respects about 4-5mm from the gingival margin and practically take up the rest of the hard palate. The patient refers to itching and discomfort often localized in this area. His clinically diagnosed was erythematous candidiasis.

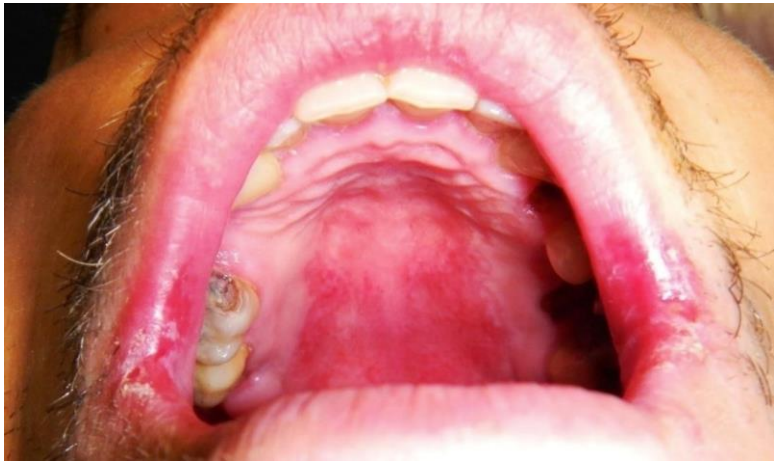

**Figure 3**: Erythematous lesions with scabby areas of the skin, localized in the corner mouth of the patient about clinical case 1. Clinically diagnosed as a bilateral angular cheilitis. On the other hand, we observed very erythematous area in the hard palate. Clinically diagnosed as candidiasis.

Candidiasis (as we have discussed in the case report on candida) is an opportunistic infection caused by the Candida fungus. Candidiasis often occurs as a secondary infection in

immunocompromised people [27]. Candida is a commensal fungus present in the oral flora of humans. It is the most common fungal infection of the oral cavity and it is usually diagnosed based on the clinical lesions. Generally, the pathogenesis of this disease is due to a different systemic factors (immunological, endocrine, etc.) and local factors (reduction of salivary flow, use of removable prostheses, shortage of hygiene, etc.) [27].

About the lingual examination, we observed slightly raised white patches on both sides, about 2 cm in length. Both are homogeneous and well delimited. They are completely painless and the patient did not know about these lesions. Clinically, we diagnosed them as hairy leukoplakia (Figure 4).

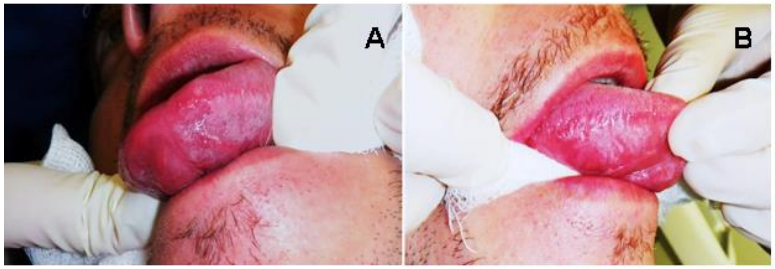


**Figure 4:** Whitish lesions at the lateral edges of the tongue. Clinically diagnosed as a hairy leukoplakia.

Hairy leukoplakia is a pathology of the oral mucosa, more specifically it be on the lateral edges of the tongue. It is associated with the Epstein Barr Virus. This pathology usually appears in immunocompromised patients, either due to an autoimmune pathology or transplantation or an infection such as HIV [28,29].

Hairy leukoplakia can be an initial indicator of HIV infection and if the patient did not have a recent laboratory test, it can be used as a clinical parameter. In addition, it is usually resolved with the taking of antiretroviral therapy. On the other hand, the clinical appearance of hairy leukoplakia may indicate adherence or resistance to antiretroviral therapy [29,30].

When exploring the rest of the intraoral mucosa, we observed several ulcers of considerable size. One of them is found in the uvula and another in the left pillar of the tonsil (Figure 5). We observed a third ulcer on the left jugal mucosa, at the level of the upper left second molar (Figure 6). These ulcers present loss of substance in the central area surrounded by a raised area with a slightly whitish halo around it. They are well delimited and they are very painful. On the other hand, the ulcer of the left jugal mucosa also presents a loss of substance in the central area, but in an irregular shape, creating a central crack. In a slightly diffuse way, we observe a whitish area in the anterior space of the ulcer that reach most of the jugal mucosa.

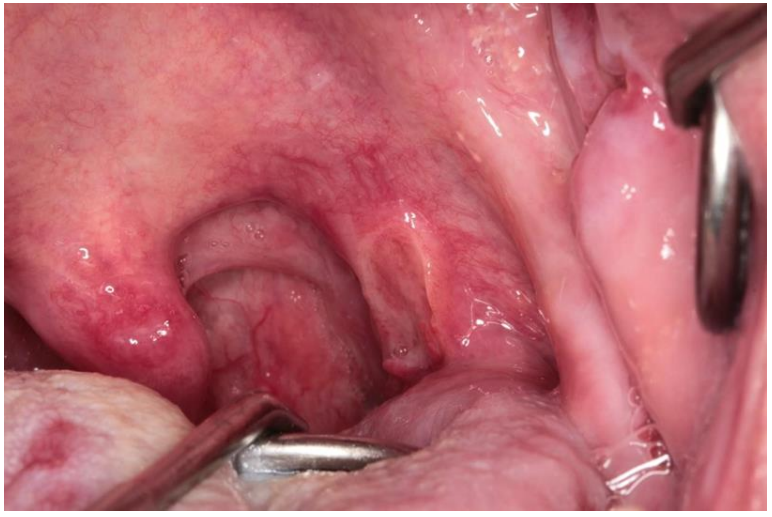

**Figure 5:** Major ulcers at the left pillar of the tonsil and uvula. Clinically diagnosed as a aphthous ulceration, ulcerations not otherwise specified (NOS).

Oral ulcers associated with HIV infection can be caused by mycotic, bacterial, protozoal, viral infect, oral neoplasia, aphthous ulceration, ulcerations not otherwise specified (NOS), or ulcerations of iatrogenic origin [31].

Clinically we diagnose these lesions as aphthous ulceration or NOS.

The clinical appearance of this type of ulcer is similar to that of immunocompetent patients. Major ulcers can appear in up to 17% of the HIV population and are usually located in the isthmus of the fauces (as in our case) or in the pharyngeal mucosa [32]. These ulcers are usually accompanied by very painful symptoms and there are associated with low CD4 counts [31,33].

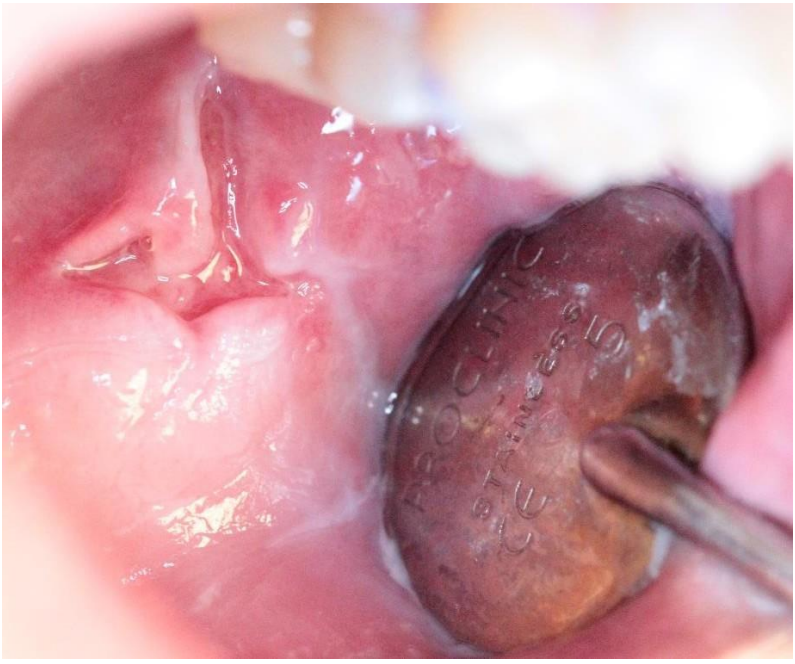

**Figure 6:** Major ulcers in the left jugal mucosa. Clinically diagnosed as a aphthspeous ulceration, ulceration not otherwise specified (NOS).

At this time and according to the 1993 CDC classification [20], our patient is in category B2, since he has CD4 lymphocytes between 14-28% or 200-499 and presents diseases related to HIV, which do not belong to category C, such as oral candidiasis and hairy leukoplakia.

For this reason, we refer the patient to their doctor to monitor their disease and start the highly active antiretroviral treatment again. In addition, we treat the patient symptomatically for oral lesions.

We prescribe Positon® 2.5mg / g + 1mg / g + 100000 IU / g cream to treat angular cheilitis, 3 times a day for 2 weeks. This product is composed of neomycin (antibiotic), triamcinolone (corticosteroid) and nystatin (antifungal). For palatal candidiasis we prescribe Fluconazole 100mg / once a day for 3 weeks. Finally, to alleviate the painful symptoms of oral aphtha, we prescribe a medicinal mouthwash composed mainly of 0.02% triamcinolone acetonide, twice a day, for 3 weeks.

Figures 7 and 8 show the improvement in the angular cheilitis and the retrocommissural lesion that the patient presents. The patient continues to complain of discomfort when opening and closing the mouth, but has less pain.

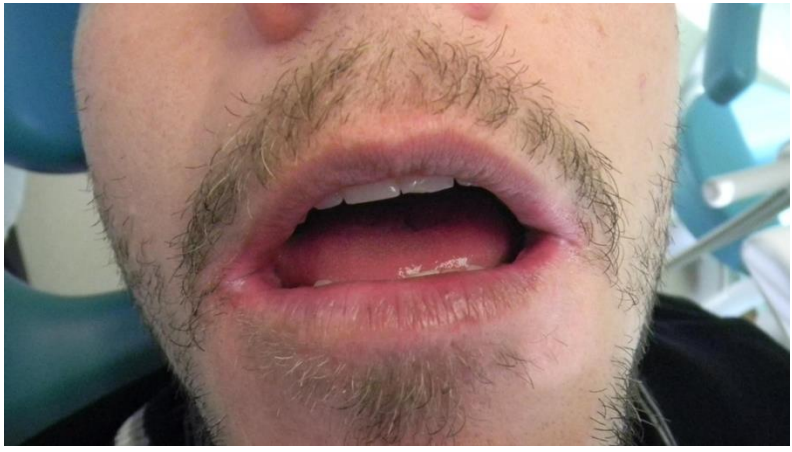

**Figure 7:** After two weeks starting angular cheilitis treatment and antiretroviral therapy.

In Figure 9, we can see a better appearance of the palatal candidiasis after treatment for 2 weeks. The area is less erythematous, but we do observe a reddish dotting that looks like an inflammation of the minor salivary glands of the palate, and nicotinic palatitis may be observed.

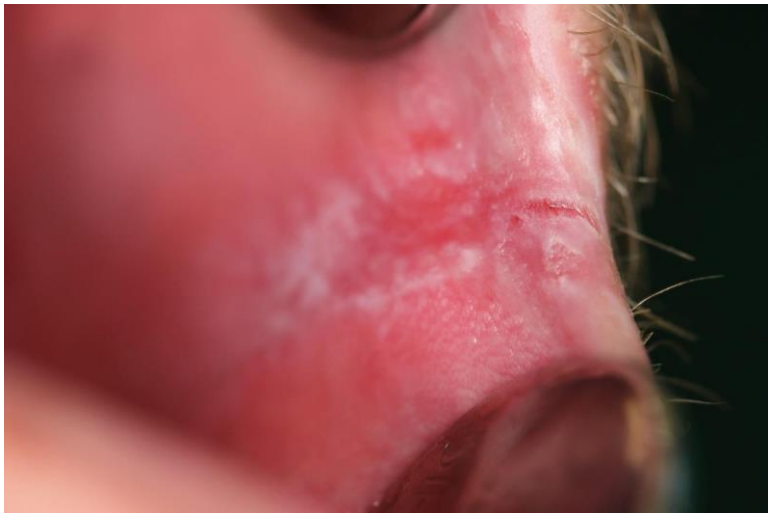

**Figure 8:** After two weeks starting treatment for retrocommissural lesion and antiretroviral therapy. It is observed slight improvement aspect.

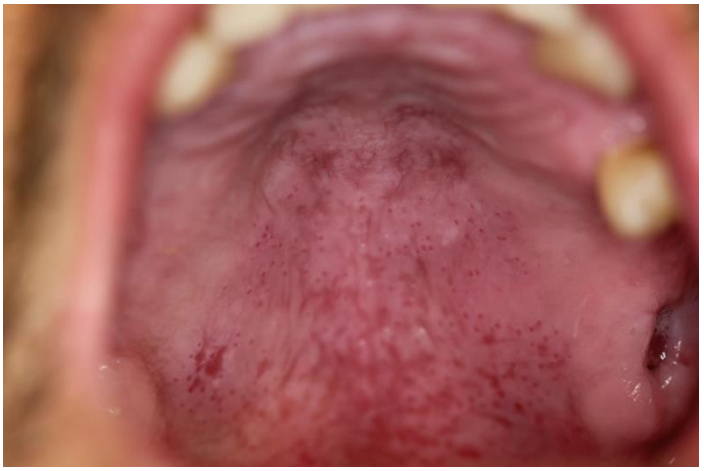

**Figure 9:** After two weeks starting treatment for palatal erythematous candidiasis and antiretroviral therapy.

After restart antiretroviral treatment, we observed that the hairy leukoplakia on the sides of the tongue completely disappeared (Figure 10).

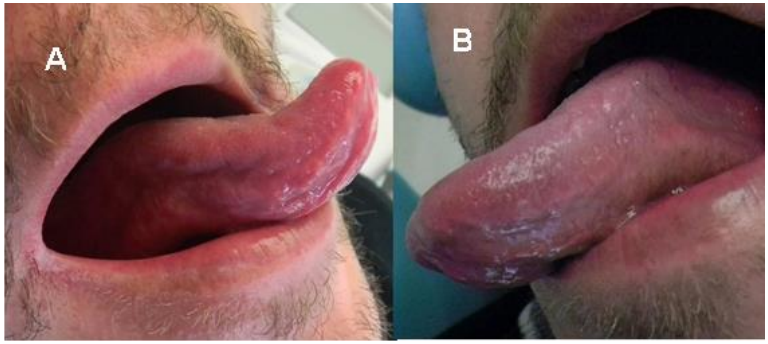


**Figure 10:** After two weeks starting antiretrovirals treatment. It is observed completely disappearance of lingual lesions.

In Figures 11 and 12 we see that with the patient's immunological improvement and with the treatment of topical corticosteroids in the major ulcers, the patient continues to present oral ulcers, but in the healing phase in addition to the generalized pain and stinging of the entire mouth has greatly decreased.

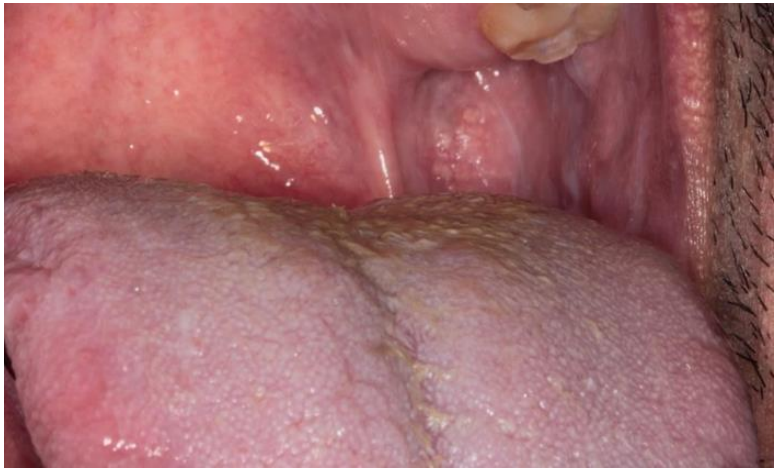

**Figure 11:** After two weeks starting antiretroviral and systemic corticoids treatment. It is observed completely disappearance of ulcers at the left pillar of the tonsil.

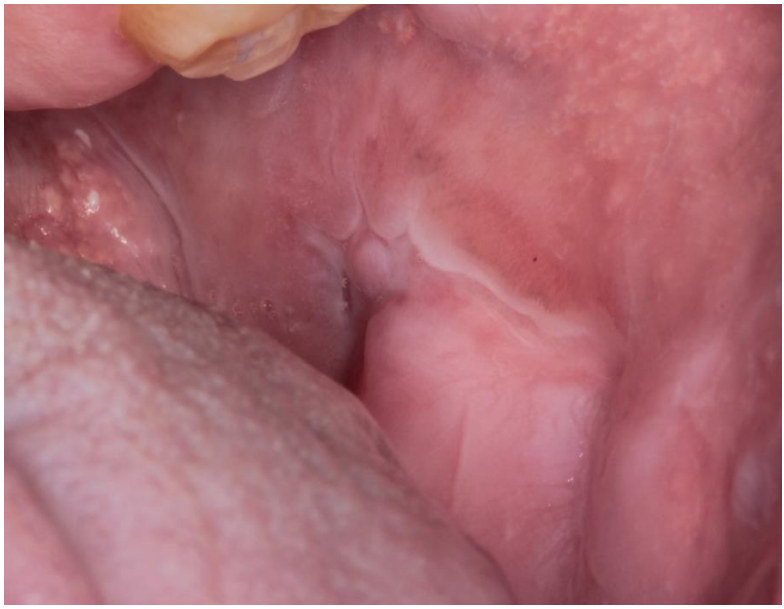

**Figure 12:** After two weeks starting antiretroviral treatment. It is observed complete healing of the ulcer of the left jugal mucosa.

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## Case Report

# Oral Manifestations of Syphilis: Clinical Case Series

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## Abstract

Syphilis is a bacterial infection that is sexual or congenitally transmitted. The disease has three stages in which different oral manifestations can arise. Oral lesions prevailing in primary syphilis are ulceration, inflammation and syphilis chancre; in secondary syphilis are mucous patches, erythematous lesions, inflammation, macular, papular and erosive lesions and in tertiary syphilis main oral lesions are the syphilitic gumma, leukoplakia lesions and lingual atrophy. Syphilis can simulate several diseases; therefore, it is important to consider it when making the differential diagnosis of various oral lesions, especially those that are ulcerative, indurated and asymptomatic. The objective of this chapter is to strengthen the oral aspects of this disease and present a series of clinical cases.

## Key Points

- Syphilis continues to be a major infectious disease that has raised in occidental countries during the last years.
- Rarely, oral lesions of syphilis may be the first manifestation of the disease and the dentist must be always aware.

## Introduction

Syphilis is a bacterial infection caused by the spirochete *Treponema pallidum* that is transmitted sexually or congenitally (mother-fetus) being humans their natural host [1-3]. Syphilis has several synonyms: "the great pox", Lúes, "the great imitator" and *Morbus Gallicius* among others [3]. Its incidence has decreased considerably since the introduction of penicillin; however, since the 1980s, there has been a resurgence of this disease attributable to HIV infection and an increasingly immunosuppressed population mainly due to an increase in risky sexual behaviors [1]. Currently, more than 5 million new cases are diagnosed annually [4]. Most cases of syphilis occur in young adults and the disease is characterized by several stages: primary, secondary and tertiary (associated with oral manifestations) and may remain latent hidden for long periods [1].

There is considerable controversy regarding the origin of syphilis and there are three main theories considered [3]: i) Columbian theory: the most accepted theory and claims that syphilis was brought to Europe by Columbus and his crew when they arrived back from the New World. At the end of the 15$^{th}$ century a pandemic known as "the great pox" spread throughout Europe and Asia, the infection was highly virulent, and many people died in its secondary stage. Soon it was known that it was a sexually transmitted infection.

ii) Pre-Columbian Theory: postulates that syphilis was already existent in Europe hundreds of years before Columbus returned from the New World. It is founded on medical archives from the 13$^{th}$ and 14$^{th}$ century which describes certain forms of leprosy that were highly contagious and transmitted sexually and from

mother to fetus. iii) Evolutionary/Unitary theory: the theory postulates that the different members of the genus Treponema evolved from a single organism responding to changes in the environment.

## Epidemiology

Before the introduction of penicillin, in the mid-20th century, syphilis was a high prevalent disease affecting 8-14% of the population in urban areas worldwide [5]. In 1999, 11.8 million cases of syphilis were estimated all over the world [2]. In the United States, during the first half of the 20th century, syphilis was a frequent disease (66.4 cases / 100 000 persons in 1947) and since 1950 to 1990 periodic epidemics with peaks has been observed followed by a decline of prevalence by the year 1993 until the year 2000 [6]. During the last decade, there has been a slow but steady increase in syphilis rates, both among homosexual population and women. The 2013 to 2014 primary or secondary syphilis rate was 6.3 cases per 100 000 population, with an increase in women of 22.7% from the year prior [7]. Ficarra et al (6) reported that 50-60% of new cases of syphilis occur in men who have sex with men and are strongly associated with HIV coinfection and high-risk sexual behavior.

Venereal syphilis, unlike the congenital or vertical transmitted disease, has a worldwide distribution that has no climatic, social, racial or geographic barriers [3]. Changes in sexual behavior, drug abuse, increased travel and migration could be related with the pandemic onset of syphilis [6]. Angus et al (8) reported that the incidence of syphilis has risen in epidemic proportions due to an outbreak since 1997 with 231% increase in heterosexual men, 1412% increase in homosexual men and 22% increase in women. Viñals-Iglesias et al [9] stated that the incidence of syphilis in Spain increased from 1.69 cases per 100 000 persons in 1999 to 4,38 cases per 100 000 persons in 2007 [remember that is a notifiable disease].

## Etiology and Mechanism of Transmission

The causative agent of syphilis is *Treponema pallidum*. It has a slender, coiled morphology and when examined by dark field microscopy it moves with a drifting rotatory motion (corkscrew). This microorganism cannot survive outside of its only natural known host (human being) and syphilis spirochetes cannot be cultivated in vitro [6]. The primary route of syphilis transmission is sexual contact. T. pallidum penetrates through the genital mucosa or abraded skin, enters the lymphatic and blood stream and disseminates to various organs. The incubation period varies from 3 to 90 days. In about 10-20% of cases the primary lesion is intrarectal, vaginal, vulvar, cervical, perianal (specially in homosexual relations but not neglecting heterosexual relations) or oral. Unlike other sexually transmitted diseases, syphilis is easily transmitted by oral sex, kissing and close contact with an infectious lesion [6].

Another important mode of transmission is vertical transmission. In addition, the transmission can occur at delivery if the newborn gets in contact with a lesion. Blood transfusions can be another way of transmission although unlikely today. Healthcare workers and laboratory personnel can acquire the infection if protective measures are not taken [6].

## Clinical Manifestations / Clinicopathological Findings

The first stage of infection with *T. pallidum* is primary syphilis. It is a local infection at the site of inoculation of the microorganism. The incubation period is 2 to 3 weeks (up to 90 days) after which a papule appears at the site of inoculation [5]. Ulceration of the papule results in what it is known as syphilis chancre (or inoculation chancre), which is painless, indurated and nonpurulent [5,6]. It can be found on the genitalia, anus, lips or mouth [5] and in more than 80% of cases regional lymphadenopathy is usually present about 7-10 days after the development of the chancre [5,6]. They heal spontaneously within 2 to 8 weeks [5,6]. Systemic dissemination of *T. pallidum* occurs during the primary stage of infection [5]. The majority of

extragenital chancres occur in the mouth (40-75%) although they can appear in any part of the body [6].

About 25% of untreated patients develop secondary syphilis within 4-6 weeks after the primary lesion [5] and 2-12 weeks after the first contact with the organism [6]. This stage is the result of hematogenous dissemination and the colonization of several organs [6]. Not all of these patients will have a history of a preceding chancre because it may have gone unnoticed [5]. Symptoms of secondary syphilis include generalized rash, fever, generalized lymphadenopathy, malaise, alopecia, aseptic meningitis, uveitis, optic neuritis and others [5,6]. Due to the wide array of signs and symptoms, syphilis is known as the "great imitator", as it can easily be confused with a variety of skin diseases [5,6]. Maculopapular lesions on the palms and soles occur in about 60-80% of patients (Figures 1-5) and about 21-58% of patients will have mucocutaneous or mucosal lesions, mucous patch or condylomata lata in the mouth or genital area (also known as flat condyloma) [5].

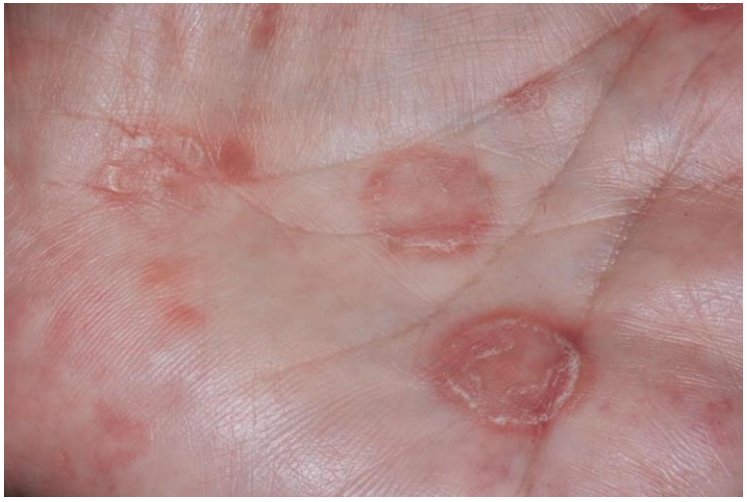

**Figure 1:** Desquamative lesions on the palm of the hand.

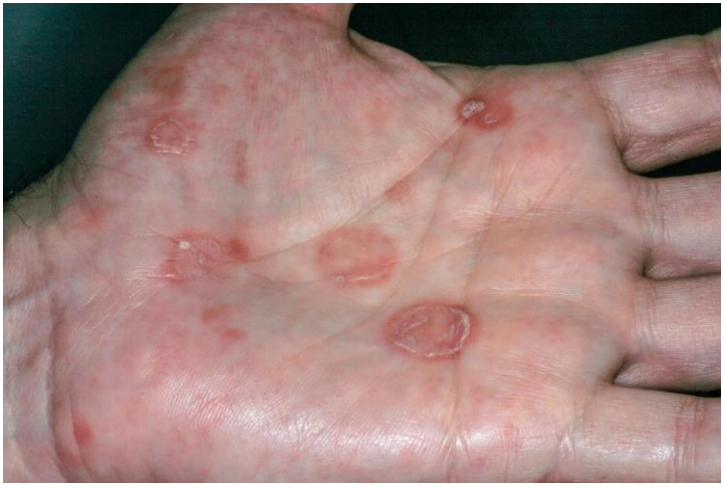

**Figure 2:** Multiple lesions on the palm of the hand.

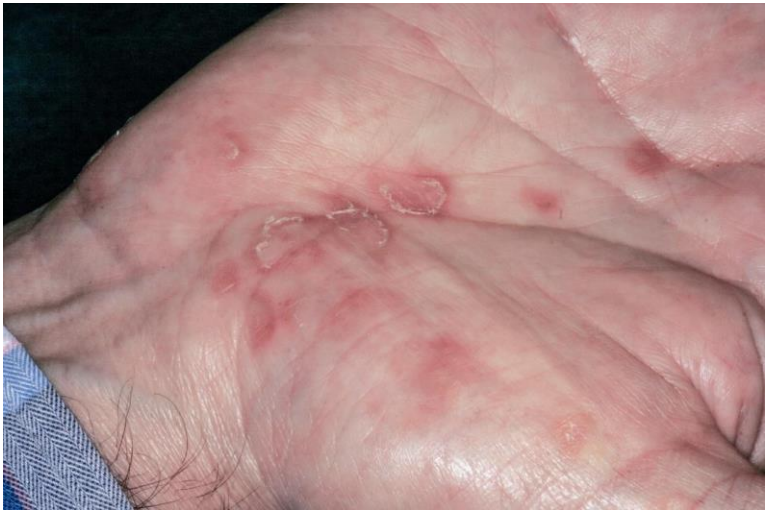

**Figure 3:** Right hand of the same patient.

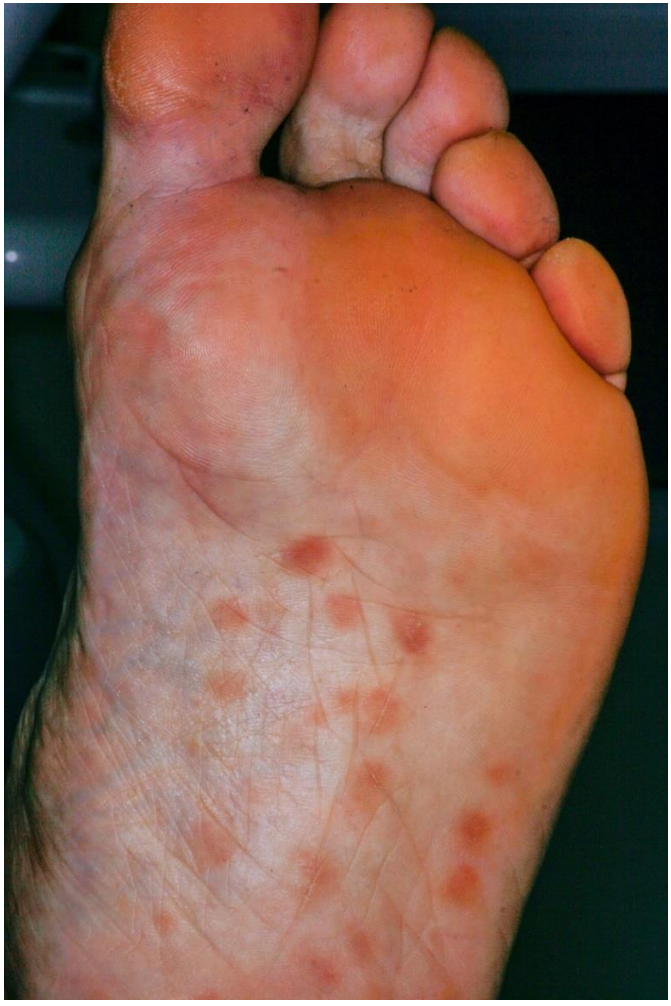

**Figure 4:** Pink macules on the feet, not itchy.

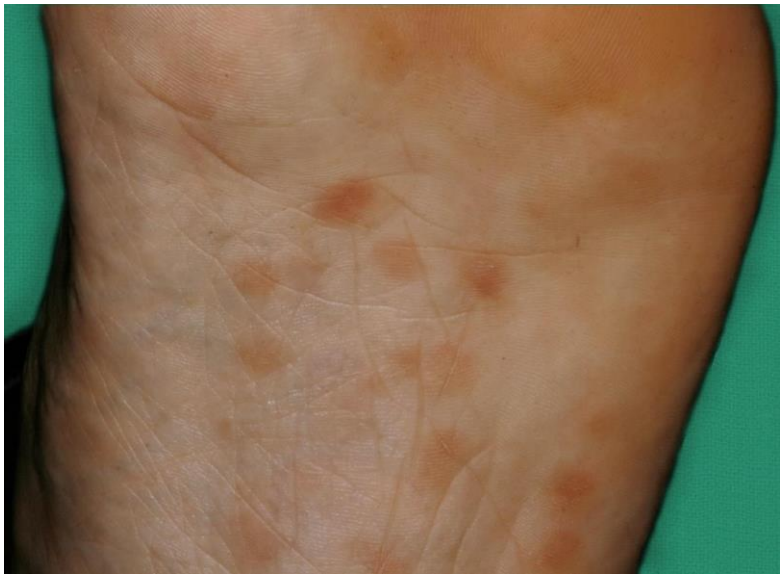

**Figure 5:** Pink macules on the feet, not itchy.

After the secondary stage, there is a latent period during which the patient does notshow any sign of infection. In this period, the diagnosis of syphilis can only be made through serological tests [6].

Tertiary or late syphilis develops in one third of untreated patients and is characterized by long-term complications [6] and may occur after primary, secondary or latent syphilis [5]. Tertiary syphilis can arise as early as 1 year after initial infection or up to 25-30 years later [5]. This stage can affect the central nervous system (CNS), cardiovascular system, skin, mucous membranes, liver, spleen, bones and other organs [5,6]. The lesions that appear at this stage are gummas, which are granulomatous lesions that are indolent, can range in size and can involve the skin, mucous membranes, skeletal system and viscera [5,6].

Finally, congenital syphilis is observed when the fetus is infected in the mother´s utero; in most cases due to untreated syphilis and is most likely to occur during the early stages of the infection [6]. Transmission to the fetus normally occurs via the placenta, but it can also occur during delivery in the presence of maternal genital

lesions. The risk of vertical transmission ranges from 70-100% in case of primary syphilis, 40% for early latent disease and 10% for tertiary or late syphilis [6]. The clinical manifestations are similar to the manifestations of secondary syphilis in adults and includes generalized lymphadenopathy, maculopapular rash, hepatosplenomegaly, glomerulonephritis, bone (tibia, hands, feet, clavicles, skull), teeth and nervous system alterations. It is important to consider the Hutchison´ triad which consists of deafness, notched incisors and/or mulberry molars and ocular interstitial keratitis [6].

## Oral Manifestations

### Primary Syphilis

Oral primary syphilis manifests as a solitary ulcer on the lip and, more rarely, on the tongue or palate; up to 65% of primary syphilis lesions occurs as ulceration [10]. The ulceration is usually deep with an erythematous base, purple or brown color and with an irregular raised border and normally accompanied by cervical lymphadenopathy. Differential diagnosis must be made from other ulcerative disorders, such as traumatic ulceration, squamous cell carcinoma, donovanosis (inguinal granuloma) and non- Hodgkin's lymphoma, among others [11].

The upper lip is more commonly affected in men, while the lower lip is more affected in women. The pharynx and tonsils may also be affected, although it is less frequent, and appears as erythema and pustules in up to 15% of cases [10].

Oral primary syphilis may also occur as inflammation in up to 5% of cases and as a syphilis chancre in 30% of cases [10]. According to their frequency, the site of oral lesions of primary syphilis are lips, buccal mucosa, tonsillar pillar and palate, tongue and gums [10].

### Secondary Syphilis

Oral manifestations of secondary syphilis are more extensive and/or variable than those of the primary disease. Mucous patches are the most prevalent lesions at this stage (44.65%) and

can be found, in order of occurrence, in the palate, lips, tonsillar pillar, buccal mucosa and tongue, retromolar area, vestibule, uvula and tonsils, floor of the mouth and gums [10]. Ulceration can also be found in up to 22.64% of cases and according to their frequency it may appear in palate, tongue, lips, buccal mucosa, commissures, retromolar area, gums and labial frenulum [10].

Almost 9% of oral manifestations at this stage are papular lesions located in gums, lips, buccal mucosa, palate, tongue and commissures (DATO DE NUESTRA REVISION) and the 6% are macular lesions located in the palate, lips, tongue and gums (Figures 6-8).

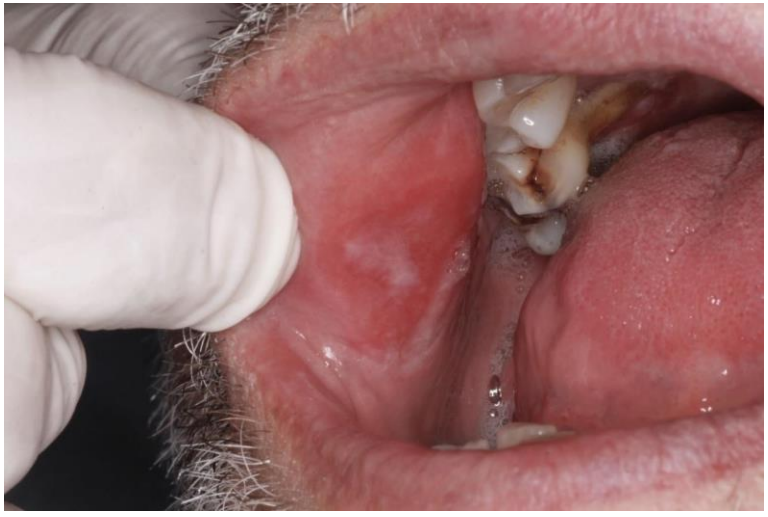

**Figure 6:** White macules/papules and erosive areas on the right buccal mucosa (same patient as Figures 1, 2 and 3).

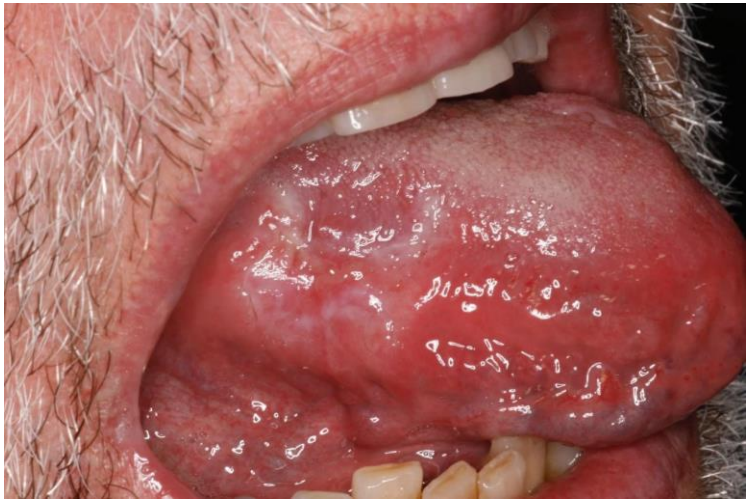

**Figure 7:** White macules/papules and erosive areas on the lateral border of the tongue (same patient as Figures 1, 2 and 3).

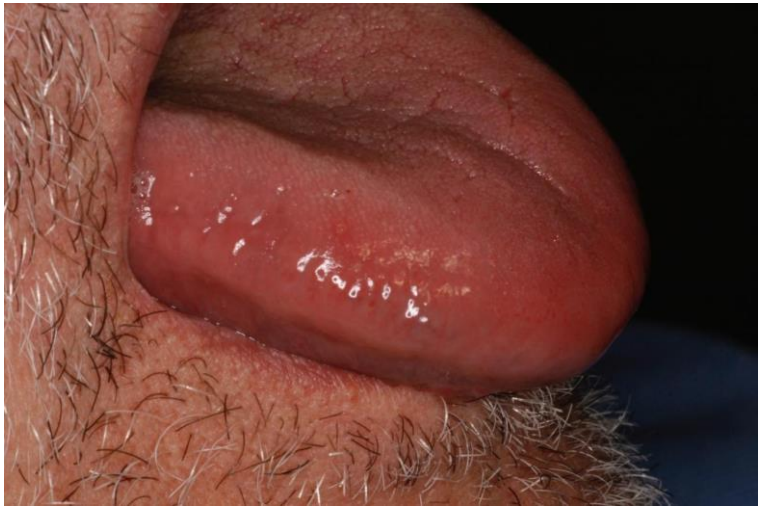

**Figure 8:** Previous patient after treatment for one month.

4.40% of lesions in this stage are erythematous plaques located on the palate, tongue and gums. Nearly 3% manifest as inflammation (Figure 9) on the lips, palate, tongue, buccal mucosa and gums [10]. Approximately 3% are nodular lesions

(Figures 10, 11) located in the tongue, commissures and palate [10]. 2.5% are erosive lesions (Figures 12, 13) founded on the lips, tongue and buccal mucosa. Almost 2% of lesions can arise as leukoplakia lesions located on the palate, tongue and buccal mucosa. Less frequently, may appear white and red lesions, atrophy, lingual fissure, lip spots and desquamative gingivitis [10].

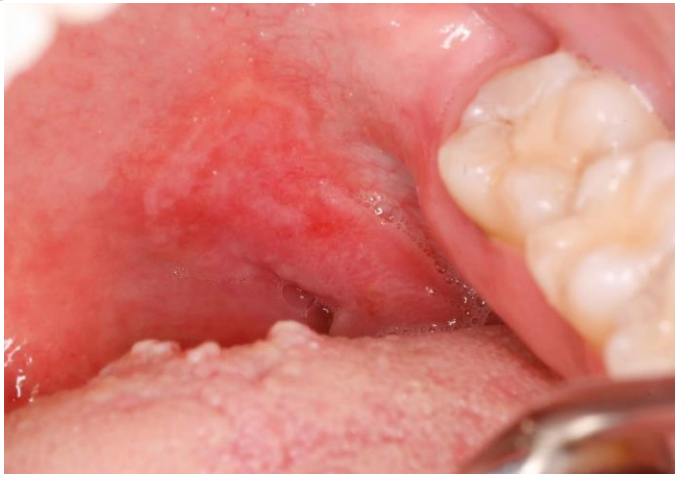

**Figure 9:** White/grey inflammatory lesions on the left anterior pillar of the pharynx.

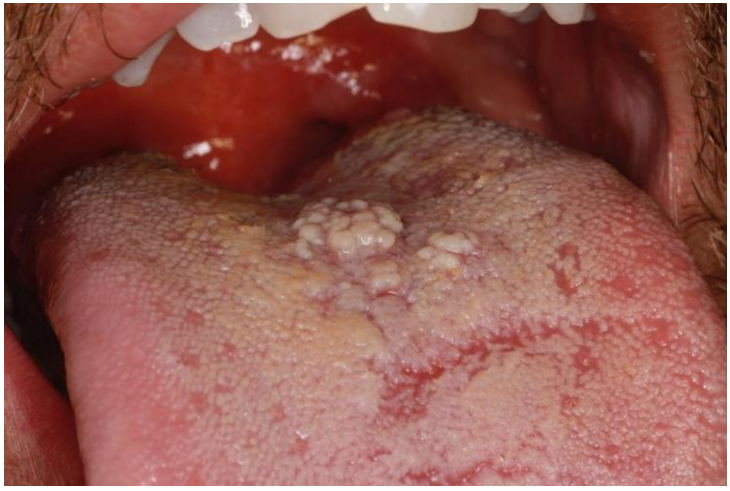

**Figure 10:** Exophytic lesion on the dorsum of the tongue.

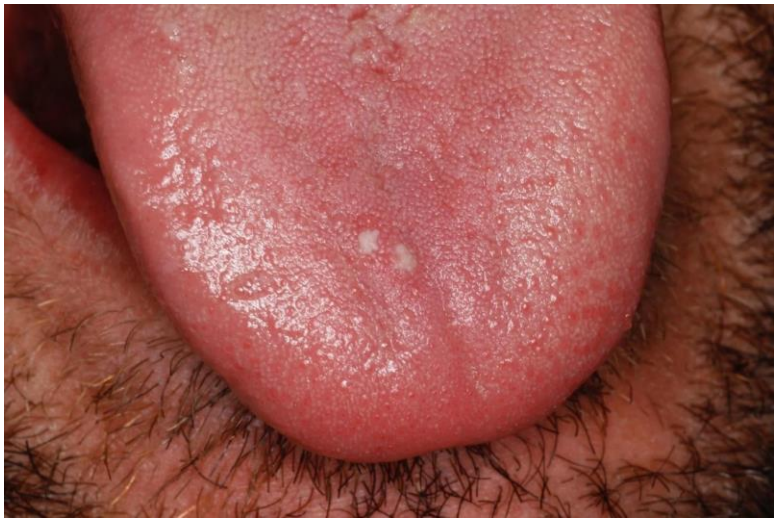

**Figure 11:** Nodular lesions on the tongue.

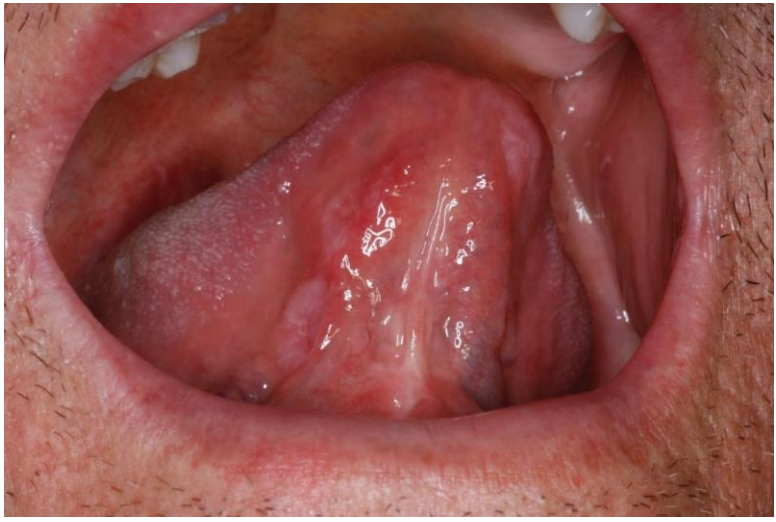

**Figure 12:** White macules and erosive areas on the ventral tip of the tongue.

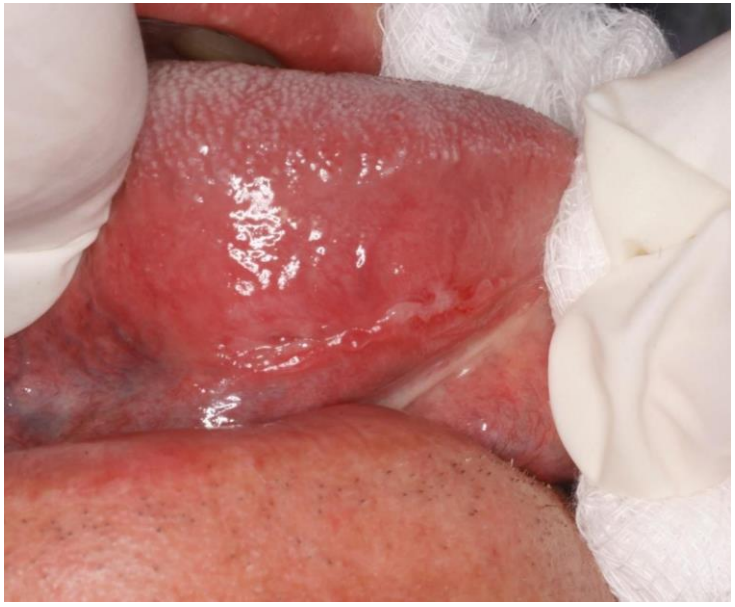

**Figure 13**: White macules and erosive areas on the ventral tip of the tongue.

## Tertiary Syphilis

Main oral manifestations of tertiary syphilis are gumma formation, syphilitic leukoplakia, neurosyphilis and cardiovascular syphilis with thoracic aortic aneurysms that may or not be associated with severe aortic insufficiency [11].

At this stage, 34% of lesions are syphilitic gumma (Figure 14) [10] and they tend to arise on the hard palate (with eventual palatal perforation DATO DE NUESTRA REVISION) and tongue. Syphilitic leukoplakia accounts for almost 36% of oral lesions [10] affecting the dorsum of the tongue.

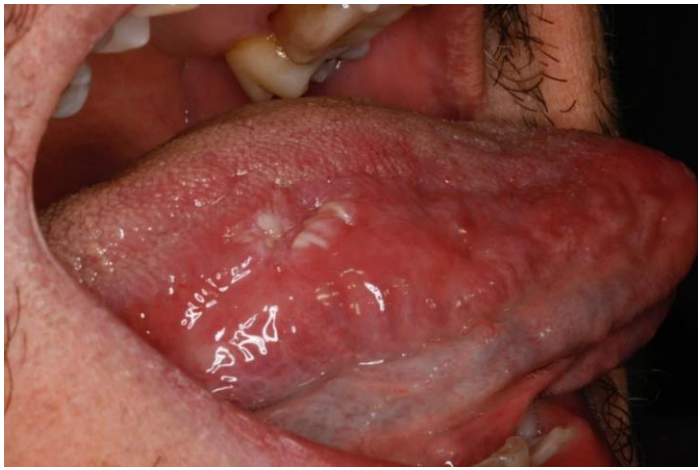

**Figure 14**: Ssymptomatic ulceration 5-6 mm with hyperkeratosis on the right lateral dorsum of the tongue.

8.6% of lesions arise as glossitis and almost 10% as lingual atrophy (Figure 15). Approximately 9% of lesions are carcinomas in the lingual location (a frequent complication of syphilitic gumma, especially those with lingual involvement). Other less frequent lesions of tertiary syphilis are ulceration and lingual necrosis [10].

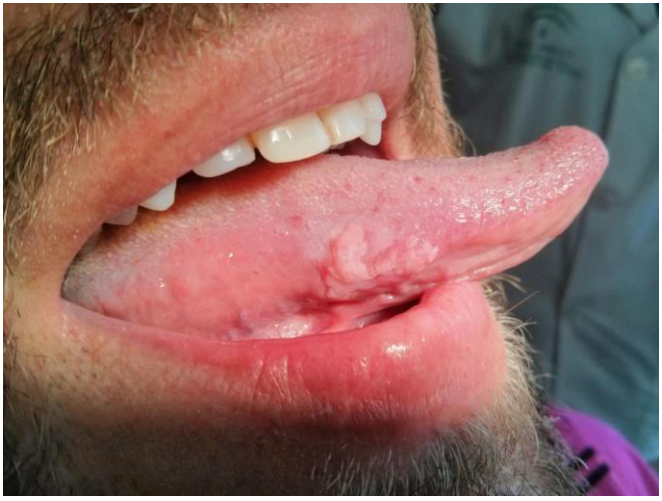

**Figure 15:** Condylomatous lesions on the lateral sides of the tongue (bilateral).

Neurosyphilis can give rise to trigeminal neuropathy and facial nerve palsy aside from the Argyll Robertson pupil (III cranial nerve injury) and tabes dorsalis [11].

## Diagnosis, Differential Diagnosis and Histopathological Features

The diagnosis of syphilis is based on clinical signs and symptoms, microscopic examination and serologic tests. Although no single histopathological feature is specific, a diagnosis of syphilis should be considered when there is unusual epithelial hyperplasia, granulomatous or plasma cell predominant chronic inflammation, endarteritis and neuritis. The definitive diagnosis of syphilis is made using indirect methods since *T pallidum* cannot be cultivated in vitro. There are two types of serological tests: reaginic or non-treponemal and specific or treponemal [5].

Serological testing is the most common method for syphilis screening, diagnosis and follow-up treatment [4]. Non-treponemal tests are based on antigens synthesized from lecithin, cholesterol and cardiolipin reacting with antibodies produced in response to T pallidum infection. These tests detect both IgG and IgM antibodies [4+. Antibody titers detected by these tests correspond with the stage of disease, increasing throughout primary infection and peaking late in the secondary or in the early latent stages of infection (it is understood as early latent stage of disease when infection is less than one year) [4]. Thus VDRL (venereal disease research laboratory) is positive from the $4^{th}$ to $6^{th}$ week of infection and becomes negative only after successful therapy, but there may be several false positives. RPP (rapid plasma reagin) is also non-specific and less used.

Treponemal tests, which detect antibodies to treponemal antigens, are also commonly used and are helpful in decreasing false-positive cases. These include TPPA (Treponema pallidum particle agglutination), ELISA (enzyme-linked immunosorbent assay for treponema) and, the most frequently used, FTA-ABS (fluorescent treponemal antibody adsorbed) [4)] Treponemal tests tend to be qualitative, rather than quantitative, but often

remain positive for life, despite successful therapy and, therefore, are not helpful for evaluation of response to therapy, with different algorithms for disease management [4] (Table 2, Figure 16) [5,12].

**Table 1:** Oral manifestations classified by stage and frequency of appearance [10].

| | |
|---|---|
| **Primary Syphilis** | - Ulceration<br>- Erythema and pustules<br>- Inflammation<br>- Syphilis chancre |
| **Secondary Syphilis** | - Mucous patches<br>- Ulceration<br>- Papular lesions<br>- Macular lesions<br>- Erythematous lesions in plaque<br>- Inflammation<br>- Nodular lesions<br>- Erosive lesions<br>- Leukoplakia lesions<br>- White and red lesions, atrophy, lingual fissure, lip spots and desquamative gingivitis |
| **Tertiary syphilis** | - Syphilitic gumma<br>- Syphilitic leukoplakia<br>- Glossitis<br>- Lingual atrophy<br>- Carcinoma<br>- Ulceration and lingual necrosis<br>- Neurosyphilis |

**Table 2:** Incubation period of each stage of syphilis [5].

| **STAGE** | **INCUBATION PERIOD** |
|---|---|
| Primary syphilis | 2-3 weeks |
| Secondary syphilis | 4-6 weeks after appearance of chancre |
| Latent syphilis<br>Early<br>Late | <br>Infection of 1 year or less<br>Longer than 1 year |
| Tertiary syphilis | Longer than 1 year; may be 25-30 years or longer |
| Congenital syphilis | In utero infection, if untreated can lead to latent and late syphilis |

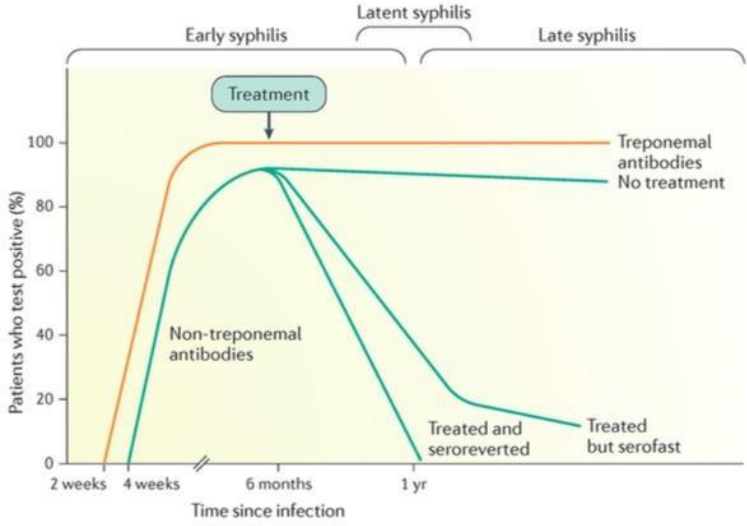


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**Figure 16**: Primary and secondary syphilis serological response [12].

Differential diagnoses are multiple, for that reason, this disease is known as "the great imitator". Among them can be found white lesions [13], erosive lesions [13,14], oral ulceration [14,15], infectious diseases [14], pleomorphic adenoma [16], tuberculosis [15- 18], traumatic ulceration [16,19,20], squamous cell carcinoma [15-17,20,21], HIV lesions [16,17], vascular lesions such as Kaposi's sarcoma [16,22], vesiculobullous lesions [16], recurrent aphthous stomatitis [17,19,23], leprosy, non-Hodgkin lymphoma, Wegener's granulomatosis, deep mycosis, leishmaniasis, inguinal granuloma, lymphogranuloma venereum, cytomegalovirus infection [16], gonorrhea [14,16], necrotizing sialometaplasia [17,22], lipoma [19], neurofibroma [19], schwannoma [15,20], granular cell tumor [19], herpes simplex [19,22,24], pemphigus vulgaris [15,19,20], cicatricial pemphigoid [15,19,22], erythema multiforme [18], lichen planus [15,20,24], angular cheilitis, nibbling lesion, pseudomembranous candidiasis [20)], histoplasmosis, hyperkeratosis, Behcet syndrome [15], erythematous candidiasis, hairy leukoplakia [24], adenocarcinoma, granulomatous infections, erythroplasia [22].

The histological findings of all stages of syphilis are characterized by vascular involvement with endarteritis and

periarteritis and granulomatous inflammation, particularly in the gummatous stage. In secondary syphilis, a wide variety of histological changes are observed, with lymphocytes and plasma cells present in the dermis in 75- 100% of patients. Silver staining reveals the presence of treponemas in around 70% of patients. The epidermis is frequently involved, with exocytosis, spongiosis, parakeratosis and acanthosis being the most frequent changes. In late syphilis, the infiltrate may become granulomatous. Histological changes correlate with the clinical features but are not always pathognomonic [8].

## Treatment

The treatment of choice for primary and non-complicated secondary syphilis is a single dose of penicillin G benzathine of 2.4 million UI administered by intramuscular route. In the case of allergy, doxycycline may be used (100mg administered orally, twice a day for two weeks) [9]. Without a clear support, some protocols recommend amoxicillin 500mg/8 hours plus probenecid 500mg/8 hours for 14 days instead of penicillin G benzathine [8]. In cases of late latent, gummatous or cardiovascular syphilis it is recommended 1 injection intramuscularly (IM) once a week for 3 weeks and in patients allergic to penicillin, tetracycline should be administered [5].

## Dental Management

The dental management of patients with sexually transmitted diseases (STD) begins with identification, since many are highly potentially infectious. However, this is not possible in every case because some patients may not provide a full history of their health status or may not demonstrate significant signs or symptoms suggestive of their disease. Therefore, all patients must be managed as though they were infectious [5].

Untreated primary and secondary syphilis are contagious, as are the patient's blood and saliva. No modifications in the technical treatment plan are necessary for a patient with syphilis. No adverse interactions exist between the usual antibiotics or drugs used to treat syphilis and drugs commonly used in dentistry [5],

but we must be aware that antibiotics used in dental infections can whiten secondary manifestations to syphilis.

## Clinical Cases

**Case 1:** Figures 1-3. Man, 56 years old. Allergic to penicillin. Moderate COPD. Ex- smoker for 4-5 months (before 20 cigarettes/day). Takes medication for hyperuricemia. On intraoral examination, white macular-papular lesions and erosive areas on the lateral border of the tongue and on the left and right buccal mucosa were observed (Figures 6 and 7). He was on 0.5% triamcinolone acetonide mouthwash prescribed by his dentist, noticing no improvement. He also presented erythematous circular lesions with a scaly peripheral collar on both palms of the hand. Similar lesions were found in the genital area. Serological tests (syphilis, HIV, EBV) were solicited showing positive results for *Treponema* infection and negative results for the other tests. Treatment indication was doxycycline 100mg/12 hours for 2 weeks. The lesions remitted with the treatment (Figure 8).

**Case 2:** 60-year-old man. Homosexual, without a stable partner and multiple sexual relations and does not usually use protection. He referred to have "sores on the tongue". On intraoral examination, white macular lesions and erosive areas were observed on the ventral part of the lingual tip (Figures 12 and 13). Extraoral examination revealed pink macules on the forearms, palms of the hand and soles of the feet that were not itchy (Figures 4 and 5). He does not recall time of appearance. He also had desquamative erythematous lesions on the scrotum and the glans. There were no lymphadenopathies. Serological tests were solicited including luetic serology, HIV and EBV. Positivity for *Treponema* was confirmed. The patient was referred to the Infectious Diseases Service (IDS) responding successfully to the specific treatment.

**Case 3:** 39-year-old man with previous history of syphilis treated a year ago. He visited the dental clinic because he presented condyloma-like plaques that joint together on the lateral side of the tongue (bilateral). He claimed to have them for a month and a half. They were slightly symptomatic, feeling

itching when eating. On extraoral examination, there were violet erythematous lesions on the glans. It was requested a luetic serology test and in the IDS, it was confirmed a luetic reinfection. The patient was successfully treated with penicillin G benzathine 2.400.000 units IM (Figure 15).

**Case 4:** 46-year-old man with previous history of Lues infection (9 years ago). On intraoral examination he had an asymptomatic ulceration of 5-6mm with hyperkeratosis on the right lateral dorsum of the tongue. There were no irritative factors associated. Without lymphadenopathy. He referred spots in the glans. Luetic serology test revealed new positivity for syphilis infection. The patient was referred to the IDS and treated with weekly penicillin G benzathine (3 weeks). He did not return to the dental clinic for the follow-up visit (Figure 14).

## Conclusions

Syphilis is a bacterial infection than can simulate several diseases. Therefore, it is important to consider it when making the differential diagnosis of various oral lesions, especially those that are ulcerative, indurated and asymptomatic.

The most frequent oral manifestations of this disease are ulceration on the lips in primary syphilis, mucous patches on the palate in secondary syphilis and syphilitic gumma on the palate and leukoplakia lesions on the tongue in tertiary syphilis.

When oral syphilis is suspected, a general extraoral examination must be performed seeking for lesions in other parts of the body.

Syphilis has a good prognosis, since with an early diagnosis and adequate treatment the lesions remit successfully. Therefore, it is important to make a correct medical history, remembering that it is notifiable disease.

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## Case Report

# Oral Leishmaniasis

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## Abstract

**Aim:** Leishmaniasis is an infectious disease caused by the *Leishmania* parasite. We present a case of leishmaniasis where the only manifestation of the disease was the presence of oral lesions.

**Case Report:** A 54-year-old patient presented oral lesions, mainly distributed in the lip and tongue accompanied by asthenia, weight loss, and low-grade fever. HIV negative serology and biopsy of the lingual dorsum with a diagnosis of leishmaniasis were performed. Treatment with AmBisome® (liposomal amphotericin B) was established in glucose serum for 5 consecutive days in a hospital. The same infusion was repeated

at 7 and 14 days. The patient's general condition improved and the oral lesions disappeared.

**Conclusion**: Early detection and rapid initiation of treatment help reduce transmission and control spread.

## Point of Interest

- Leishmaniasis is an infectious disease caused by a protozoan parasite of the *Leishmania* genus transmitted by the bite of an infected sand-fly.
- There are three main forms of leishmaniasis: visceral (the most severe form of the disease, often known as kala-azar), cutaneous (the most common), and mucocutaneous.
- Early detection and rapid initiation of treatment help reduce transmission and control the spread and burden of disease.

## Introduction

Leishmaniasis is a disease caused by a protozoan parasite of the *Leishmania* genus, with more than 20 different species. It is transmitted to humans through the bite of an infected female sand-fly. The disease can present three clinical manifestations: visceral (the most severe, known as kala-azar, which can be fatal), cutaneous (the most common), and mucocutaneous [1].

Despite being a rare zoonosis in humans, it is endemic in 98 countries. Approximately 90% of cases worldwide are located in India, Bangladesh, Nepal, Brazil, and Sudan. According to the World Health Organization (WHO), the annual incidence of this disease is 1.5-2 million new cases, while the prevalence is 12 million. The population at risk of contracting Leishmaniasis is 350 million people. On the other hand, in Spain, it is considered endemic in the entire Mediterranean basin due to the high number of cases present in animals, especially in dogs [2]. It is considered a notifiable disease (3). The main aim is to present a case of leishmaniasis whose only manifestation of disease was the presence of an oral lesion.

## Case Report

### Background

A 54-year-old male patient with residence in Murcia went to the Oral Medicine unit. The patient is a type II diabetic in treatment with Tesavel (sitagliptin), an oral antidiabetic. When it comes to toxic habits, he is an occasional drinker and smokes around 20 cigarettes a day. He did not refer to any displacement abroad recently.

The patient in his report communicated that approximately 8 months before the first visit, he presented a medical chart of lingual inflammation and intense xerostomia. Motivated by these symptoms, the patient goes to his reference hospital service where they perform a first blood test where the values fell within normal limits. Subsequently, the patient was referred to the maxillofacial surgery service where a minor salivary gland biopsy was performed, the result of which did not show relevant alterations. Simultaneously, the patient was receiving antibiotic treatment due to pulp necrosis of an upper incisor.

The patient reports that four months later, from this episode, lesions appeared on the tongue, that inflammation evolved to a notable painless protuberance on the back of the tongue, as well as the presence of "ulcers" in different locations. Besides, he reported that he felt general discomfort and had a low-grade fever every day, which experienced in the hours afternoon, making him feel chills and the need to "cover himself with a blanket." During this period, the patient reports a considerable loss of weight, around 7 kg, which was verified with the contribution of the values of the measurements that the patient carried out monthly. Along with the sudden loss of weight, the patient suffered from asthenia, anorexia, night sweats and they carried out an analysis where the AST and ALT values were higher, the rest being normal.

It is at this time that he is referred to the Oral Medicine unit of the University of Murcia.

## Anamnesis in the Oral Medicine Unit

Patient data were collected in a standardized way. It was then that all the data mentioned above was collected, as well as the remarkable weight loss.

### Extraoral Exploration

The patient comes to the visit calmly, he does not present anxiety, agitation, or behavioral alteration. The physical aspect, the breathing, the communication, the level of consciousness, the movements, and the posture are completely normal. Absence of facial asymmetry, tumors, or fistulas. Lymph node examination reveals no cervical lymphadenopathy. The oral opening is normal (Figure 1).

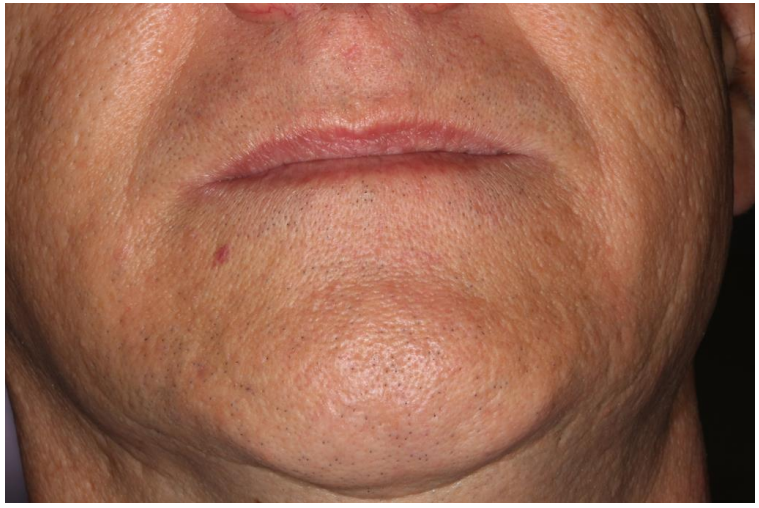


**Figure 1:** Image of the patient's lower facial third.

### Intraoral Exploration

On the upper lip, the patient presents a homogeneous white lesion in addition to a lip fissure (fissured cheilitis,). As well, there is an increase in volume and hard consistency in the center of the lingual dorsum of approximately 2 x 3.5 cm. This lesion presents central ulceration, with a dirty bottom and irregular

edges. In some areas, it is lined with normal-colored mucosa. Other areas of superficial necrosis appear on the back of the tongue. On the other hand, the body of the tongue is edematous and presents an ulcer in its 1/3 middle, on the left side. The rest of the patient's oral mucosa is healthy, without relevant alterations (Figure 2-5).

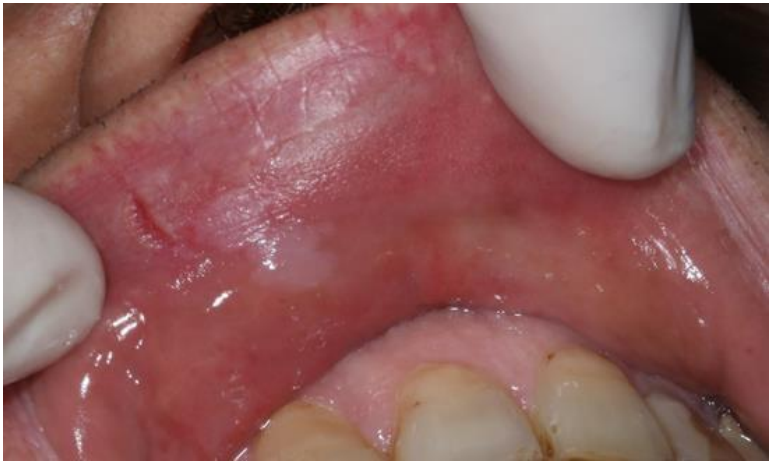


**Figure 2:** Upper lip.

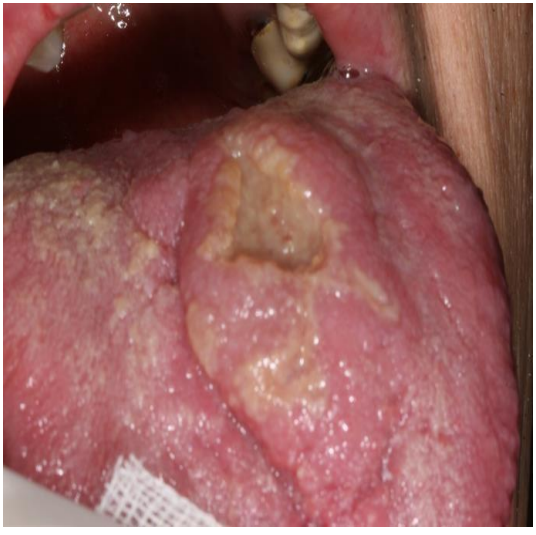


**Figure 3:** Dorsal surface of the tongue.

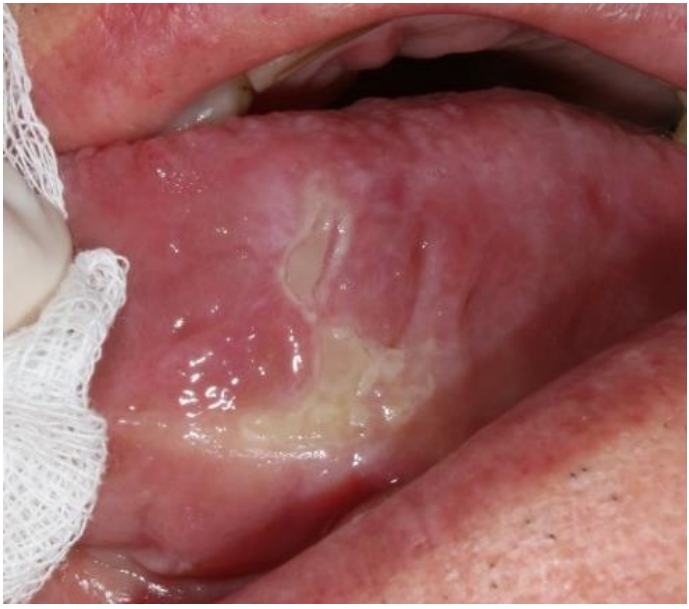


**Figure 4:** Ventral surface of the tongue.

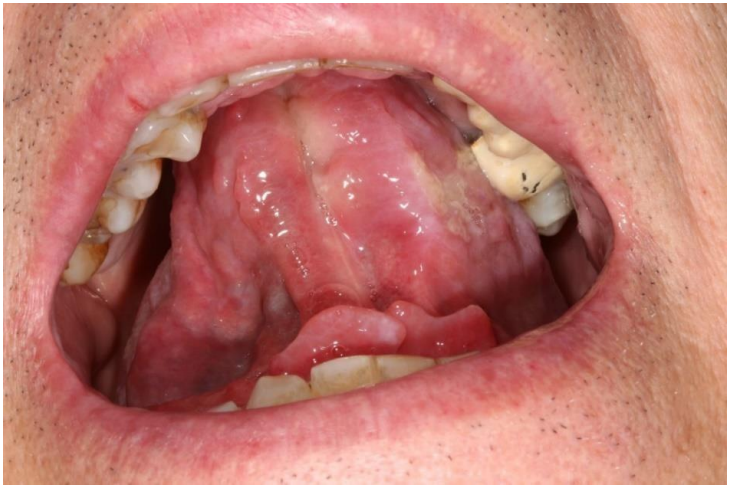


**Figure 5:** Ventral surface of the tongue.

## Differential Diagnosis

We must make a differential diagnosis with other oral lesions such as reactive, infectious, malignant, or granulomatous diseases. The presence of an ulcerated, dirty-bottom, indurated lesion with irregular edges and in a patient who has suffered significant weight loss, as well as general discomfort and low-grade fever, suggests in the first place the possibility of being an entity of Malignant character such as oral squamous cell carcinoma (OSCC). Other malignant pathologies must be taken into account, such as lymphoma or distant metastasis from another malignancy.

On the other hand, benign and infectious pathologies were considered. Traumatic ulcer, tuberculous ulcer, chancre characteristic of primary syphilis, or other infectious diseases that occur with oral ulcers were included among the possible diagnoses.

## Evolution of the Case

Due to the alarming appearance of the patient's lesions, it was decided to take the biopsy the same day of the first visit. This was performed under local anesthesia and using a cold scalpel/punch. The sample was preserved in formaldehyde and sent to the Pathology Department. The haste that was necessary for that situation was indicated and the day after the sample had been sent, the results had already been sent (Figure 6). The pathological study of the lesion confirmed that it was **Leishmaniasis** with *C. Albican* infection (Figure 7-9).

Servicio Murciano de Salud

Hospital General Universitario Reina Sofía
SERVICIO DE ANATOMÍA PATOLÓGICA

**INFORME ANATOMOPATOLOGICO** Nº de estudio: **19B0010026**

NHC: **20000890**
Nº S.S: **30/89602787-9**

Servicio de Origen: **ANATOMIA PATOLOGICA**
Solicitante: **Martínez Díaz, Francisco**

Tipo de Estudio: **BIOPSIA**

Fecha de Entrada: **11/06/2019**

**Datos Clínicos:**
CASO CONSULTA. (ODONTOLOGÍA).
Neoplasia. Úlcera tuberculosa. Úlcera traumática.
**DESCRIPCIÓN MACROSCÓPICA :**
Se reciben múltiples fragmentos de 0,2 cm.
**DESCRIPCIÓN MICROSCÓPICA :**
Se observa una mucosa oral ulcerada con hiperplasia reactiva seudoepiteliomatosa, en la zona supercial se disponen hifas y esporas tipo candidas y tanto colonizando células epiteliales como en la lamina propia em el interior de macrofagos se disponen numerosos parasitos tipo leishmanias, asociados a un tejido de granulacion y fibrino-necrotico con inflamacion aguda y cronica.

**Diagnóstico:**
**MUCOSA ORAL CON LEISHMANIASIS Y CANDIDIASIS.**

Código SNOMED:

**Figure 6:** Pathology study result.

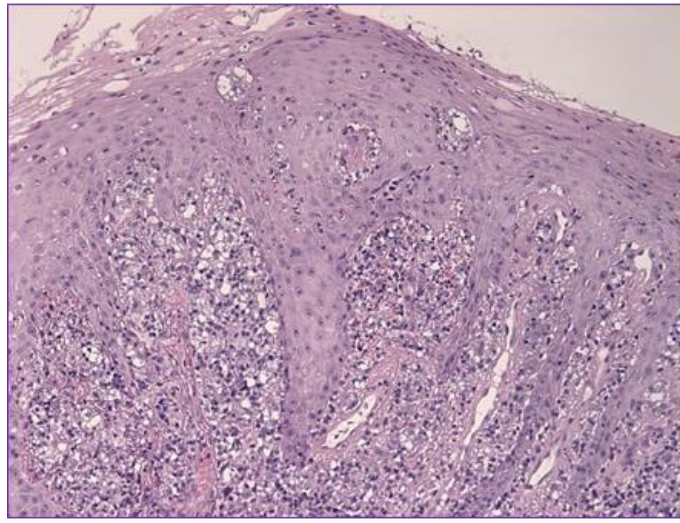


**Figure 7:** Histopathological image Hematoxylin-Eosin staining.

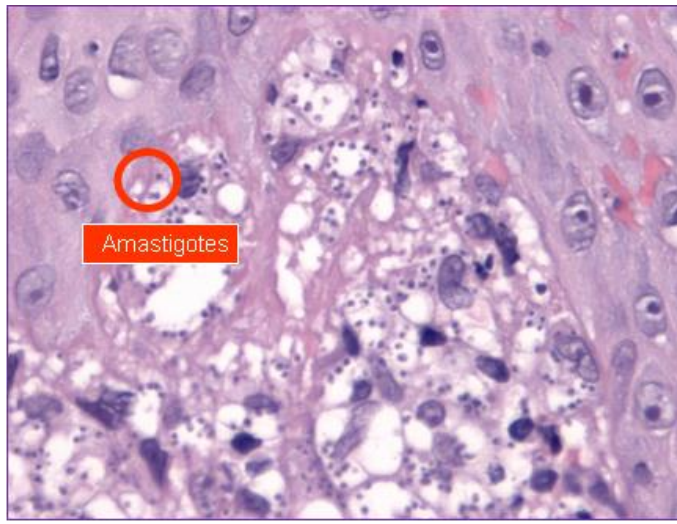



**Figure 8:** Presence of amastigotes, rounded protist cells and lacking flagella that appear inside macrophages and are characteristic of leishmania lesions.

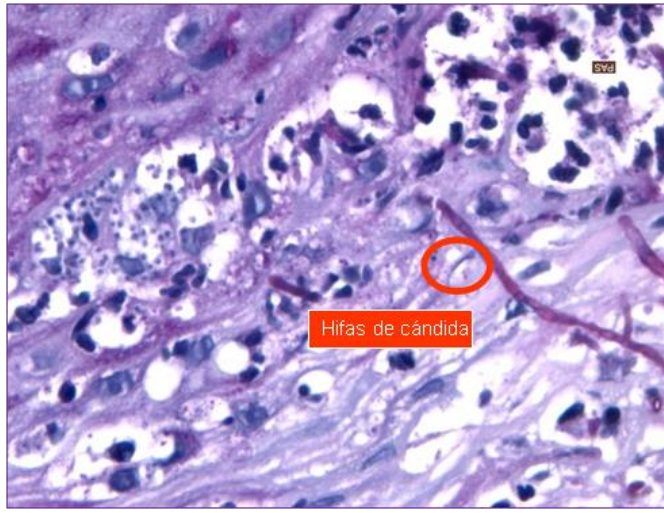



**Figure 9:** *C. Albicans* hyphae.

Simultaneously with the sending of the sample to pathology, the patient was referred to the Internal Medicine Service and applied the treatment considered necessary. Also, serological tests for infectious diseases were suggested (Figures 10 and 11).

INFORME DEL SERVICIO DE MICROBIOLOGIA

[redacted]

DR CARRILLO RAMIREZ

SUERO

SEROLOGÍA

| | | |
|---|---|---|
| LUES | | |
| Anticuerpos sífilis (IgG+IgM) | Negativo | MLNT |
| HEPATITIS | | |
| Antígeno HBs | Negativo | MLNT |
| Anti - VHC | Negativo | MLNT |
| VIH | | |
| Anti - VIH 1+2 (Ag - Ac) | Negativo | MLNT |
| NEUMONIA ATIPICA | | |
| Anti - M. pneumoniae (Ig G) | La muestra queda guardada, pendiente de recibir la segunda muestra a las 2 o 3 semanas, para seroconversión. | MLNT |
| Anti - L. pneumophila (Ig G) | La muestra queda guardada, pendiente de recibir la segunda muestra a las 2 o 3 semanas, para seroconversión. | MLNT |
| Anti - C. pneumoniae (Ig M) | La muestra queda guardada, pendiente de recibir la segunda muestra a las 2 o 3 semanas, para seroconversión. | MLNT |
| Anti - C. trachomatis (Ig M) | La muestra queda guardada, pendiente de recibir la segunda muestra a las 2 o 3 semanas, para seroconversión. | MLNT |
| Anti - C. burnetii (Ig G) | La muestra queda guardada, pendiente de recibir la segunda muestra a las 2 o 3 semanas, para seroconversión. | MLNT |



INFORME DEL SERVICIO DE MICROBIOLOGIA

[redacted]

SUERO

SEROLOGÍA

VARIOS

| | | |
|---|---|---|
| Ac. Leishmania (IgG+IgM) | POSITIVO | MLNT |

**Figure 10 & 11**: Microbiology Service Report.

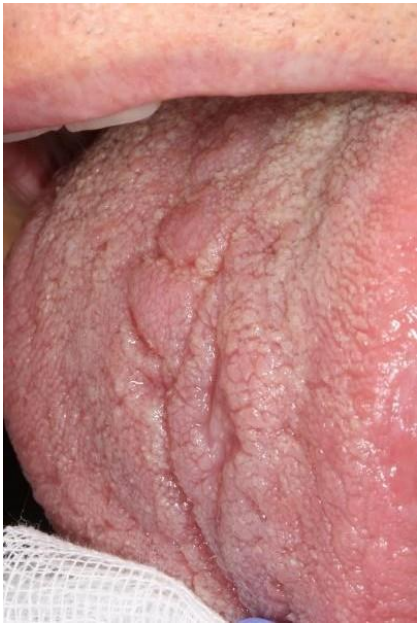
The serological report revealed Ac. Leishmania (+) and HIV (-). Therefore, the diagnosis of Leishmaniasis was confirmed, as well as that the patient was immunocompetent. Together, an extension study was carried out on the patient to determine what clinical form of leishmaniasis it was. The alteration of the oral mucosa turned out to be the only location that was affected in the patient; therefore, it was mucocutaneous leishmaniasis. The patient was treated by administering a slow intravenous infusion

of 210 mg of AmBisome (liposomal amphotericin B) in glucose serum at 1:30h and for 5 consecutive days. This was done in a hospital setting with the hospitalized patient. The same infusion was repeated 7 and 14 days after the end of hospital treatment. This time, it already took place on an outpatient basis. Finally, the patient was summoned at 3 months for review in the Internal Medicine Service.

## Review in the Oral Medicine Service

Once the treatment in internal medicine was concluded, the patient was reviewed in the Oral Medicine service. On intraoral examination, the lesions in both the tongue and other locations had completely healed. However, reparative signs (scar) characteristic of extensive leishmania lesions were observed. In addition, the patient reported that the general discomfort and daily fever had disappeared.

Subsequent clinical follow-up is essential since the disease can reactivate many years after the primary infection (Figure 12, 13).



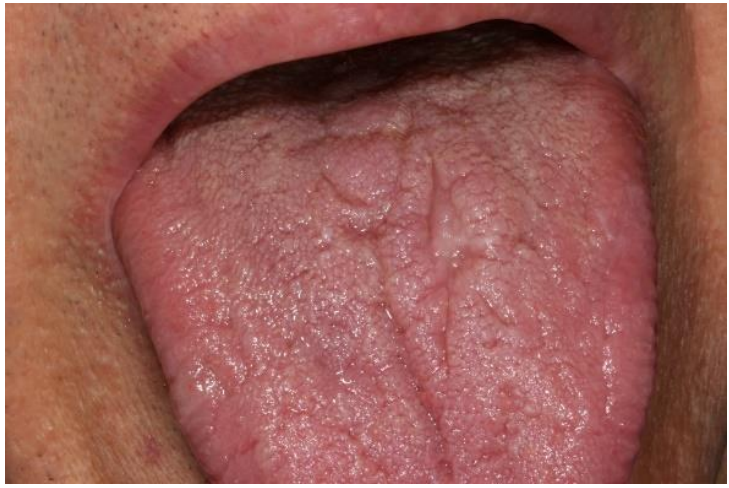


**Figure 12 & 13:** Post-treatment images where the reparative signs are observed.

## Discussion

Leishmaniasis is a parasitic disease caused by more than twenty species of the *Leishmania* genus and transmitted by the sand-fly vector (*Phlebotomus*). Many mammals are a natural reservoir for the disease, including dogs, humans, cats, lagomorphs, and rodents, it has been reported in some birds [4] (Figure 14).

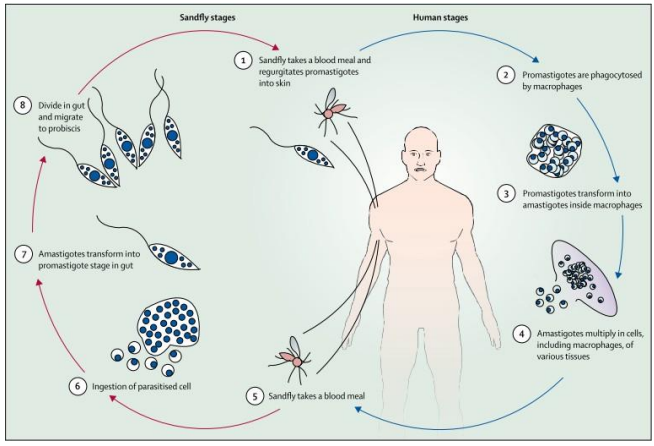



**Figure 14**: Leishmaniasis cycle. Taken from Burza et al., 2018 [4].

According to the WHO, 3 clinical forms can occur in this pathology:

1. **Visceral L.**: systemic involvement, cytopenia, and hepatosplenomegaly.
2. **Cutaneous L.**: the most prevalent, it is usually located in exposed body regions and with multiple injuries.
3. **Mucocutaneous L.**: less frequent clinical form. It usually presents as a late stage of skin involvement after hematogenous or lymphatic spread. It is not frequent that skin and mucosal lesions occur simultaneously. Furthermore, oral involvement as an initial, and only manifestation is rare [3].

Although mucosal involvement is rare, some authors have described oral lesions in patients with leishmaniasis:

Thus, in 2018, **Ruiz-Martín** and his team reported a 47-year-old immunocompetent patient with a single oral lesion that was raised and indurated and presented a white color and erythematous central ulceration. It extended from the jugal mucosa to the corner of the left lip. Incisional biopsy revealed that it was leishmaniasis. The patient underwent an extension study, determining that it was exclusively a mucocutaneous form. The patient was treated with intravenous liposomal amphotericin B (3mg / kg/day) for 7 days in a slow infusion. In the monthly review, the lesions had completely disappeared. **García de Marcos et al**., described in 2007 3 cases of leishmaniasis. The size of the lesions varied from 2 to 5 cm, the location being variable from one case to another. All three patients claimed pain. Two of them had HIV co-infection, so they were immunosuppressed. Two of them were treated with 20mg / kg/day intramuscular meglumine antimoniate for 28 days, resulting in the healing of the lesions [5]. In 2014 in India, **Passi et al**. reported the case of a 51-year-old man with lesions of less than 1 cm on the hard and soft palate and the presence of swollen cervical nodes. The biopsy of the lesion revealed that it was leishmaniasis. The patient was treated with 100 mg of oral miltefosine for 28 days and 20 mg of intravenous sodium stibogluconate (Pentosam) for 30 days. In the review the lesions had completely healed [6]. Finally, **in 2016**, **Almeida et al.** reported the case of a 41-year-old Brazilian male with

asymptomatic, erythematous, and edematous lesions on the upper alveolar ridge and hard palate. Despite taking a biopsy of the lesion, the definitive diagnosis of leishmaniosis was confirmed by immunohistochemical analysis for L. brazilensis. The patient was treated with 20 mg/kg/day N-methyl-glucamine intramuscularly. After 4 weeks, the injuries had improved considerably [7].

The prevention and control of leishmaniasis require a combination of intervention strategies since transmission occurs in a complex biological system that includes the human host, the parasite, the vector sand-fly, and, in some cases, an animal reservoir. Thus the WHO indicates that the main strategies take into account the following [8]:

- **Early diagnosis and effective case management** reduce the prevalence of the disease. Early detection and rapid initiation of treatment help reduce transmission and control the spread and burden of disease.
- **Vector control** helps reduce or interrupt disease transmission by reducing the number of sandflies. Control methods include aerosol insecticides, insecticide- treated mosquito nets, environmental management, and personal protection.
- **Effective disease surveillance** is important. Rapid reporting of data is essential for monitoring and taking action during epidemics and situations where there is a high case fatality rate despite treatment.
- **Control of animal reservoirs** is complex and must be adapted to the local situation, it is advisable to collaborate with different interested sectors and other programs to control vector-borne diseases are essential at all levels.

## Conclusions

The presence of these lesions must be considered and we should not delay their study by performing the appropriate procedures for their early diagnosis. Leishmaniasis is a notifiable disease. Greater dissemination of therapeutic protocols is necessary since Spain is an endemic country.

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## Case Report

# Oral Schwannoma

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## Abstract

Schwannoma or leurinemoma is a benign tumor which arise from Schwann cells. It was firstly described in 1903 by Verocay and the etiology is still unknown.

About 25% of the schwannomas are located at head and neck but only 1% appears intraorally being the tongue the preferent location.

A 16 -year-old female Chinese patient reported to our dental office with her mother with a chief complaint of a painless mass in tongue. After extraoral and intraoral examination we found a

mass of 1.5 centimeters. Six months later the same lesion had doubled in size.

A biopsy followed by a histological examination were performed to confirm the schwannoma diagnosis.

## Keywords

Oral Schwannoma, Oral Tumor, Schwann Cells, Diagnosis, Treatment, S-100

## Key Points

Oral tumors in dentistry

## Introduction

Schwann cells arise in the 4th week of intrauterine development. They come from a population of neural cells. The main function of this cells is to cover each axon improving the nerve impulse [1]. They are involved in the axonal regeneration through their interaction with other cellular types which do not belong to nervous system [2].

Schwannoma is a rare benign tumor which arise from Schwann cells [2,3]. It was firstly described in 1903 by Verocay [4] and it is also known as leurinemmoma, neurinoma or perineural fibroblastoma [3]. The etiology is still unknown, but it seems that these lesions emerge from a proliferation of Schwann cells in one perineurium´s point [5].

These tumors appear in nerves that are recovered by Schwann cells, including cranial and spinal nerves (excluding optic and olfactory), and those from autonomous nervous system [6].

Occasionally, the tumor growth might cause displacement and compression of the affected nerve [7].

About 25% of the schwannomas are located at head and neck but only 1% appears intraorally[7]. When oral structures are affected,

tongue is the preferent location[8,9] probably because the movements could stimulate the tumor growth. Moreover, lesions in the tongue are easily detectable when compared with other anatomic locations [7].

Clinically, it appears as a solitary, asymptomatic, nodular lesion, although larger tumors could cause symptomatology. Schwannomas appear between 2nd and 3rd decade of life independently of patient's gender [10,11]. However, some studies suggest they are more prevalent in women [12].

Schwannoma grown is usually painless, but they cause pressure if they overrun adjacent tissues. Depending on the anatomic structures close to schwannomas they can even cause facial paralysis or Horner´s syndrome. In addition, when presented intraorally it might cause paresthesia, dysphagia or pain while chewing [13].

Differential diagnosis was made with other exophytic or tumor lesions like neurofibroma, lipoma o fibroma. Instead, at histological level, differential diagnosis should be done with other lesions with neural origin [14].

The gold standard in schwannoma´s treatment is the complete excision of the lesion and the risk of recurrence or malignancy are exceptionally low when they are completely excised [11,15,16].

## Case Report

A 16 -year-old female Chinese patient reported to our dental office with her mother with a chief complaint of a painless mass in tongue. She had no allergies and her personal medical history did not have important records, only an hamartroma in right fallopian tube, that was removed and an adnexectomy two years before.

We found in left side of the tongue a solitary exophytic lesion, of 1-1.5 centimeters length, which have well defined and regular edges, solid consistency and similar color of the tongue.

We decided to evaluate it one week later to value if the lesion had changed its appearance, but the patient didn´t come to her appointment. Instead, she came 6 months later having a bigger lesion which reach 3 millimeters of diameter.

We explained the patient and her mother the necessity of practice a biopsy to confirm the presumptive diagnosis. Table 1 summarizes the injuries considered for differential diagnosis.

**Table 1:** Differential diagnosis.

| **Differential diagnosis** |
|---|
| Filiform papilla hypertrophy |
| Vulgar wart |
| Diapneusia |
| Fibroma |
| Lipoma |
| Schwannoma |
| Neurofibroma |
| Granular cell tumor |
| Lymphangioma |
| Benign tumor of salivary glands |

A biopsy followed by a histological examination were performed to confirm the schwannoma diagnosis.

## Histological Analysis

Schwannoma is an entity that might have two different histological patterns, known as Antoni A, and Antoni B. In our case, we observed that the pattern displayed was Antoni A. This pattern is characterized by bundles of Schwann cells with very organized spindle cores and placed in parallel rows which constitutes the typical pattern “in palisade”, surrounded by acellular and eosinophilic masses establishing the “Verocay´s bodies”[11].

In Antoni B pattern the cellular density is lower and the spindle cells disposition is less organized [11].

Furthermore, schwannomas are positive to immunohistochemical

staging S-100. This protein is produced by regular and neoplastic cells with mesodermic, ectodermic and epithelial origins expected, we observed the presence of S-100 in glia cells, Schwann cells, melanocytes, myoepithelial cells, some glandular epithelium, adipocytes, skeletal and cardiac muscle, chondrocytes, and dendritic follicular cells.

## Discussion

As is shown in Table 2, schwannoma do not depend on patient gender, although some authors think it might be more prevalent in women [12], and the age range observed in the reviewed literature varies from 9 to 71 years. Noteworthy, in younger patients, the preferential location is the soft palate.

The standard treatment lies in complete surgical removal of the lesion. When the intervention is successful, recurrences are not frequent. Currently, the $CO_2$ laser has also been used for the surgical removal of this entity [17,18] but radiotherapy is excluded as these tumors have been shown to be radioresistant [19].

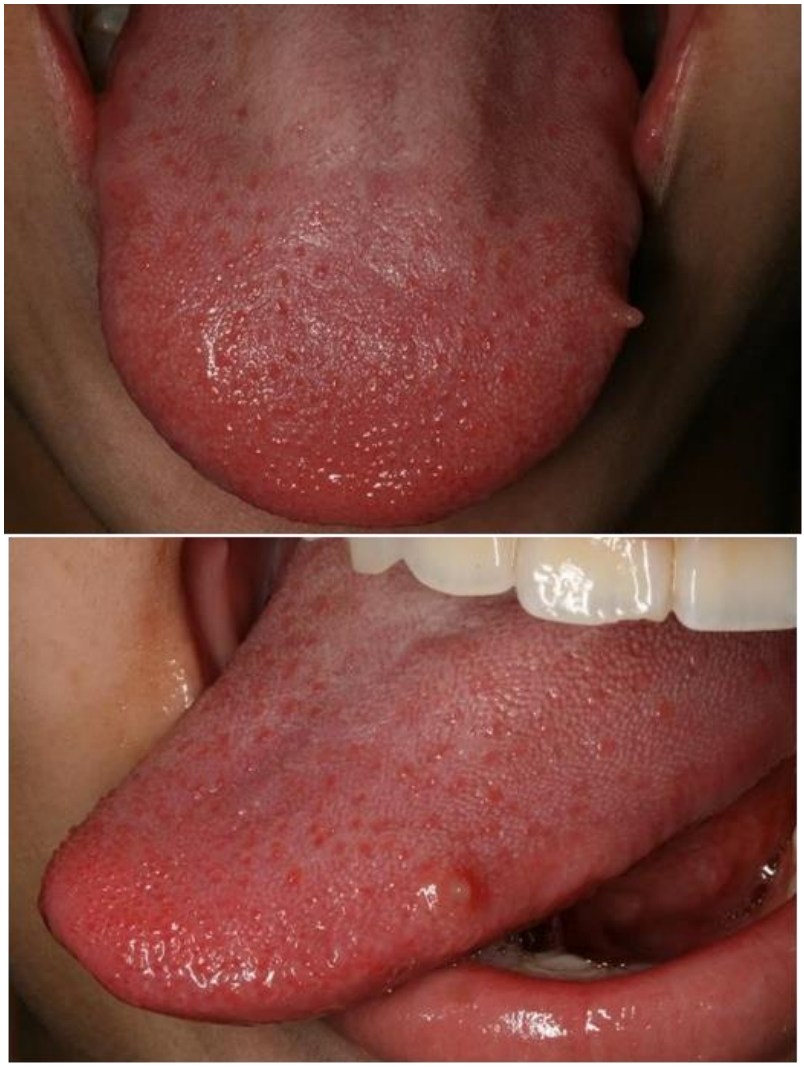
Histopathologically, five types of schwannoma are differentiated: common, plexiform, cellular, epithelioid and old schwannoma [20], being the last one of a rare occurrence. As referred in Table 2, only two cases turned out to be old schwannomas in the consulted literature.

Interestingly, in our case the histological pattern corresponded exclusively to Antoni A. However, a combination of both Antoni A and Antoni B patterns is usually observed according to the literature. Moreover, and consistently with our case, when immunohistochemistry is performed, the test is always positive for S-100.

**Table 2:** Reviewed literature between 2003-2018.

| *AUTHORS* | *YEAR* | *SEX* | *AGE* | *LOCATION* | *THERAPY* | *A.P* | *S-100* | *REC* |
|---|---|---|---|---|---|---|---|---|
| Saqulain G | 2018 | M | 12 | soft palate | excisional biopsy | Antoni A+ B | | no |
| Lee EY et al | 2017 | F | 71 | posterior tongue | excisional biopsy | Antoni A+ B | | no |
| Eroglu CN et al | 2017 | M | 29 | palate | excisional biopsy | Antoni A | | no |
| | 2017 | M | 33 | alveolar ridge | excisional biopsy | Antoni A+ B | | no |
| Bansal V et al | 2017 | M | 26 | Submandibulargl | excisional biopsy | Antoni A+ B | | |
| Sicca C et al | 2015 | F | 13 | soft palate | I.B+surgical excision | Antoni A+ B | + | no |
| Parhar S et al | 2014 | F | 34 | palate | excisional biopsy | Antoni A+ B | | no |
| Moreno-Garcia C et al | 2014 | F | 13 | tongue | excisional biopsy | Antoni A | + | no |
| Khiavi MM | 2014 | M | 21 | palate | I.B+surgical excision | Antoni A+ B | + | no |
| Raikwar KR et al | 2014 | F | 35 | lower lip | excisional biopsy | Antoni A+ B | + | no |
| Lira RB | 2013 | F | 26 | tongue | excisional biopsy | Antoni A | + | |
| Jadwani S et al | 2012 | F | 24 | alveolar ridge | FNAC+excisional biopsy | Antoni A | | no |
| Shilpa B | 2012 | F | 40 | lower lip | excisional biopsy | Antoni A+ B | + | no |
| Rahpeyma A et al | 2012 | F | 12 | soft palate | excisional biopsy | Antoni A+ B | + | no |
| Mirza AA et al | 2012 | M | 15 | tongue | FNAC+excisional biopsy | | | |
| Chawla O et al | 2011 | M | 9 | soft palate | excisional biopsy | Antoni A+ B | | no |
| Shetty SR et al | 2010 | F | 70 | palate | excisional biopsy | Antoni A+ B | | no |
| Andrade Santos PP et al | 2010 | F | 41 | palate | excisional biopsy | Antoni A+ B | | no |
| | 2010 | M | 22 | floor of mouth | excisional biopsy | Antoni B | | no |
| | 2010 | M | 18 | posterior tongue | excisional biopsy | Antoni A+ B | | no |
| | 2010 | F | 46 | oral mucosa | excisional biopsy | Antoni A | | no |
| | 2010 | F | 53 | palate | excisional biopsy | Antoni A+ B | + | no |
| | 2010 | - | 10 | oral mucosa | excisional biopsy | | | no |
| | 2010 | M | 32 | oral mucosa | I.B | Antoni A | | no |
| Lopez-Carriches C et al | 2009 | - | 15 | palate | I.B+surgical excision | | + | |
| Khonsari RH et al | 2008 | F | 19 | alveolar ridge | excisional biopsy | Antoni A | + | no |
| Chen CY et al | 2006 | M | 34 | floor of mouth | excisional biopsy | Antoni A | + | no |
| López-Jornet P et al | 2005 | M | 39 | tongue | excisional biopsy | Antoni A+ B | + | no |
| Bansal R et al | 2005 | M | 26 | tongue | excisional biopsy | Antoni A+ B | + | no |
| Yang SW et al | 2003 | F | 22 | upper lip | excisional biopsy | Antoni A+ B | + | no |

F: Female. M: Male. I.B:Incisional Biopsy. gl: glandula. FNAC: Fine Needle Aspiration Citology. Rec: Recurrence



**Figures 1 & 2**: Lesion on the left side of tongue. Clinical appearance in first visit.

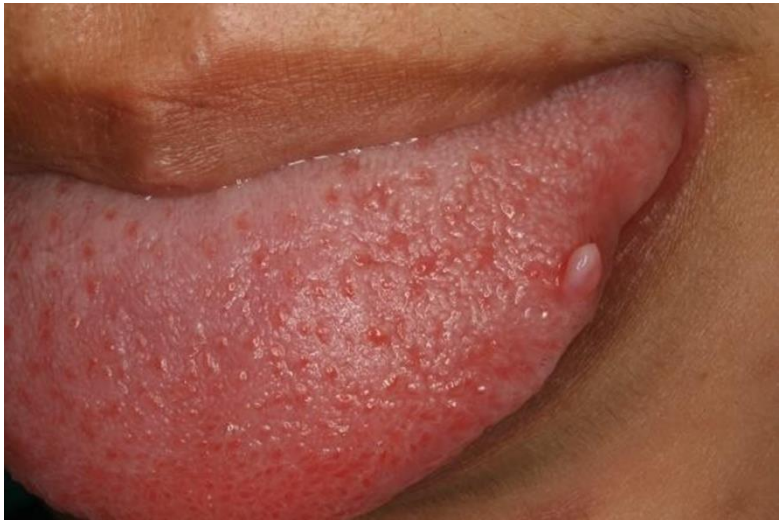


**Figure 3:** Clinical appearance 3 months later.

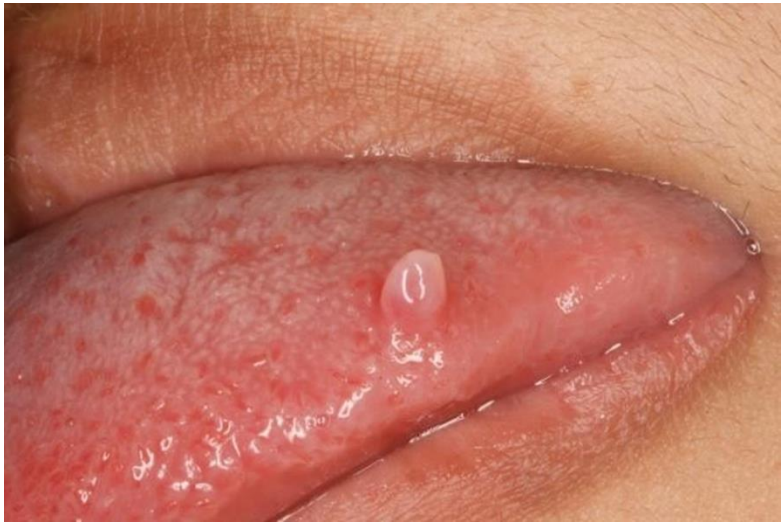


**Figure 4:**Clinical appearance of the lesion previously to the excisional biopsy.

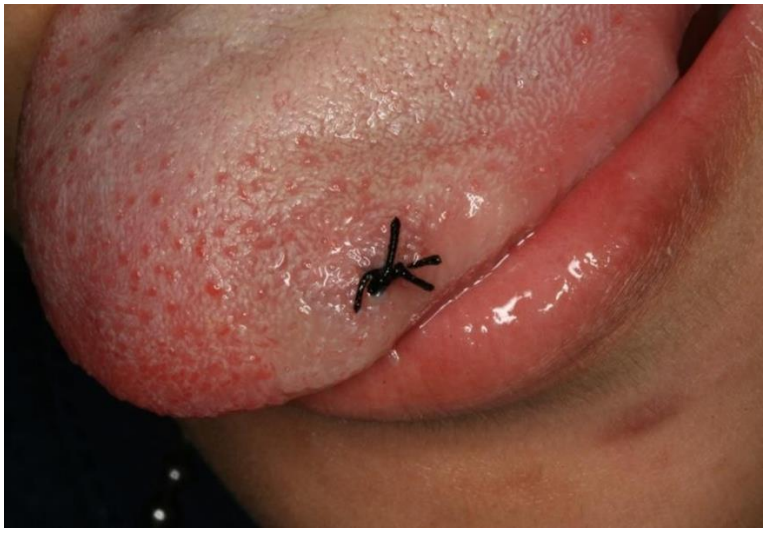


**Figure 5:** Review 7 days after the biopsy to suture removal.

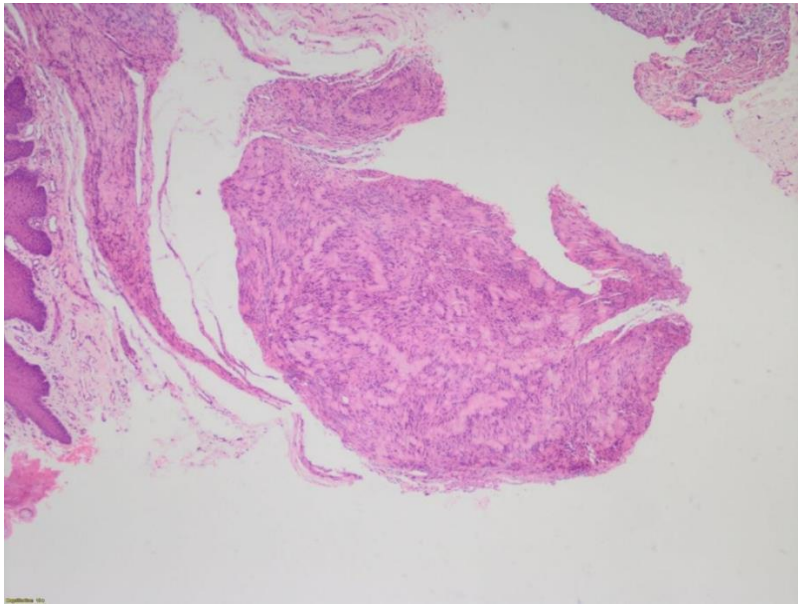
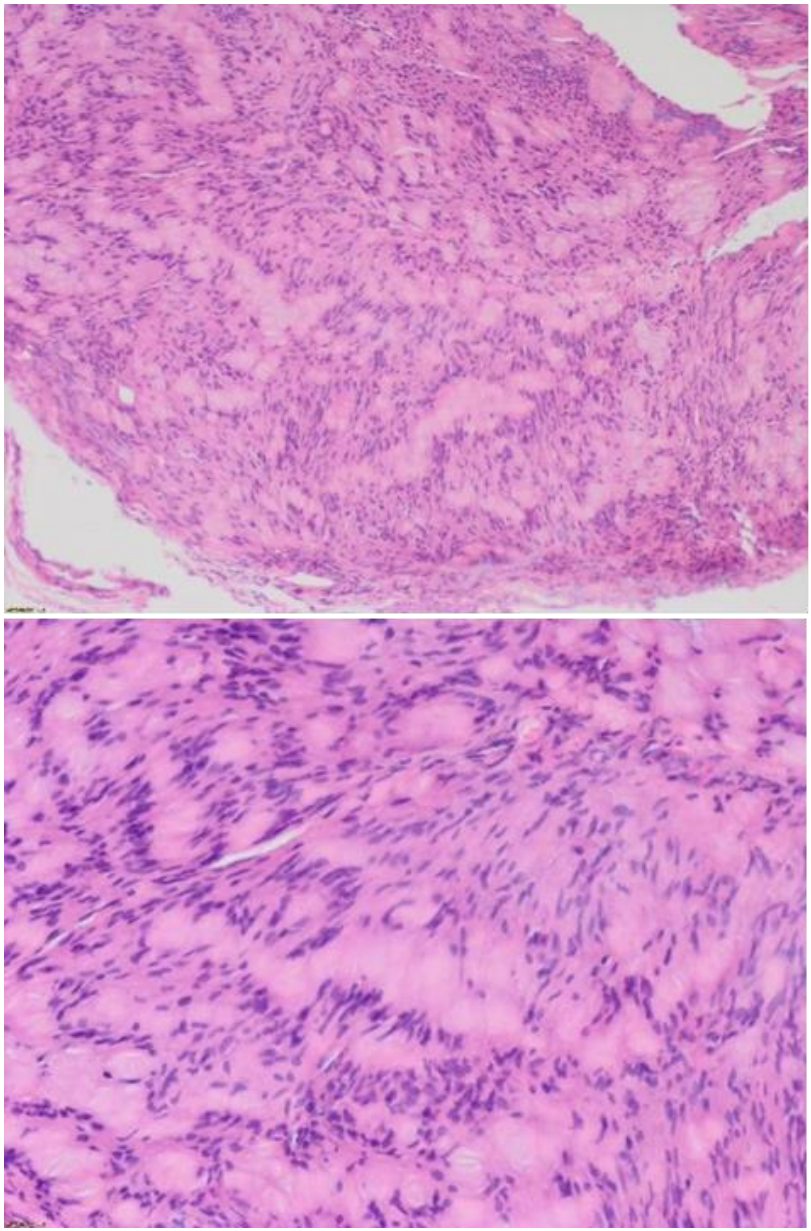


**Figure 6:** Histological section which shows the complete lesion.



**Figures 7 & 8:** Histological section to higher magnification. We can observe more cellular density composed by spindle cells with elongates cores organized in "palisade form". It could be observed amorphous substance´s bands placed between the cores. This establish the know "Verocay´s bodies".

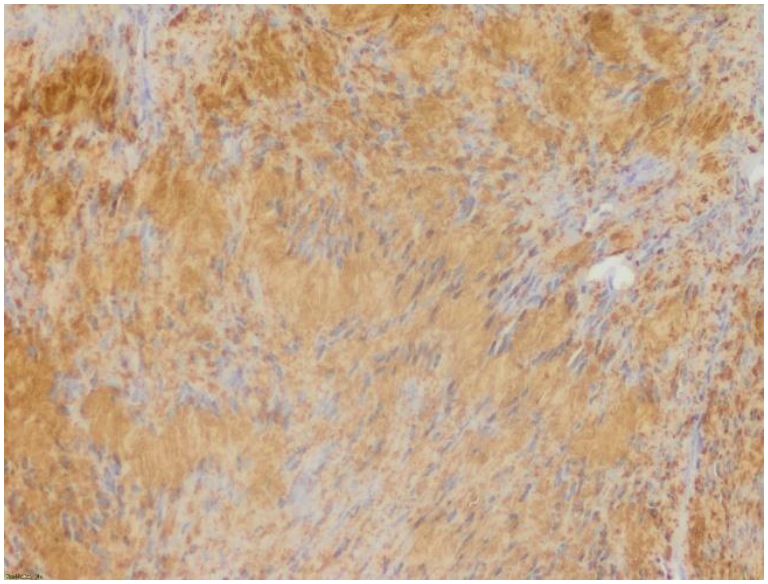


**Figure 9:** Schwannoma is positive to S-100.

## Conclusions

Schwannoma is a rare benign tumor that might appear in oral cavity presenting a combination of two histological patterns called Antoni A and Antoni B characterized by the presence of "Verocay´s bodies" and a positive S-100 protein staining. The diagnosis is performed by biopsy and the preferential treatment is the surgical excision which correlates with favorable prognosis.

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## Case Report

# Benign Tumors of the Oral Cavity: Epulis Fissuratum

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## Abstract

The benign tumors of the oral cavity are classified according to the type of tissue they developed from; they can be from epithelial lineage, connective tissue, nervous, vascular or melanic. The definitive diagnosis will be achieved through histological examination; they present a benign behavior, slow growth, low tendency to invade adjacent tissue and low chance of relapse after treatment. They can appear in jugal mucosa, lips, gingiva, palate, mouth floor or even the tongue. A clinical case

of an epulis fissuratum is presented. It is a benign tumor that develops from the connective tissue that is defined as an excessive overgrowth of intraoral tissue as a result from chronic irritation and trauma caused by ill-fitting prosthesis. We will perform the differential diagnosis with other benign tumors of the oral cavity.

## Points of Interest

- Benign tumors of the oral cavity
- Epulis fissuratum
- Benign tumors of epithelial lineage
- Benign tumors of connective lineage
- Benign tumors of vascular lineage
- Benign tumors of nervous lineage
- Melanic benign tumors

## Introduction

The epulis fissuratum is considered an excessive overgrowth of the intraoral tissue as a result from the chronic irritation and trauma caused by ill-fitting prosthesis [1,2]. The epulis fissuratum can cause pain and incommodity thus affecting negatively to chewing, esthetics and overall wellbeing of the patient [1]. The chronic trauma of the oral mucosa is considered a risk factor for the development of carcinoma [1,3]. A clinical case of an ill-fitting maxillary prosthesis on a 63 year old male with the development of an epulis fissuratum.

## Clinical Case

A 63 year old male was referred to the Oral Medicine, Surgery and Implantology service of the University of Barcelona Dentistry Hospital (HOUB) due to mobility and discomfort with the use of the maxillary removable prosthesis, given the gradual overgrowth of a fibrous tissue mass on the superior maxillary over the past 6 months that coincides with the flange of the prosthesis (Figure 1). The prosthesis was approximately 6 years old. The patient's medical history reflected arterial hypertension

and hypercholesterolemia treated with Enalapril 5mg and Atorvastatin 40mg. No toxic habits or allergies were referred.

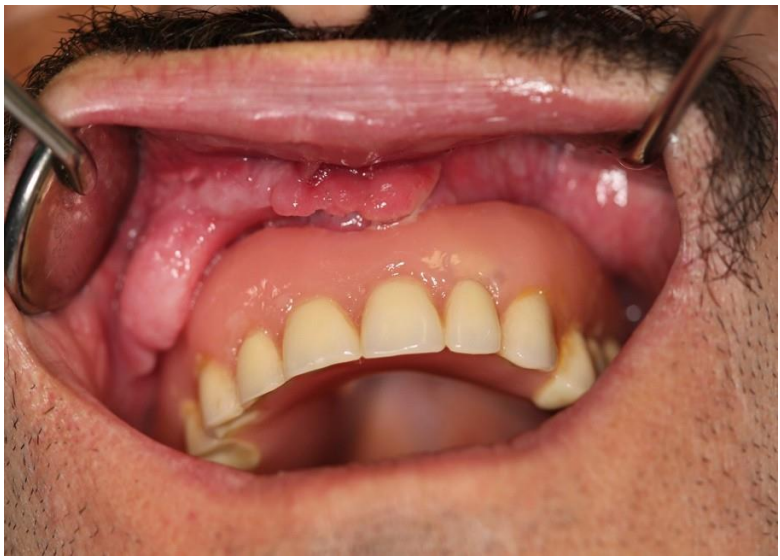

**Figure 1:** Image of the prosthesis and the lesion surrounding the prosthesis.

During clinical exploration an ill-fitting maxillary complete removable prosthesis and two fibrous, smooth, pediculated and eritematose lesions on the buccal area of the superior maxillary were observed. No presence of associated ulcers were observed (Figure 2). The presumptive diagnosis of an epulis fissuratum was reached and proceeded with the exeresis of the lesions with an electric scalpel (Figure 3 and 4). Once the extirpation of the lesion was performed a Linitul dressing was applied, that acts as a healing agent stimulating blood flow, and a soft relining of the prosthesis was performed with Visco-gel (Figure 5). The patient was referred to the prosthodontic service after the wound was healed for the confection of a new prosthesis (Figure 6). The anatomopathological study of the lesion provided the diagnosis of "Fibrous hyperplasia with chronic inflammation, compatible with Epulis Fissuratum".

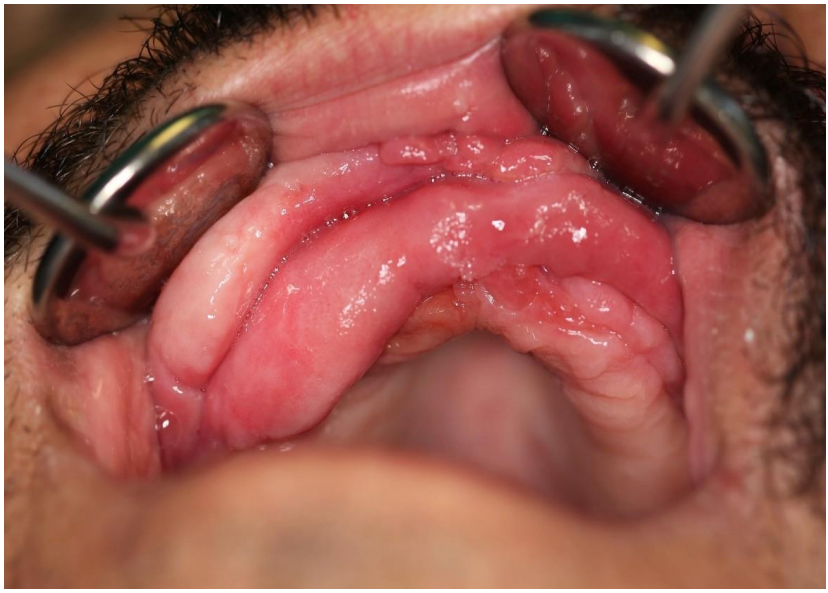

**Figure 2:** Appearance of the lesion without the prosthesis.

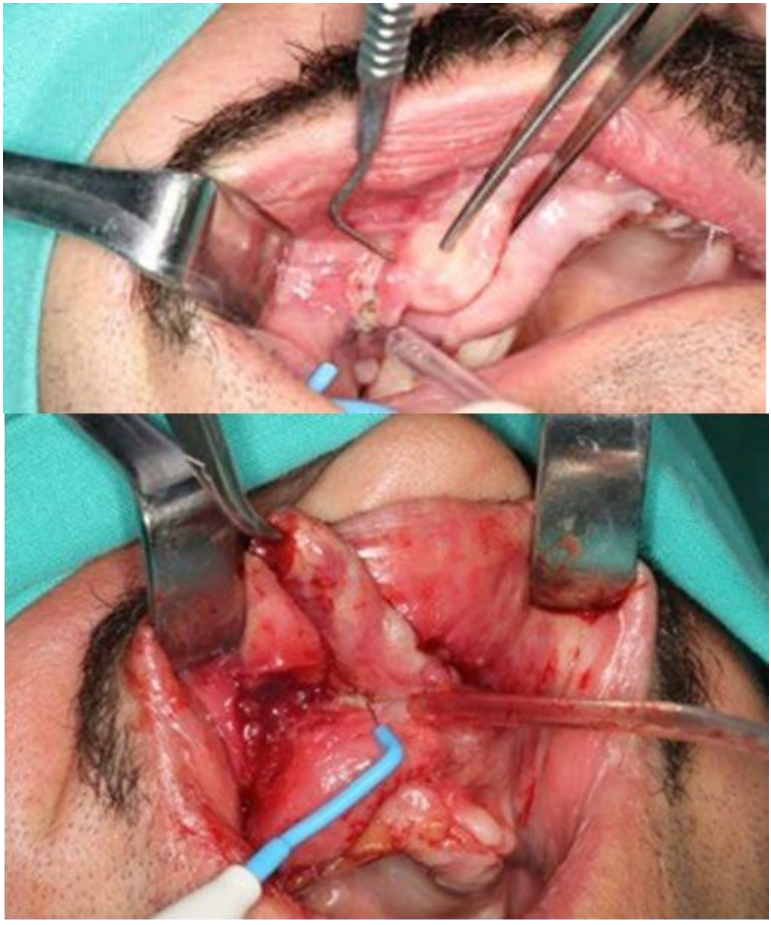

**Figure 3:** Excision of the lesion with electric scalpel.

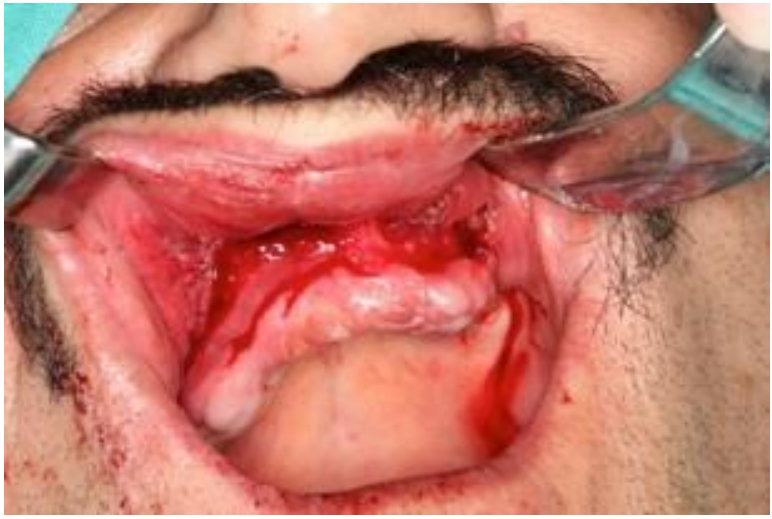

**Figure 4:** Result of the lesion excision.

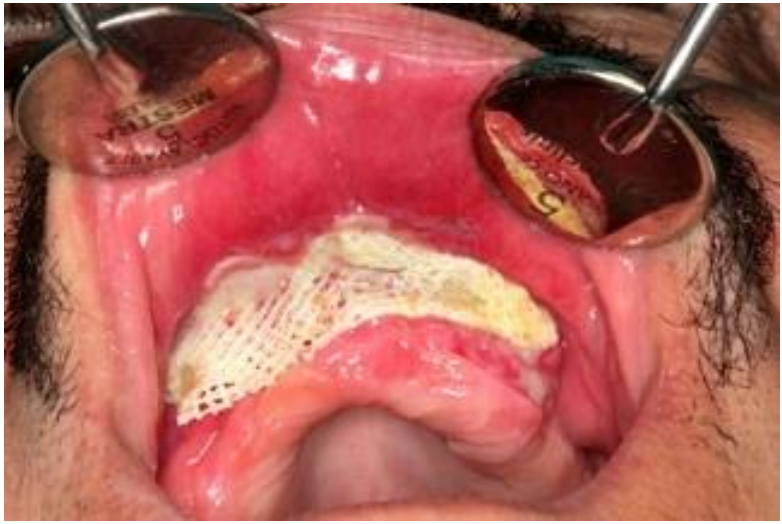

**Figure 5:** Application of Linitul® dressing.

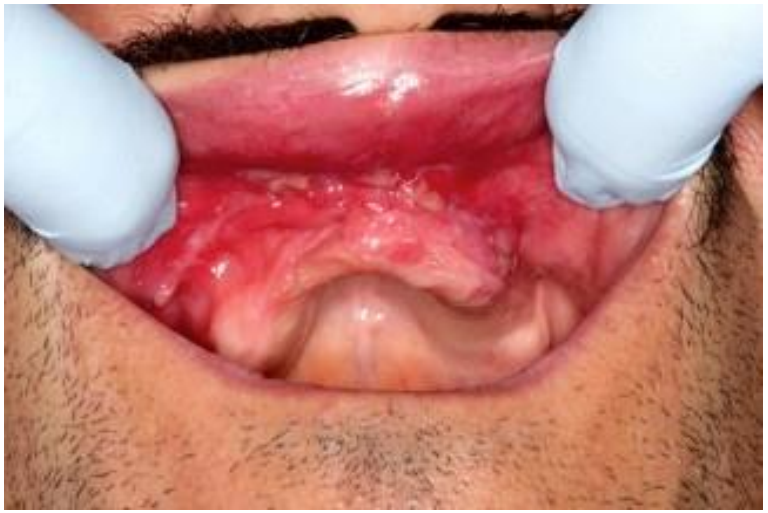

**Figure 6:** Image after a week of the intervention.

The epulis fissuratum is also referred as reactive fibrous hyperplasia or fibrous hyperplasia induced by prosthesis. This benign tumor presents itself clinically as a sessile elevated lesion that forms folds with a smooth surface and the overlying mucosa normal or erythematous. It is usually found in the gingival buccal sulcus, even though it is sometimes found as well in the palatal mucosa [1].

The size of the lesion varies in size from a localized hyperplasia of less than 1 cm to massive lesions that involve the majority of the length of the buccal vestibule. The prevalence is established between the 5 and 10% and is found more frequently in the maxilla than the mandible and in females [2].

Due to the chronic irritation, it can become traumatized and present itself as with an ulcerated surface [1,4].

The exact etiopathogenesis is unknown, but the most accepted theory is that it develops from a chronic low intensity trauma; generally due to poorly fitting prosthesis or even parafunctional habits [4]. The alveolar bone resorption produces an overextension of the prosthesis borders that will cause a chronic irritation in the oral mucosa of the sulcus. Other etiological

factors are the bad oral hygiene that can produce a local infection due to candidiasis, the constant daily use of oral prosthesis, sensitivity to the basing materials of the prosthesis, smoking, age related changes and systemic conditions. Furthermore, the irritation and trauma of the salivary palatal glands and the inadequate suction chambers in the prosthesis can also be considered possible etiological factors [2].

The histopathology characterizes itself by the presence of fold like lesions in the buccal area formed by connective tissue hyperplasia, covered by stratified squamous epithelium. In the bottom of the fissures, severe inflammation and ulceration can occur [5] (Table 1).

**Table 1:** Histological characteristics of the epulis fissuratum.

| Epithelial Changes | Conective tissue changes |
|---|---|
| Acanthosis Hyperkeratosis<br>Ulceration<br>Papilla Inflammatory hyperplasia<br>Espongiosis<br>Diskeratosis | Bone metaplasia Cartilage metaplasia<br>Limphoid Nodular Hyperplasia<br>Microabscess<br>Ectopic sebaceous glands |

## Discussion

The treatment of the epulis fissuratum can be either surgical or non-surgical. The non- surgical approach will consist of the removal of the acrylic prosthesis edge followed by several rebasings until the lesion completely heals and disappears. Never the less, this method is slow and not always possible or effective [2].

The complete removal of the lesion is usually the elected treatment. The surgical approach contemplates the use of conventional surgical blade, electrocautery, soft tissue laser and cryosurgery with liquid nitrogen [2]. As with many surgeries the primary inconvenient is the management of the epulis fisuratum in elderly patients, population within which it prevails. Frequently elderly patients present systemic disorders that complicate the management; such as diabetes or the

anticoagulant/antiplatelet medication amongst other alterations. The new surgical techniques allow for an easier management of this lesions [3].

The differential diagnosis will be established amongst other benign tumors of the oral cavity. These are generally solitary lesions of slow growth. They can appear in the jugal mucosa, lips, gingiva, palate, the floor of the mouth or the tongue. The diagnosis must be clinical and corroborated by the biopsy and histological analysis (6). The classification of the benign tumors of the oral cavity is based around histological criteria according to the origin of the tissues [6] (Table 2).

**Table 2:** Classification of the benign tumors of the oral cavity.

| | |
|---|---|
| **Epithelial lineage tumors** | Lesions related with the human papilomavirus:<br>-Common wart or Verruca vulgaris<br>-Squamous papylloma<br>-Focal epithelial hyperplasia<br>-Acuminate Condyloma Keratoacanthoma |
| **Connective tissue lineage tumors** | From fibrous tissue:<br>-Fibroma<br>-Hereditary gingival fibromatosis<br>-Fibrous hyperplasia or epulis fissuratum<br>- Bilateral Fibrous Hyperplasia of the Tuberosity<br>-Drug related gingival hyperplasia From adipose tissue |
| **Vascular tumors** | Hemangioma Linfangioma<br>Trigeminal encephalic angiomatosis<br>Hemorragic hereditary telangiectasia |
| **Nervous tumors** | Neuroma Schwannoma Neurofibroma<br>Neurofibromatosis |
| **Melanic tumors** | Melanocytic nevus |

# Epithelial Line Tumours

## Lesions related with the Human Papillomavirus (HPV)

### Verruca Vulgaris or Common Wart

The common wart is the primary expression of the cutaneous infection from Human Papilomavirus (HPV) and represent 70% of warts [7]. The autoinoculation by means of the hand warts is the primary vector of transmission and affects mainly children [7,8]. The periungueal area of the hands is the most frequent location, even though it can be found in any part of the skin. It is found in the oral mucosa with relative frequency, being the labial mucosa and the palatal area the most commonly affected.

They appear clinically as solitary lesions, with pink [7] or white colour, exofitic, circumscribed, firm consistency and sessile. In the histological examination they present hyperkeratinization of the epithelial surface and elongation of the papillary crests [9].

The differential and histological diagnosis includes benign papillary lesions and malignant entities. The verruciform xantoma, the squamous papilloma and the acuminate condyloma are found amongst the benign lesions. The hyperplasia/ verrucous carcinoma are malignant and premalignant variations of the squamous cell carcinoma that must be taken into consideration for the differential diagnosis with the common wart [7].

### Squamous Papilloma

Most frequently found amongst children and adults within the fourth or fifth decade of their life [10]. It is characterized by presenting digitiform exofitic projections or with cauliflower like form [7] (Figure 7). The squamous papilloma is presented usually as a unique lesion, sessile or pediculate with a colour that varies from white to pink and of at least 1 cm in diameter [9]. The palate and tongue are the most commonly affected areas [7].

Histologically the papillomas are constituted by stratifies squamous epithelium, the majority are queratinized and have a white colour. Only in a small part koilocytes can be recognized

("ball cells" characteristic keratinocytes usually associated to a viral infection); generally the HPV is found at very low levels or has disappeared in high levels [8]. Usually associated with type 6 and 11 HPV [8,9].

The clinical and histological differential diagnosis includes the common wart, verruciform xantoma, acuminate condyloma, giant cell fibroma and the squamous papillary cell carcinoma [7]. The treatment is the excision and the histopathological analysis [9].

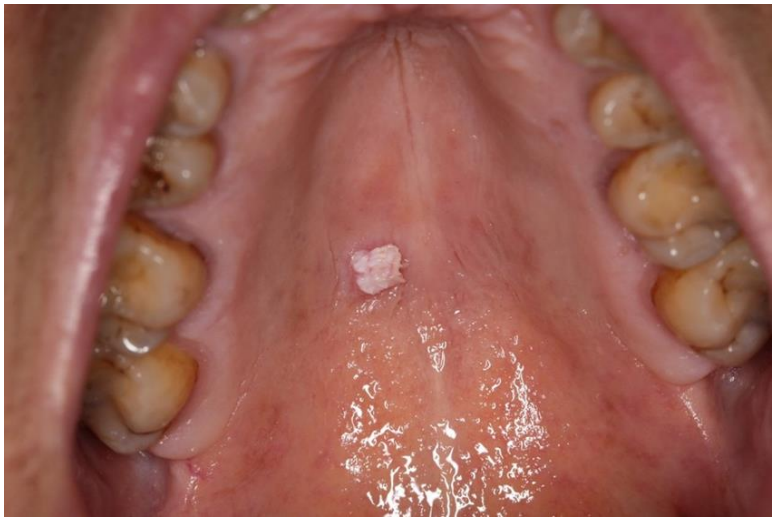

**Figure 7:** Squamous papilloma on the hard palate.

## Focal Epithelial Hyperplasia (Heck's disease)

The focal epithelial hyperplasia is a hereditary disorder with autosomal recessive inheritance. Numerous rounded papilloma appear in the mucosa, that can reach 1 cm [7]. In the oral mucosa it can appear as multiple elevations, white, tender and nodular, that can disappear and reappear. They are usually confluent and can cause raised plaques or a cobbled like appearance. It is usually found in the labial mucosa, vestibular or in the tongue [8] (Figure 8). It usually affects children, teenagers and young adults with familiar relation [8]. Associated with type 13 or 32 HPV

[8,9]. With histological examination acanthosis with prolonged epithelial crests can be observed [9], mytosoid bodies [7,8] and the presence of koilocytes [7].

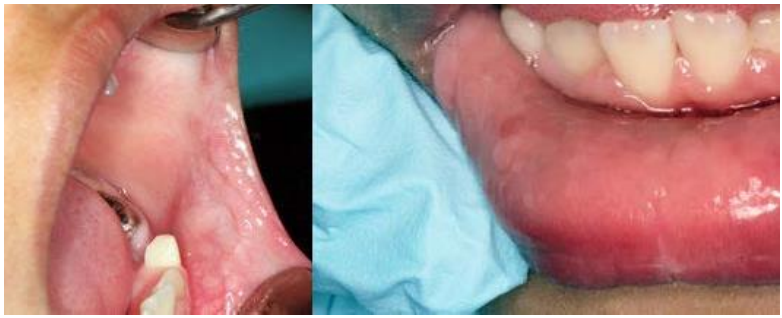

**Figure 8:** Young patient with focal epithelial hyperplasia.

Generally, no treatment is needed and spontaneous resolution is usually observed [8,9]. In case aesthetic alterations are produced or the lesions become frequently traumatized the surgical excision will be performed [9].

## Acuminate Condyloma

The acuminate condyloma generally presents itself as anal or genital warts from sexual transmission [7]. Generally associated with type 6 and 11 HVP [9]. Never the less, despite being infrequent, they can appear in the oral cavity. Even though the presence of lesions simultaneously in genitals and oral cavity suggest sexual transmission, it is possible that other infection vectors exist, such as through fomites. Adults are most commonly affected, especially within the third and fourth decade of life [7]. Clinically it can present itself as a unique lesion or multiple, some of which can unite [7]. Normally they appear as small nodules of white or pink coloration. The tongue or superior lip are the most common intraoral affected sights [9].

The differential diagnosis includes the squamous papilloma, wartlike xantoma, the squamous cell carcinoma and the focal epithelial hyperplasia [7].

## Keratoacanthoma

The keratoacanthoma, also know and self-healing carcinoma [9], is a benign epithelial neoplasia, even when there is presence of invasive growth [6]. A differential diagnosis must be performed with the squamous cell oral carcinoma. It has a frequent appearance on skin, especially on areas exposed to sunlight [6,9], and it rarely appears in the oral cavity. More frequent on males and on patients of 50 years and over [9].

The onset of this lesion is clinically observed as a nodule that grows fast and a characteristic central crater on the indurated corneal mass appears [6]. After 1 or 2 months without changes, there is a spontaneous regression that happens within 5 to 10 weeks [9].

The histologic characteristics include a crater full of central keratin, a lip of normal epidermis around the crater, dermic isles of vitreous hialin eosinofile keratinocites and inflammatory cells marked around the periphery of the lesion, that consists mainly of linfocites, eosinofiles and neutrofiles [11].

The diagnosis will be clinical and histopathological. Despite the spontaneous regression, the surgical excision will be performed to confirm the diagnosis by histopathological examination [6]. Other techniques such as the intralesional injection of methotrexate, 5-fluoracil, bleomycin or interferon alfa as alternatives to the surgery have been proposed, the previous biopsy will always be necessary to differentiate it histologically from a squamous cell carcinoma [11].

# Conective Lineage Tumors

## Fibrous Tissue

### Fibroma

The fibroma (Figure 9) is the most common benign neoplasia in the oral cavity. It consists of fibroconective tissue of the oral cavity. Clinically appears as a nodule of 1 cm in diameter approximately [6], well circumscribed, sessile or pediculated, with a smooth surface with normal epitelium, asymptomatic and

with a long evolution [9]. The real fibroma is very rare, the majority of the fibromas are reactive hyperplasia caused by chronic irritation [12]. They are usually developed on zones where there is friction or other irritative factors [9+. The most common location is the jugal mucosa on the occlusion line [13]; followed by tongue, palate and gingiva [9]. The histopathology of the fibrous hyperplasia is characterized primarily by the presence of fibroblast proliferation and collagen fibers, surrounded by a layer of thin squamous stratified epithelium with shallow crests [14]. The diagnosis is clinical and the anatomopathological examination confirms the diagnosis [9].

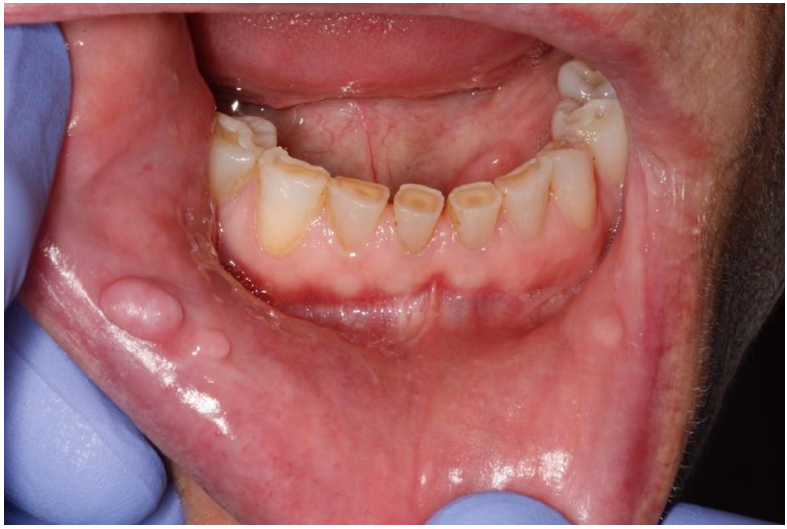

**Figure 9:** Fibroma in the lower lip.

## Hereditary Gingival Fibromatosis

The gingival fibromatosis is a rare benign pathology that manifests itself as a volume increase of the gingiva, generally the fixed gingiva, hindering the speech and oral hygiene. This growth is slow and asymptomatic. It is autosomal dominant and can be part of a genetic syndrome or present itself isolated or with previous family history [15]. This gingival growth can appear previous to the eruption of the teeth or appear even in later stages of childhood [8]; it can also cause aesthetic problems

and functional, such as diastemas, chewing problems or prevent the normal closure of the lips [15]. The gingiva can grow to the extreme of completely covering the crown of the teeth or even preventing eruption [8]. The gingival enlargement has the same colour as normal gingiva of firm consistency, there is no haemorrhage or symptoms related [16].

In the histological examination the gingival tissue is formed by thick bundles of collagenous connective tissue [8] within which long epithelial papilla extend. There have also been some bone spots and calcified particles reported [15].

This can form part of syndromes associated with other manifestations, such as rough facial features (similar to acromegalia), epilepsy or deafness and querubism [8]. The excess of gingival tissue can be removed with surgery, but its relapse is frequent. Treatment must be postponed until puberty is reached when tissues grow slower and a good oral hygiene must be maintained [8].

## Bilateral Fibrous Hyperplasia of the Tuberosity

The fibrous augment of the tuberosities is a little known bilateral fibrous proliferation of the alveolar maxilla behind the premolar area. In some cases a milder form of hereditary gingival fibromatosis can be observed, even though the onset of this growth is usually during the adulthood [8], or due to pharmacological influence or for idiopathic reasons. It is clinically characterized by an increase in size of the gingival tissue of the maxillary tuberosity area, with a pink colour and firmness of the tissue [17].

The diagnosis of the maxillary tuberosity bilateral hyperplasia meets 3 criteria:

- The mases are almost always specular images of each other, they are not only bilateral;
- The mases primarily originate on the lateral posterior surfaces of the hard palate, not on the gingiva;
- The mases have typically a very wide base, following the pattern of a fibromatosis more so than a fibroma [18].

The primary histologic characteristic is the subepithelial hyperplasia due to the increase in connective tissue. The treatment is the gingivectomy, even though a relapse can occur.

## Drug related Gingival Hyperplasia

The gingival hyperplasia due to medication (Figure 10) or gingival overgrowth is a reactive phenomenon that occurs due to different therapeutic agents with which the interdental papilla acquires a bulbous form that covers the teeth and can surpass the occlusal or incisal border of the teeth. The gingiva is firm, pale and present a speckled texture. Antiepileptics, fenitoin, some calcium antagonists such as nifedipin, diltiazem and cyclosporine amongst other pharmaceutical drugs can induce a hyperplasia of the gingival fibroblasts [8]. The onset of this phenomenon, in particular advanced cases, can interfere with speech, chewing and the dental eruption, as well as hinder the aesthetics [19].

**Figure 10:** Patient with gingival hyperplasia due to the use of Amlodipin 5mg once a day douring 18 months.

The control over the inflammatory component through a program of adequate oral hygiene can benefit the patient and limit the severity of the excessive gingival overgrowth [19]. Never the less, it is often necessary to resort to gingivectomy in order to facilitate the hygiene or due to aesthetic reasons [8].

## From Adipose Tissue: Lipoma

The lipoma (Figure 11) is a benign mesenquimatous tumor composed of mature adipocytes [20]. They are frequent in the head and neck region, but it's appearance in the oral cavity is uncommon [6,20]. We can find them generally in patients between the ages of 40 and 60 years of age [9]. The most commonly affected areas are the oral mucosa, lips, tongue, palate, vestibule, floor of the mouth and the retromolar area; even though they can be found in any area where adipose tissue is present normally [6,20].

Clinically they are well circumscribed tumors, painless, slow growing [20] and yellowish [9]. The aetiology and pathogenesis are not clear, even though endocrine factors, inflammatory, hypercholesterolemia, obesity or chromosomic anomalies have been considered amongst the possible causal agents. Histologically they present mature adipose cells with squamous stratified paraqueratinized epithelium and stroma of connective fibrocelular tissue. The most commonly accepted treatment is the surgical excision and its recurrence is rare [20].

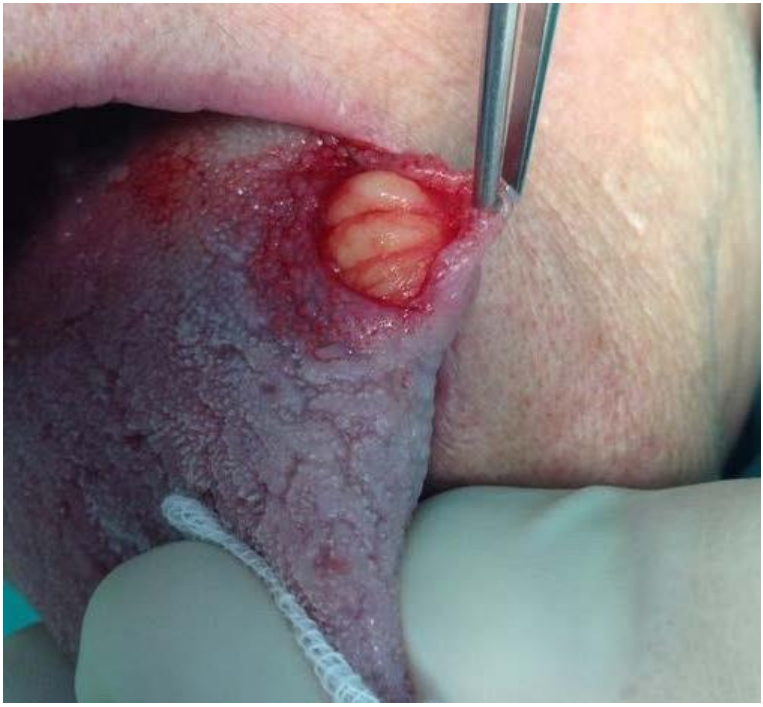

**Figure 11:** Excision of a lipoma on the lateral side of the tongue.

## Vascular Tumors

### Hemangioma

Hemangiomas (Figure 12 & 13) are formed by an accumulation of blood vessels. Some hemangiomas are congenital malformations or hamartomas [9]. Oral hemangiomas are common and are present since birth or appear during childhood [6]. The aetiology is unknown, even though premature birth or low weight are known as risk factors for its appearance [21].

They appear clinically as red bright papules or nodules of varying size [21] when pressured their colour turns whiter or they even disappear [6,9]. The most frequent localizations are lips, jugal mucosa, tongue and palate [9].

They are histologically divided into two types:

-Capillary hemangiomas: comprised of capillary vessels and appear during childhood; they tend to dissipate with age. Clinically observed as a red flat surface or raised surface.
-Cavernous hemangioma: formed by bigger blood vessels. Appear as a raised lesion of red or bluish colour [8,9]

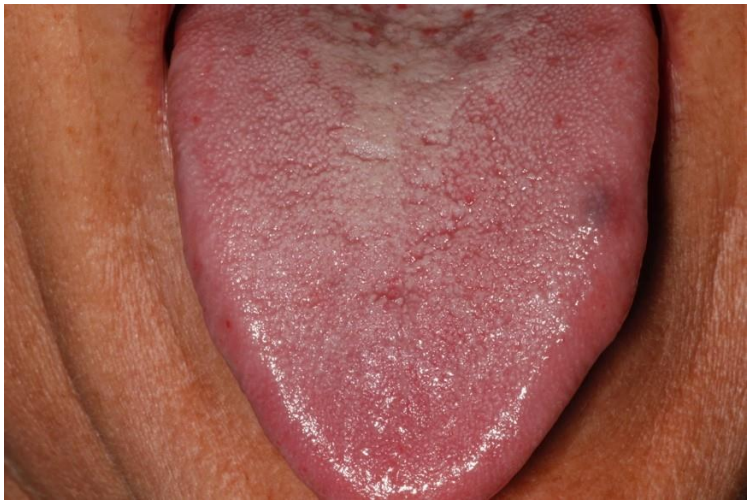

**Figure 12:** Hemangioma on the back of the tongue.

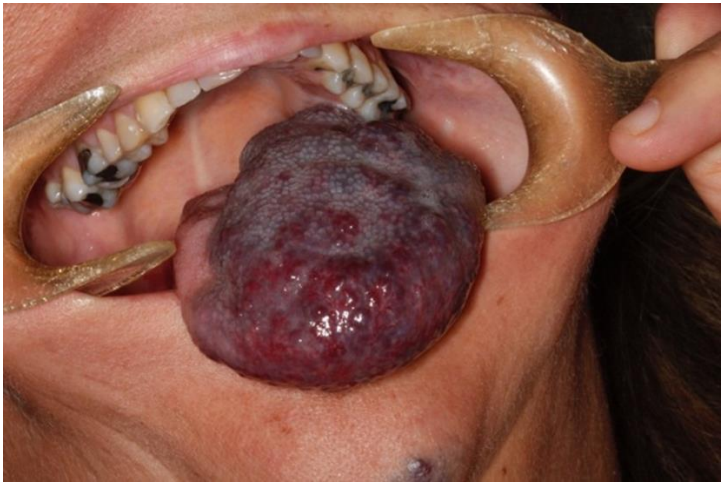

**Figure 13:** Cavernous hemangioma of the tongue.

The diagnosis is clinical, vitropressure is a complementary test. Biopsy is not recommended due to the risk of hemorrhage [9]. Hemangiomas can disappear spontaneously, so wait and see conduct is recommended. Another therapeutic approach is the surgical removal of the lesion, laser treatment, cauterization, cryotherapy, radiotherapy or sclerotherapy [21].

## Lymphangioma

Lymphangiomas are hamartomatous masses rarely found in the oral cavity [6], constituted by an accumulation of lymphatic vessels. They usually appear during the perinatal period up to 3 years of age. Also classified by the varying size into capillary or cavernous form [9].

The most common place of appearance is the tongue [6,8] and, when lymphangiomas are big and diffuse, they can be the cause of generalized macroglossia [8].

This lesion is asymptomatic [8] and appears in the form of small raised soft nodules; their colour may vary from regular colour of the tissue to red [9]. Histologically lymphangiomas are constituted by several lymphatic vessels with thin walls, that contain lymph.

The treatment must be to wait for its spontaneous regression, and in the case that this is not possible surgical treatment with sclerosing agents [8].

## Encephalic-Trigeminal Angiomatosis (Sturge-Weber Syndrome)

The Sturge-Weber syndrome (Figure 14) is a congenital neurocutaneous disorder [22]. It is characterized by cutaneous and mucosal capillary malformations that follow the ophthalmic branch of the trigeminal nerve (“port-wine birthmark”), leptomeningeal angiomas and brain calcifications [9]. The venous malformation can develop hypertrophy of the soft tissues, bone tissue and formation of proliferative nodules or progressive ectasia. Can be associated with an excessive growth

of the maxilla and mandible, producing malocclusion and excessive exposure of the teeth, causing a facial deformity. It can be also associated with neurological manifestations, ocular or endocrine [22].

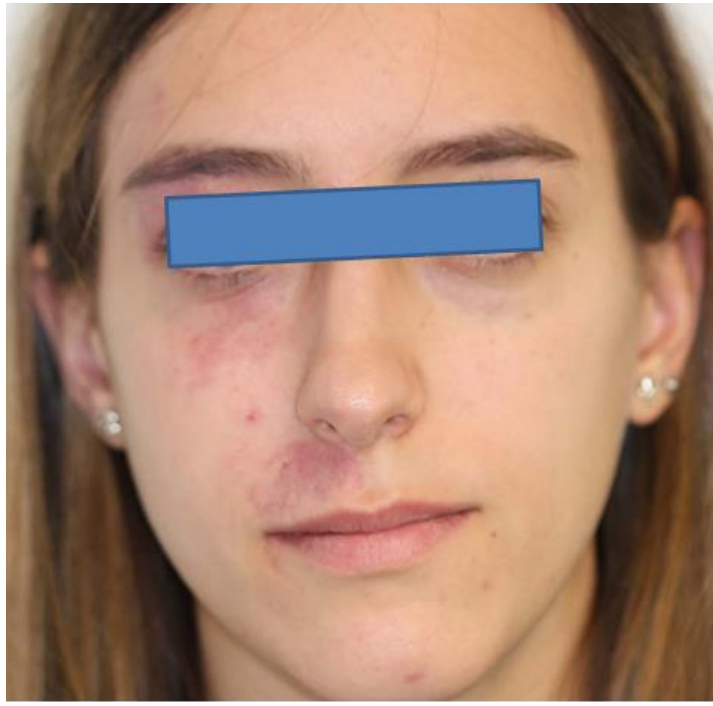

**Figure 14:** Young patient with Sturge-Weber syndrome.

## Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome)

Autosomal dominant hereditary syndrome [8,23].

Characterized by presenting arteriovenous malformations in which telangiectases are observed in skin, mucosa and solid organs. The majority of patients only present mucocutaneous telangiectases [23] (specially on lips, nose, mouth and hands [8]), epistaxis and anemia due to the lack of iron. The lesions in other organs are the real threat to the life of the patient, such as alteration in the central nervous system, gastrointestinal or lungs [23].

## Neurological Tumours

### Neuroma

Also named traumatic neuroma (Figure 15). The traumatic neuroma consists on a reactive proliferation of the peripheral nervous system after an aggression to this tissue [24].

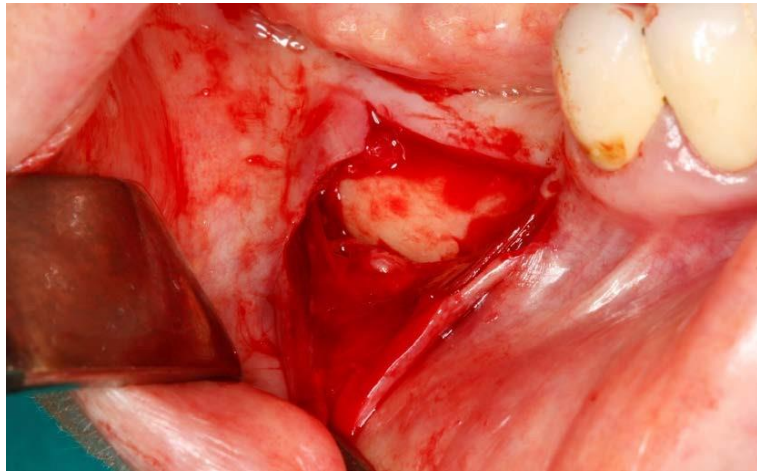

**Figure 15:** Intraoperative image of the excision of a traumatic neuroma caused by removable prosthesis.

They are the consecuence of a reaction associated to the severing of the neuronal bundle. During the repair process, the proximal neuronal fibbers proliferate and form an irregular agglomerate associated with healed connective tissue [9]. The factors for the origination of this are previous surgical procedures, pressure, lacerations, cuts and bleeding to the surrounding tissues. Clinically appears as a smooth surface nodule sensible to palpation [24]. The most frequent location is the mental nerve zone, tongue, and lip [9]. Histologically, the traumatic neuromas consist on a random proliferation of vascular bundles, including axons, Schwann cells and fibroblasts over a collagen bed [24].

The ideal treatment is the surgical excision of the traumatic neuroma, being uncommon to suffer a recurrence [9].

## Schwannoma

The Schwannoma (Figure 16), also known as neurilemoma [8,9,24], are uncommon neoplasias developing from the peripheral nerve sheath in the Schwann cells [9,24]. They are localized in the tongue, palate, jugal mucosa, lip or gum (9). Clinically appear as solitary masses, non-fixed and of slow growth [24]. Histologically corresponding to an encapsulated mass of fusiform elongated cells with the formation of nuclear palisades and a varying quantity of lax mixoid conjunctive tissue **[**8]. The surgical excision is the preferred treatment [9].

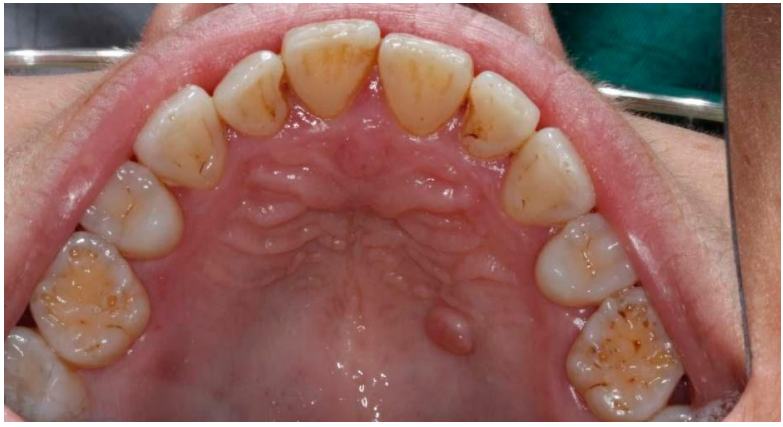

**Figure 16:** Schwannoma on hard palate.

## Neurofibroma

Neurofibromas (Figure 17) are benign proliferations that derive from peripheral nerves and represent one of the most frequent neurogenic tumors. Its origin seems to be related with the Schwann cells and perineural fibroblasts. They can appear as multiple lesions, associated with neurofibromatosis, or unique [25]. Clinically appear as pediculated or sessile nodules, of slow growth which can affect skin and mucosa. The most frequent localitzation is the tongue, jugal mucosa and palate [9]. Histologically, neurofibromas are cellular with chubby nucleus separated by thin sinuous collagen fibbers, amongst which it is frequent to find mastocytes. The treatment is the surgical excision [25].

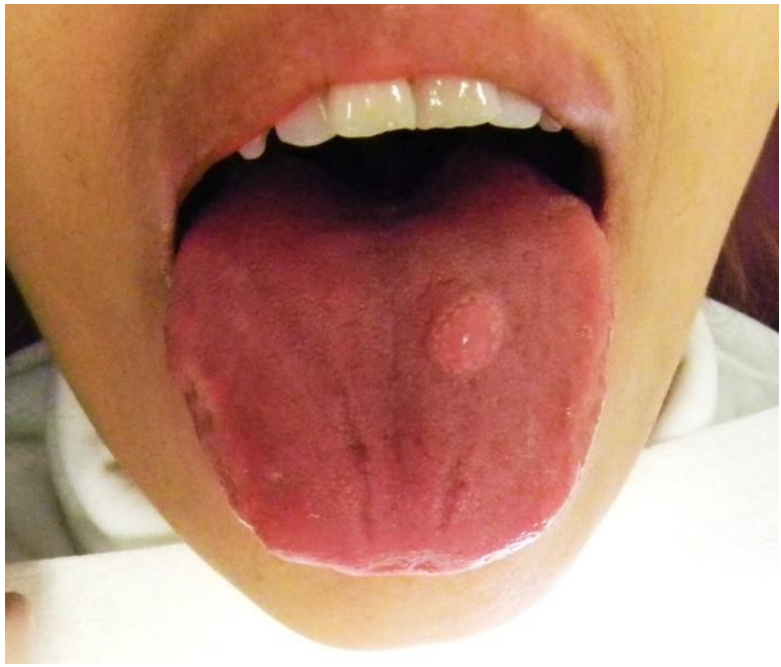

**Figure 17:** Neurofibroma on the back of the tongue.

## Neurofibromatosis: von Recklinghausen Disease

The neurofibromatosis is a group of autosomal dominant genetic disorders characterized by multiple cutaneous lesions and tumors in the central and peripheral nervous systems. Oral manifestations of neurofibromatosis are soft tissue oral and perioral fibromas with subsequent periodontitis, impacted and supernumerary teeth, morphological changes on the teeth and Angle class III, amongst other manifestations [26]

## Melanic Tumors: Nevus

Melanocytic nevus (Figure 18) are benign congenital proliferations or acquired from melanocytic origin cells derived from the neural crest. These lesions are typically found on the skin and are less frequent on the oral mucosa. Within the oral cavity they are most frequently found on the hard palate and the buccal mucosa [27]. Clinically observed as circumscribed

pigmented lesions. The treatment is the excision and their anatomopathological study to differentiate from the early stage melanoma [9].

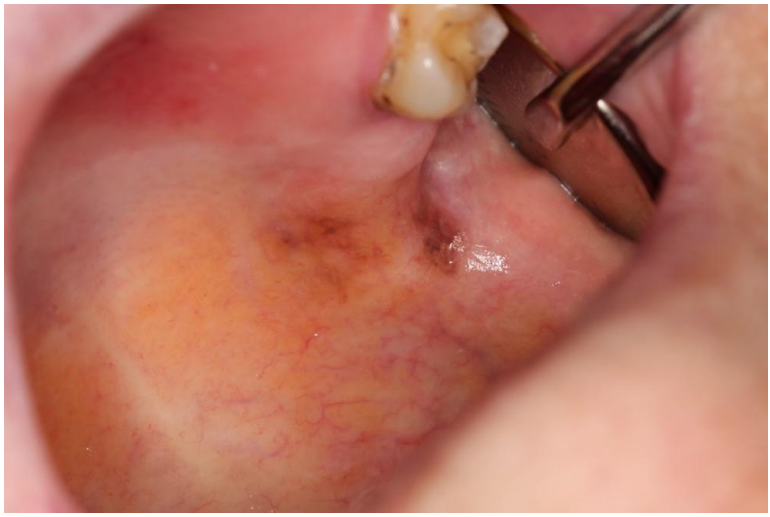

**Figure 18:** Melanocytic nevus on the retromolar area.

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## Case Report

# Fibrous Dysplasia in the Posterior Maxilla: A Case Report

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## Abstract

Fibrous dysplasia (FD) is an uncommon disease that represents between 5-7% of all the benign osseous tumors. It is characterized by the progressive replacement of normal bone with atypical fibrous-osseous tissue. This replacement of normal bone shows a shorter, thinner, irregularly shaped, and a larger

trabeculae area. It usually affects long bones, craniofacial bones, ribs, and pelvis. FD has a rare but clear potential for malignant transformation. Two types of FD can be distinguished: monostotic, if only one bone is affected or polyostostic when multiple bones are involved.

## Keywords

Fibrous Dysplasia, McCune-Albright Syndrome, Fibrous Osseous Lesions, Ossifying Fibroma, Ossifying Dysplasia, Osteosarcoma

## Key Points

Bone diseases in dentistry

## Introduction

Fibrous dysplasia (FD) is a rare congenital disease characterized by the progressive replacement of normal osseous tissue by abnormal fibroustissue [1]. The replaced bone shows a shorter, thinner and more irregular trabeculated area [1]. It affects long bones such as the femur, craniofacial bones, ribs and pelvis [1-3]. It was first described in 1938 by Liechtenstein [4], who differentiated it from the studies by McCune-Bruch and Albright et al. These authors described it as a disseminated fibrous osteodystrophy featuring endocrinopathies, hyperpigmentation of the skin and early puberty in women,which would later be known as McCune-Albright syndrome [5,6]. The gene involved in the pathogenesis of FD is the alpha subunit of the G protein receptor, found in chromosome 20. This will produce an increase in cyclic adenosine monophosphate (cAMP), leading to inappropriate proliferation and differentiation of bone cells [1,3,7,8]. There are two types of FD depending on the number of bones affected. Monostotic, where only one bone is affected, or polyostotic, when two or more bones are affected [1,9]. Although unusual, the potential for malignant transformation should not be underestimated. FD has a malignancy potential of approximately 1%, especially in the polyostotic forms: the

McCune-Albright syndrome, can have a malignancy potential of up to 4%. (10). Malignancy derived from FD can be osteosarcoma (70%), fibrosarcoma (20%), chondrosarcoma (10%) and malignant fibrous histiocytoma (4%) [8-11].

## Epidemiology

Fibrous dysplasia represents 2.5% of all bone tumors and approximately 7% of all benign bone tumors [12-14].

Regarding the prevalence: monostotic forms represent 75% of cases, while polyostotic FD represents 20-30%. The most frequent (up to 90%) location of monostotic FD is the maxillae[7,15] with a ratio of 2:1[15], in particular the zygomatic area[16]. In relation to the polystotic forms, the locations in order of frequency are the femur, tibia, craniofacial bones, pelvis, ribs, humerus, radius, ulna, lumbar spine, clavicle, and cervical spine. Lesions are usually unilateral [7].

Patients with monostotic form are between 10 and 30 years of age [7], while the polyostotic form is found in children under 10 years of age [1].

In some studies, it seems more prevalent in women, although others report a similar prevalence between genders [3,13,14]. It can be associated with syndromes such as McCune-Albright syndrome [1,7,17].

## Clinical Features

Most commonly, a slow-growing, painless lump is present. It can cause asymmetries and facial deformity with displacement of teeth, eruption anomalies and malocclusion. The progression may cause loss of vision and hearing, obstruction of the airways, anosmia and paresthesia. In long bones, fractures, limb deformities or pain may occur [7,8,17-19].

## Diagnosis

The diagnosis of FD is based on the combination of clinical, radiographic, histological observation and genetic study of GNAS [7-9]. It is incidentally diagnosed on a panoramic radiograph: the trabecular bone is replaced by a more radiolucent bone, displaying a "ground glass" pattern (opaque) making the trabecular bone non-perceptible [3,7,11,17]. CBCT and histopathological analysis help to confirmthe diagnosis [1,7].

Histologically, immature trabecular bone surrounded by a fibrous stroma including osteoclasts can be seen. The trabeculae are thin and fine, not connected to each other and show a characteristic "Chinese letters" pattern [7].

For the diagnosis, genetic studies based on the GNAS (Guanine Nucleotide binding Alpha Stimulating) mutations are used as "gold standard", improved with the new generation sequencing system (NGS) [20,21].

FD is classified within the group of benign fibro-osseous lesions, with common histological patterns including a hyperproliferative fibrous material mixed with bone structures and some elements of bone tissue [22]. The clinical and radiographic images will help us obtain the definitive diagnosis and determine the appropriate treatment plan[8].

## Treatment

Patients not presenting functional problems, deformities, and without a higher risk of fractures, will benefit from disease progression control [23]. If surgical treatment is necessary, it usually consists of bone remodeling or surgical excision along with posterior reconstruction [24]. The recurrence rate ranges between 25-50% [22,25]. The use of corticosteroids for the treatment of visual symptoms is mainly preferred due to compression of the optic nerve [26]. Other authors suggest the use of bisphosphonates to reduce both pain and the risk of fracture [7,23].

## Case Presentation

A 44-year-old female patient attended a dental consultation for periodontal review and maintenance. No relevant medical history or documented allergies were reported. No further relevant issues were found.

While performing the periapical X-rays, in the second quadrant, a rare bone anatomy was observed, with an apparent absence of cortical bone and indefinite trabeculae. At this stage we consider the possibility of a bone disorder, and from the appearance and location, perhaps a Fibrous Dysplasia (Figure 1). Subsequently, a CBCT was performed: invasion of the maxillary sinus and thickening of the bony structures on the left side of the maxilla were confirmed (Figure 2). With the suspicion of FD, the patient was referred to the Maxillofacial Surgery Service, where FD was confirmed after performing a bone biopsy. Periodic clinical controls are carried out by the periodontist, along with any necessary complementary radiographs.

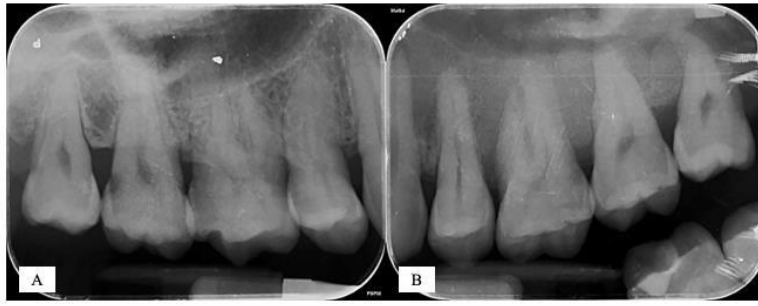
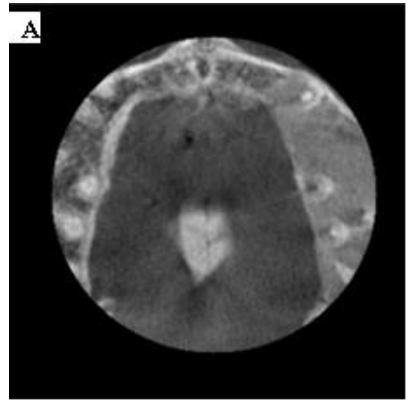



**Figure 1:** Periapical Images.Normal bone appearance on the right side (A). Rare bone anatomy with an apparent absence of cortical bone and indefinite trabeculae in the left side (B).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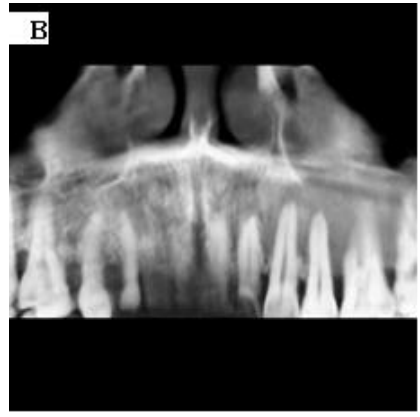
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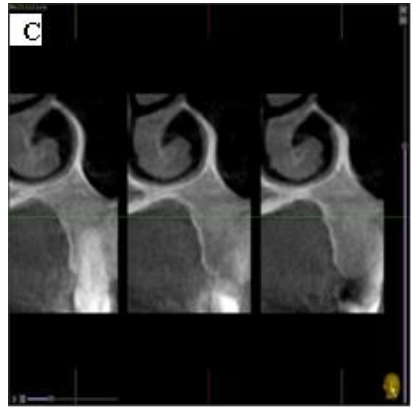
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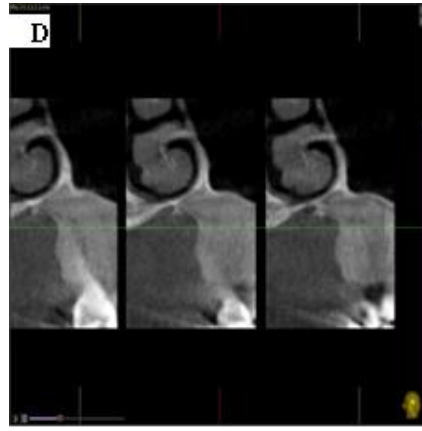


**Figure 2:** CBCT Images. Axial view showing the lack of trabeculae bone (A). Panoramic view (B). Sections corresponding to zones 2.5 and 2.6 (C and D).

The histopathology result reporting a fibro-osseous lesion comprised of immature, curvilinear trabeculae bone without osteoblastic rim, and arranged on a collagenous stroma with fusiform cells without cytological atypia (Figure 3).

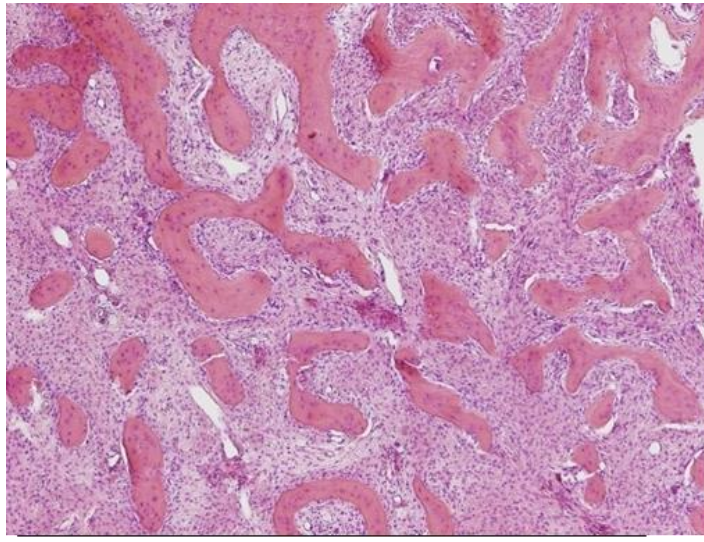

**Figure 3**: Hematoxylin-eosin staining featuring the typical "Chinese letters".

## Discussion

A common feature of all forms of benign fibro-osseous lesions (LFOB) is the replacement of normal bone by fibrous hyperproliferative tissue with varying amounts of mineralized substance, bone, or cement. The three most common forms of LFOB are FD, ossifying fibroma (OF) and osseous dysplasia (OD) [22,27]. The clinical presentation and radiographic images aid us in order to obtain the definitive diagnosis and be able to establish the appropriate treatment [8].

Thus, it is important to perform a correct differential diagnosis (Table 1). Radiographically, OF is a well-defined lesion that does not merge with the surrounding bone compared to FD. The histopathology shows normal bone replaced by a fibroblastic stroma with calcifications, surrounded by osteoblasts [28]. In relation to OD, radiographically, it is diffuse and amorphous, with mixed radiopaque and radiolucent lesions. The histological features include a stroma of cellular connective tissue infiltrated with irregular bone and/or cement-like masses [29].

**Table 1**: Differential diagnoses of craniofacial FD (modified by Burke et al).

| | |
|---|---|
| **Bone Diseases** | Ossifyng Fibroma |
| | (Cemento-)Osseous Dysplasia |
| | Giant Cell Tumor/Cherubism |
| | Aneurysmal BoneCyst |
| | Simple (Idiopathic) Bone Cyst |
| | Osteoblastoma * |
| | Osteosarcoma |
| | Osteoma/Cementoma |
| | Pagetoid Disease |
| | Langerhan´s Cell Histiocytosis |
| **Odontogenic Diseases** | Ameloblastoma |
| | Ameloblastic Fibro-odontoma |
| | Adenomatoid odontogenic tumor |
| | Calcifying epitelial odontogenic tumor |
| **Inflammatory Process** | Sclerosing osteomyelitis |
| **Metabolic Bone Disease** | Hyperparathyroidism (Brown's Tumor) |

Central giant-cell tumor is an intraosseous lesion consisting of cellular fibrous tissue with numerous foci of hemorrhage, multinucleated giant cell aggregation, and occasionally trabeculae of bone tissue. Histologically, it is practically indistinguishable from cherubism and aneurysmal bone cyst [30].

Osteoblastoma is a benign bone-forming osteolytic neoplasm. It is rare in the jaws, most often found in the vertebral column, long bones and in small bones of hands.Osteoblastoma is a constant slow-growing tumor. The main characteristic to be able to differentiate this lesion from a FD lesion is the stroma does not consist of cellular spindle cells but rather a loose vascular stroma with numerous prominent epithelioid-like osteoblasts [31].

Osteosarcoma is a malignant bone tumor, easily distinguishable from FD because the stroma shows typical pleomorphic cells with abundant atypical mitotic bodies [31]. Likewise, Paget's disease (PD) can produce a similar pattern with bone expansion; however, PD usually appears in older patients and involves the entire jaw (in contrast to the unilateral tendency of FD) [24].

Ameloblastoma is a benign, slow-growing odontogenic tumor like FD, locally invasive and unilateral. It can be asymptomatic or in more severe cases, can produce cortical expansion. Radiographically uni- or multilocular radiolucency can be observed with a "soap bubble" appearance.

Another disease to be discarded especially in children is chronic osteomyelitis. Although osteomyelitis can cause a mandibular enlargement, an apposition of new bone occurs on the surface of the external cortical bone. A CBCT Scan, will produce evidence of the original cortical plate within the expanded portion of the mandible. FD on the other hand, expands the bone in a centripetal manner, displacing and thinning the external cortical plate. The remainder of the cortex maintains its position on the external surface of the bone. Furthermore, the presence of bone sequestra can help with the diagnosis of osteomyelitis [24].

Other metabolic bone diseases, such as hyperparathyroidism, can produce a similar bone pattern. However, these diseases are bilateral and do not cause bone expansion.

## Conclusion

Dentists have an important role in identifying these types of lesions when they are located in the maxillary bones. Carrying out a good medical history and complementary tests are of paramount importance.

A correct diagnosis is crucial for an adequate treatment plan in order to improve the quality of life of our patients.Patients with FD should be treated by a multidisciplinary team, consisting of doctors, surgeons, and dentists[8]. Currently, treatment options are limited and it is possible that, with a better understanding of the pathogenesis, case management is improved[7]. At present and relying on molecular technology, it seems that FD treatment research is focused on gene therapy.

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## Case Report

# Laugier-Hunziker Syndrome: Case Report

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## Abstract

Introducción. Esta enfermedad fue descrita en 1970, por Laugier y Hunziker. En la actualidad es considerada una patología benigna, de etiología desconocida. Cursa con presentación de máculas lenticulares, de color marrón oscuro al negro, normalmente aparece en labios, mucosa yugal y paladar. *Caso clínico*. Paciente femenino de 72 años, que acude a consulta para extracción de restos radiculares. En la exploración sorprende la presencia de extensas lesiones melanóticas que abarcan toda la mucosa oral. La paciente refiere que de siempre ha presentado estas lesiones.

This disease was described in 1970, by Laugier and Hunziker. At present it is considered a benign pathology of unknown etiology. It presents with lenticular macules, from a dark brown to black in color, usually appearing on the lips, jugal mucosa and palate. *Case report*: 72-year-old female patient who comes to the clinic for the extraction of remaining roots. On examination, the presence of extensive melanotic lesions that cover the entire oral mucosa is surprising. The patient reports that she has always presented these lesions.



## Keywords

Laugier-Hunziker Syndrome; Macules


## Introduction

Laugier-Hunziker syndrome is also named idiopathic lenticular mucocutaneous pigmentation and was described by Laugier and Hunziker in 1970 [1]. It is considered a benign acquired condition of unknown etiology, and is characterized by isolated or confluent lenticular macules of about 5mm, and totally asymptomatic, with a color that varies from dark brown to black that are usually located on the lips, jugal mucosa and palate [2-4].

From the histological point of view, the mucous macules present an epithelial acanthosis with pigmentation in the basal layer due to accumulation of melanin in the basal keratinocytes. Melanocytes are completely normal [5].

The differential diagnosis must be made with drug stains, racial spots, Peutz-Jeghers syndrome, multiple neurofibromatosis, Addison's syndrome, and other systemic conditions associated with melanosis [6-8].

It does not need treatment, as there is no association with systemic pathology, nor has malignancy been described. Only in the case of an aesthetic compromise, treatment with cryotherapy or laser has been indicated, but the lesions tend to recur, being minimized, with little sun exposure [9,10].

## Case Report

A 72-year-old female patient comes to the consultation for the extraction of remaining roots. On examination, the presence of extensive melanotic lesions that cover the entire oral mucosa is surprising. The patient reports that she has always presented these lesions (Figures 1-4). After the anamnesis and due to the absence of any other associated pathology, the diagnosis of Laugier-Hunziker syndrome was established.

## Discussion

The chapter on pigmentary lesions developed by the authors Eric T. Stoopler and Faizan Alawi, in the work on oral pathology that we already mentioned in the presentation of this work [11]; gives us a magnificent review of this disease and, in addition, invites us to classify this entity, which presents with oral pigmentation, within the section of syndromes or systemic diseases (Figure 5) (Table 1) [11].

**Table 1:** Pigmented lesions of the oral mucosa. Adapted from Camile et al. [11].

| **Focal pigmentation conditions** |
|---|
| Freckle/ephelis |
| Oral/labial melanotic macule |
| Oral melanoacanthoma |
| Melanocytic nevus |
| Malignant melanoma |
| **Multifocal/diffuse pigmentation conditions** |
| Physiologic pigmentation |
| Drug-induced melanosis |
| Smoker's melanosis |
| Post-inflammatory (inflammatory) hyperpigmentation |
| *Laugier-Hunziker pigmentation* |
| **Pigmentation associated with systemic or genetic disorders** |
| Adrenal insufficiency (Addison disease) |
| Cushing disease |
| Human immunodeficiency virus (HIV) – associated pigmentation |
| Peutz-Jeghers syndrome |
| **Exogenous causes of clinical pigmentation** |
| Tattoos – amalgam, graphite and ornamental |
| Metal – induced discololoration |

From the epidemiological point of view, this disease, also called Laugier-Hunziker-Baran syndrome, and which, as we have said, is characterized by melanotic pigmentation in the oral mucosa, it is rare and usually begins between the 5th and 6th decade and is almost twice as high in women as in men [12]. It appears to be more prevalent in Caucasian or fair-skinned individuals [11]. The etiology is unknown and there appear to be no hormonal and / or genetic alterations [13]. Today it is considered that there is an acquired disorder of pigmentation that involves an increase in melanin without an increase in keratinocytes. Clinically the lesions can be solitary or multiple, any area of the mucosa can be involved and their color can vary from brown to gray-black. Sometimes the skin can be affected and more preferably there is a certain degree of dystrophy in the nails (for some, up to 60% of the cases) [12], being more affected, those of the feet [14] and occasionally there are other associated alterations [15]. Aspect that does not appear in our case.

As mentioned in the introduction, melanin incontinence and acanthosis are not accompanied by inflammation or abnormality in keratinocytes [5]. We have already commented that patients do not require treatment [10,13]. Even so, lasers and cryotherapy have been used for aesthetic and / or psychological reasons [13]. What is important is to take a good clinical history and a correct differential diagnosis (Table 1, Figure 5), making a diagnosis by exclusion, which usually does not require a biopsy and it is important to know that malignancies have not been described [14,16,17].

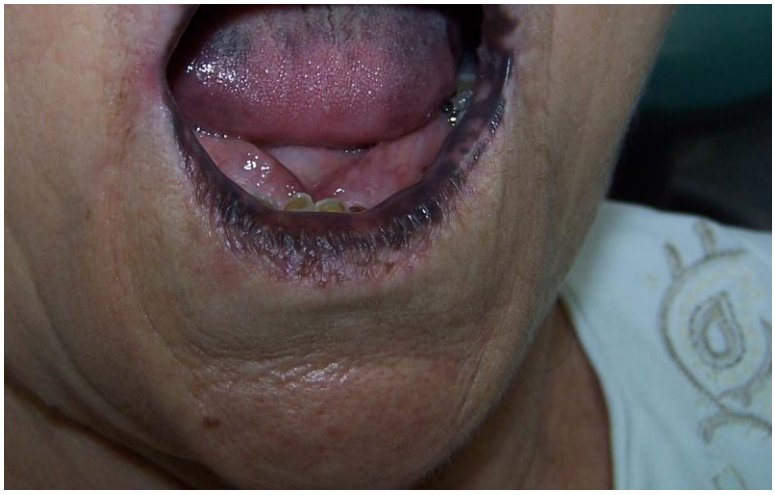

**Figure 1:** Labial melanosis.

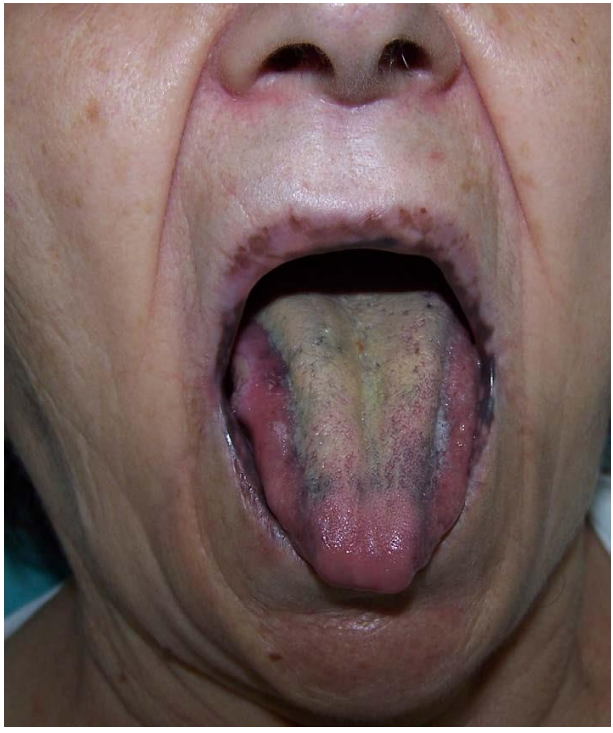

**Figure 2:** Melanic stains on the tongue.

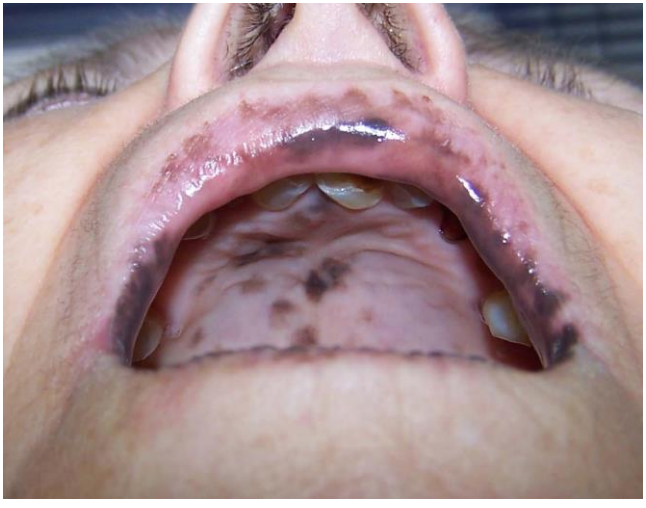

**Figure 3:** Palatal stains.

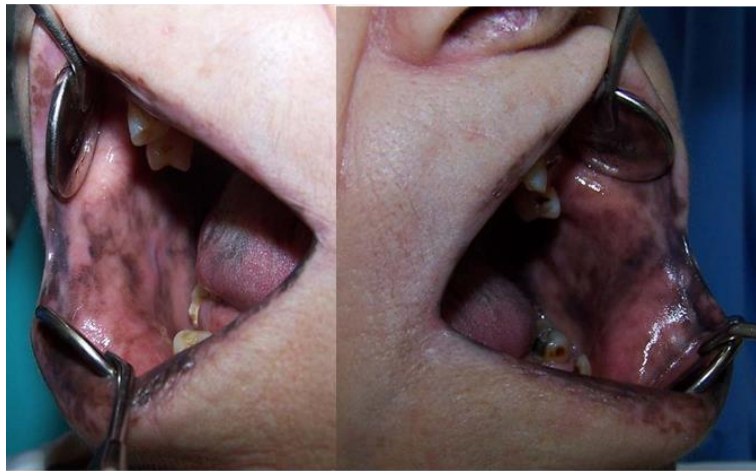

**Figure 4:** Melanosis in both mucous membranes.

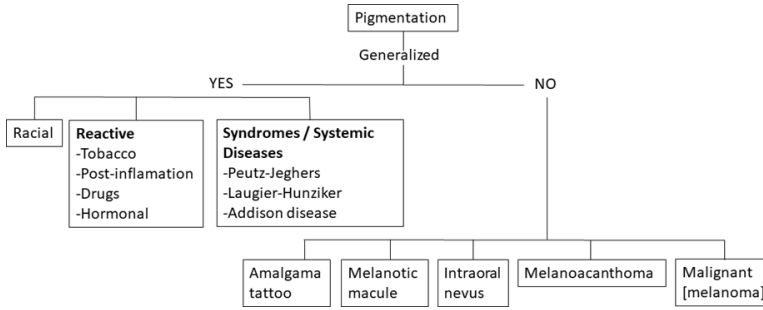


**Figure 5:** Algorithm for the differential diagnosis of pigmented lesion. Adapted from Camile et al. [11].

## Conclusion

It is a benign, rare disease that is diagnosed by exclusion through an exhaustive medical history.

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## Case Report

# Medication-Related Osteochemonecrosis of the Jaw

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## Abstract

Medication-related osteochemonecrosis of the jaw (MRONJ) is a type of chronic osteomyelitis that is originally attributed to taking bisphosphonates in patients who had not undergone radiotherapy of the head and neck. Since the 19th Century, the pathogenesis of this process has been extensively studied, and today, the list of medications that can produce ONJ (osteonecrosis of the jaw) is very extensive, including antiresorptives, antiangiogenics, immunomodulators, chemotherapeutics, etc. When caring for a patient in treatment

with one of these medications it is critical to carry out a good interview and obtain a complete clinical history and, if necessary, consult with their specialist if there is any doubt the patient cannot resolve for us. The risk of ONJ in these patients depends primarily on two factors: the type of treatment they are undergoing (dose, time, and route of administration) and the type of intervention it requires (surgical interventions carry the greatest risk). With regard to the second aspect, good surgical planning, and appropriate pre-, intra- and post-operative measures will help diminish the risk. It is very important to keep in mind that the patient should be aware of their situation, as their involvement with regard to oral hygiene and periodic reviews is fundamental as, ultimately, the lowest risk interventions are those that do not need to be performed, and so prevention is key in these patients.

## Points of Interest

- Origin and pathogenesis of medication-related osteonecrosis of the jaw.
- Different drugs that can cause ONJ and risk factors to keep in mind.
- How should we act when faced with a MRONJ lesion?
- Prevention: how can we tell if a patient is low or high risk?

## Introduction

### Historical Background

Medication-related osteonecrosis of the jaw (MRONJ) is a type of chronic osteomyelitis that develops in patients who are taking or have taken bone-modifying agents (Biphosphonates (BP) and Denosumab) or angiogenesis inhibitors, whether oral or intravenous, and who do not have a history of having received radiotherapy of the head and neck. It is a rare but serious pathology. The majority of cases are defined by one or more lesions of necrotic bone, generally exposed, or bone with extraoral fistula(e) drainage, that does not heal in 8 weeks [1-4].

The frequency of this pathology, if associated with medications, is estimated to be between 0.05% (low dose, oral and patients with osteoporosis) to 6.7%, always dependent upon the type of medication, the dose, route of administration and the underlying pathology for which the patient is prescribed the medication [1-7].

In 2003, thanks to a publication by Marx [8], cases of medication-related osteonecrosis of the jaw began to come to light. Specifically, in this first publication, 36 cases associated with treatment with intravenous biphosphonates (Pamidronate and Zoledronate) were presented in patients with multiple myeloma or breast cancer. One year later in 2004, Ruggiero et al. [9] published a series of 64 cases, this time associated with oral biphosphonates. And in 2005, the first series was published from Spain and Europe [10]. These authors describe attending to cases with a very similar clinical presentation to radiotherapy-induced osteonecrosis, with fast-progressing lesions resistant to debridement and surgical treatment, but in patients who had never received radiotherapy treatment but who were undergoing treatment with biphosphonates [9]. There are records of cases of chemotherapy-induced osteonecrosis from 20 years prior, but these dealt with lesions that mainly responded well to surgical treatment associated with the brief interruption of chemotherapy. This is the primary difference between chemotherapy- or biphosphonate-induced osteonecrosis [11].
In 2004, Dr. Hellstein et al. [12] published an article where they call attention to the "remarkable" similarity between cases of biphosphonate-associated osteonecrosis in the 21st Century and cases of osteonecrosis due to exposure to phosphorus suffered by workers in 19th Century white or yellow phosphorus mines. To put it into context, the disease to which Hellstein refers is known as "Phossy jaw" (phosphorus necrosis of the jaw), arose in concurrence with the marketing of commercial matches under the "Lucifer" brand in 1833, and the exposure of factory workers (mainly women) to white phosphorus fumes during their manufacture [13]. The first series of cases published in 1845 in Vienna [14], dealt with 22 cases of workers who had been exposed to phosphorus fumes an average of 5 years, although some had developed the disease after just a few months. In 60%

of cases, there was involvement of the jaw bones. It was estimated that over 11% of workers developed the disease. Some other authors estimate that the figure was higher, as not all workers were examined, some cases developed the disease years later, and the mortality rate was already fairly high among miners, and so many died before noticing the problem. On the other hand, we must take into account that, at that time before antibiotics, more than 20% of cases died due to septicaemia [14]. It was not until 1906 that the Berne Convention prohibited the manufacture and export of white phosphorus matches, as it was considered a highly toxic product with a high content of pyrophosphate that produced osteonecrosis and other serious pathologies after being inhaled by workers who handled it. The matches were substituted by the ones we use today, which contain phosphorus sesquisulfide or amorphous red phosphorus, compounds which do not have the toxic properties of their predecessor [12,15,16].

Initially and for historical purposes, the term Bisphosphonate-associated osteonecrosis of the jaw was established, but with the discovery of other medications that also produced this adverse effect, such as anti-RANK antiresorptive agents (Denosumab) or the anti- VEGF angiogenesis (bevacizumab) or the tyrosine kinase inhibitor (TKI, sunitinib), since 2014, the term used to define this pathology is Medication-related osteonecrosis of the jaw (MRONJ) as per the recommendation of the *American Association of Oral and Maxillofacial Surgeons* (AAOMS) [1].

There is currently an extensive list of medications that are considered to be potential causes of developing osteonecrosis of the jaw (ONJ), with varying levels of evidence, and over the last 3 decades, various newer-generation medicines have been added and developed in hopes of improving the risk/benefit ratio of the classical drugs [17].

In 2008, the first case of ONJ associated with an angiogenesis inhibitor, Bevacixumab specifically [18], was published, and one year later, cases began to appear associated with Aunitinib [19], and since 2016, anti-angiogenics with a potential to provoke ONJ have been added to the list such as Aflibercept, Dasatinib or

Erlotinib [200-26]. More recently, mammalian Target of Rapamycin (mTORE) inhibitors, other monoclonal antibodies, chemotherapeutic agents, etc. have been added.

At first, many of the cases associated with these newcomer drugs had been treated or were in concomitant treatment with biphosphonates, but soon cases of osteonecrosis came to light in patients treated exclusively with each of those drugs [27-29].

In 2010, the Food and Drug Administration (FDA) approved a well-known antiresorptive agent which has been discussed and published about a great deal since, Denosumab. The intent of this drug in many cases was to replace biphosphonates, as the indications are nearly identical, but by not integrated into the bone matrix, its half-life is shorter and it presented better tolerability [30]. That same year when it was first prescribed, in 2010, is when the first case of ONJ was published associated with is ingestion [31,32].

Figure 1 shows the timeline and progression of this disease.

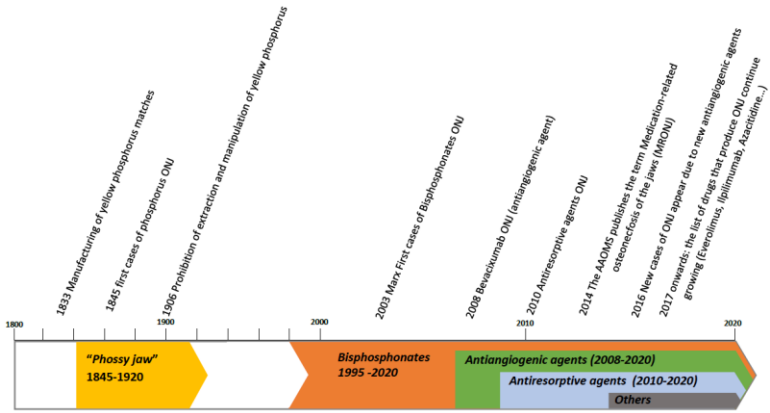



**Figure 1:** Timeline of the historical evolution of osteonecrosis of Medication-related osteonecrosis of the jaws (MRONJ).

## Diagnosis: Stages of Progression and Additional Tests

The basic diagnostic criteria for ONJ are: a patient who received or is receiving treatment with a medication with potential risk of osteonecrosis, who had never received radiotherapy, and who presents one or more ulcerated lesions in the mucosa of the alveolar processes, with necrotic appearance of exposed bone (although there could also be cases in which there is no clinical exposure, but there could be an intraoral fistula, pain, or suspect radiological findings that require an in-depth and more careful study); the lesion(s) may appear spontaneously, though most commonly, they appear after a history of alveolar surgery, especially extractions, after which there is an absence of tissue healing after 6-8 weeks [33].

Since 2003, after the publication of Marx et al.[8], there have been many published cases about this pathology, and its association with biphosphonate ingestion is widely known, as well as that of other medications with ever-growing scientific support, and there are numerous guides and protocols that have been published in order to facilitate diagnosis and management [34-36]. Below in Table 1 we present the staging used most widely over the last 15 years due to its clarity, efficacy and simplicity, as well as the most recent classification.

**Table 1:** Medication-related osteonecrosis of the jaws (MRONJ) evolution stages.

| **Author/date** | **Staging** |
|---|---|
| Ruggiero et al [36] 2009 (upgrade Ruggiero et al [34] 2006) | Classification of the AAOMS (American Association of Oral and Maxillofacial Surgeons) Risk category:<br>There is no apparent necrotic bone in patients who have been treated with intravenous or oral bisphosphonates.<br>*-Stage 0:*<br>There is no clinical evidence of necrotic bone, clinical findings or non-specific symptoms.<br>*-Stage 1:*<br>Exposed necrotic bone in asymptomatic patients who present no evidence of infection.<br>*-Stage 2:* |

| | |
|---|---|
| | Exposed necrotic bone associated with infection, with pain and erythema in the exposed bone area with or without purulent drainage.<br>*-Stage 3:*<br>Exposed necrotic bone in patients with pain, infection and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone (that is, the lower border and ramus of mandible, the maxillary sinus and maxillary zygoma).<br>Pathologic fracture, extraoral fistula, oral antral / oral nasal communication or osteolysis extending to the lower border of the mandible of sinus floor. |
| Bagán et al [38] 2009 | *-Stage 1:*<br>Presence of exposed necrotic bone or small oral fistula with no exposure of the necrotic bone. Asymptomatic.<br>*-Stage 2a:*<br>Presence of exposed necrotic bone or small oral fistula with no exposure of the necrotic bone. Patient with symptoms controlled by medical treatment.<br>*-Stage 2b:*<br>Presence of exposed necrotic bone or small oral fistula with no exposure of the necrotic bone. Patient with symptoms not controlled by medical treatment.<br>*-Stage 3:*<br>Pathologic fracture, extraoral fistula, osteolysis extending to the inferior mandibular margin<br><br>**Upgrade Bagán et al [40] 2012:<br>Stage 3:<br>Exposed necrotic bone or oral fistula with no exposed bone, in patients with pain, infection and one or more of the following: radiographic evidence of bone necrosis extending beyond the alveolar bone, pathological fracture, extraoral fistula, oronasal communication, osteolysis extending to the inferior mandibular margin or sinus floor. |
| Yoneda et al [46] 2017 | Proposal by the Japanese Committee on Osteonecrosis of the jaw<br>*-Stage 0 **<br>Clinical symptoms: no bone exposure or bone necrosis, deep periodontal pocket, loose tooth, oral mucosal ulcer,swelling, abscess formation, |

| | |
|---|---|
| | trismus, hypoesthesia / numbness of the lower lip (Vincent's symptom), non- odontogenic pain.<br>Image findings: sclerotic alveolar bone, thickening and sclerosis of the lamina dura, remaining tooth extraction socket.<br>*(Care should be taken to avoid over-diagnosis given that half the stage 0 ARONJ cases do not progress to ONJ)<br>-*Stage 1*<br>Clinical symptoms: asymptomatic bone exposure / necrosis with no sign of infection, or fistula in which the bone is palpable with a probe.<br>Image findings: sclerotic alveolar bone, thickening and sclerosis of the lamina dura, remaining tooth extraction socket.<br>-*Stage 2*<br>Clinical symptoms: bone exposure / necrosis associated with pain, infection, fistula in which the bone is palpable with a probe, or at least one of the following symptoms, including bone exposure / necrosis over the alveolar bone (for example, reaching the mandibular inferior border or mandibular ramus, or reaching the maxillary sinus or mandibular ramus), resulting in a pathologic fracture, extraoral fistula, nasal / maxillary sinus fistula formation, or advanced osteolysis extending to the mandibular inferior border or maxillary sinus.<br>-*Stage 3*<br>Clinical symptoms: bone exposure / necrosis associated with pain, infection or at least one of the following symptoms, or a fistula in which bone is palpable with a probe. Bone exposure / necrosis over the alveolar bone (for example, reaching the mandibular inferior border or mandibular ramus, or reaching the maxillary sinus or mandibular ramus or the cheekbone). As a result, pathologic fracture, or extraoral fistula, nasal / maxillary sinus fistula formation, or advanced osteolysis extending to the mandibular inferior border or maxillary sinus.<br>Image findings: osteosclerosis / osteolysis of the surrounding bone, pathologic mandibular fracture and<br>osteolysis extending to the maxillary sinus floor. |

Just as the clinical picture is very important, alongside a detailed interview, the complementary imaging tests are fundamental for the proper diagnosis and staging of ONJ [47-48]. First, the reference standard and most widely-used diagnostic tool in dentistry and maxillofacial surgery to this day is the panoramic radiograph. It is a very useful tool to obtain a general view of the jaw bones and identify the periodontal status or changes in the trabecular pattern of the bone [1,49,50]. The panoramic radiograph can aid us in identifying cases in early stages, showing, for example, post-extraction sockets that do not heal after 6-8 weeks or sclerotic or diffuse radiolucent areas [36]; as well as more advanced stages with bony sequestra, narrowing of the cortices or pathological fractures [51].

For a more detailed examination, CBCT (Cone-Beam Computed Tomography) shows us digital images where we can identify diffuse oseosclerosis, resorption areas, and degeneration of bony cortices, periostal reaction and fistulae or orosinusal or oronasal communications, which are often difficult to identify in panoramic radiographs [47-49].
There are authors that also defend the use of MRI (Magnetic Resonance Imaging) for diagnosis and staging of osteonecrosis. The diagnostic value of magnetic resonance is not yet well-established. However, it has an advantage relative to other tests in that it allows delimitation of the extension of the lesion in both bone tissue and soft tissue, which helps greatly in planning resective surgery [27,48-50].

More recent studies use SPECT (Single-Photon Emission Computed Tomography) to locate sites where physiological and metabolic changes are occurring in the bone [47,79].

Its primary function is to determine the metabolic activity of the bone surrounding the lesion, also focusing surgical planning [50].

## Associated Risk Factors

The appearance, progression, and treatment for MRONJ depend on several factors [1- 4,27,28].

The risk of ONJ varies considerably among the various medications, but in all cases, it is dependent upon the route of administration, dose, exposure time, and existence or lack of concomitant systemic pathology such as, for example, Diabetes Mellitus [1- 3,27,28,52,53].

It is important to take into account that the mandible and upper maxilla are the bones at highest risk of developing medication-related osteonecrosis of the jaw, with risk rates of 73% and 22.5%, respectively [1]. But, why are the jaw bones at high risk of suffering osteonecrosis? Marx [8] provided an explanation for this question. He argued that it was due to the presence of teeth. In the jaw bones, we find teeth that are exposed to the external environment, that can suffer aggression, periodontal problems, periapical pathology, iatrogenesis, endodontic treatments, extractions, and other pathologies or treatments that require an increase in the rate of bone turnover in the jaw bones [53]. Several studies have published that between 52 and 77% of patients who developed MRONJ had a history of extraction [38,54]. Another key factor is that the mandible, where osteonecrosis is most common, has a limited blood supply, with arteries mainly being terminal arteries, and this fact has also been proposed to explain osteonecrosis of the jaw due to radiotherapy and would also explain why the bone with the highest rate of osteonecrosis is the mandible [53].

Both jaw bones are subject to near-constant forces of mastication, which routinely leads to microfractures in the bone and dentition. In patients in treatment with biphosphonates or antiresorptives, these microfractures could form the origin of an osteonecrotic lesion. But what has been demonstrated is that the need for one repair, remodeling and new growth is essential when there is an infectious process in the jaw bones and/or following a surgical intervention that involves bone tissue such as extraction or implant placement [55-57].

Of all the factors upon which the appearance and severity of medication-related osteonecrosis depends, we can classify and speak of local factors such as periodontal disease, periapical

infectious processes and surgical interventions that involve the jaw bones; patient-dependent factors such as age and sex and underlying pathology; and medication-associated factors, the active ingredient, route of administration, dose, and exposure time [58].

The risk of drug-related osteonecrosis is greater in a patient whose pathology and prescription for the risk medication is cancer, and not as high for osteoporosis or chronic inflammatory diseases. This is because the risk of osteonecrosis is dose-time dependent, and in cancer patients, the therapy tends to be more aggressive. Overall, a strong relationship has been observed for developing MRONJ in patients with renal cancer [59].

The literature supports that the factors most involved in the appearance and severity of osteonecrosis are: advanced age, female sex (oestrogens), tobacco use, the type of medication and its route of administration, the association with corticosteroids, trauma, and surgical interventions (mainly extracion and implants) [60].
Retrospective studies have shown the approximate relative risk of each local factor. A review by Kuroshima et al. [60] published in 2019 directly related to biphosphonate consumption reported that 14.8% of cases that develop MRONJ had not been subjected to any surgical intervention and did not present other local risk factors such as the presence of implants, periodontal disease or trauma; 61.7% of cases had undergone 1 or more extractions; 84% presented periodontal disease but the osteonecrotic lesion only coincided with a periodontal sac in 5%. On the other hand, 7.4% presented trauma by prosthesis in the area of the osteonecrosis; in 7.2% of cases, periodontal or periapical surgery had been performed and in 4%, an osteonecrotic lesion appeared in peri- implantation bone tissue. As an interesting note from the work published by Marx et al.[59] in 2005, of the cases presenting tori, nearly 40% presented the osteonecrotic lesion in areas of exostosis, with no apparent trauma (prosthesis, orthopaedics, etc.).

## Medications causing Osteonecrosis of the Jaw: types, Epidemiology and Aetiopathogenesis

### Biphosphonates

Are used in the treatment of some skeletal dysplasias such as imperfect osteogenesis or Paget's disease, osteoporosis and the prevention of hypercalcaemia, as well as in cases of bone metastases [8-10,27,28,61].

Table 2 shows the different biphosphonates currently on the market, their routes of administration, dosing and most common trade names (FDA). In the case of those administered intravenously, they are primarily prescribed for bone metastases of breast, prostate, lung, and kidney tumours and in some lympho-myeloproliferative processes[8- 10,27,28].

**Table 2:** Types os bisphosphonates and characteristics.

| Active ingredient | Brand names (FDA) | Nitrogenous | Power | Dose and route administration |
|---|---|---|---|---|
| Etidronate (Etidronate disodium) | Didronel®, Ostopor® | NO | 1 | 200-400mg (PO) |
| Clodornate (Clodronic Ac.) | Clasteon®, Clodron®, Clody®, Difosfonal®, Lodronat®, Loron®, Lytos®, Motivlod®, Neogrand®, Niklod®, Ostac®, Osteonormv, Sindronat®, Traxovical® | NO | 10 | 400-800mg (PO) |
| Tiludronate (Tiuldronic Ac.) | Fármaco retirado | NO | 50 | 240mg (PO) |
| Alendronate (Alendronic Ac.) | Alendronato sódico. Fosamax® (comercializado en Europa con más de 100 nombres diferentes) | YES | 1000 | 1, 10, 35, 40, 70mg (PO) *5mg/ml (IV) |
| Risedronate (Risedronic Ac.) | Risedronato sódico. Atelvia® Actonel® (comercializado en Europa con más de 50 nombres | YES | 1000 | 5, 35, 75, 150mg (PO) |

| | | | | |
|---|---|---|---|---|
| | diferentes) | | | |
| Ibandronate (Ibandronic Ac.) | Ibandronato sódico. Boniva®, Bondeza®, Bondronat®, Bonviva®, Iasibon® | YES | 1000 | 150mg (PO) 3mg (IV) |
| Pamidronate (Pamidronic Ac.) | Pamidronato disódico. Aredia® (comercializado en Europa con más de 50 nombres diferentes) | YES | 1000-5000 | 30, 60, 90mg (PO) |
| Zoledronate (Zoledronic Ac.) | Ácido zoledrónico. Zometa®, Reclast® | YES | 10000 | 4mg/ml (IV) |

These medications are integrated in the bone matrix and, once released during the bone resorption process, induce apoptosis of the osteoclasts [61]. Because of this ability to integrate into the bone matrix, their effects can extend up to 10 years after discontinuing administration[1]. Though their mechanism of action is well known, their real relationship with ONJ pathogenesis is not entirely clear [27,28].

The risk of ONJ in patients in treatment with biphosphonates depends on various factors, with the most significant being an intravenous route of administration, high doses or extended exposure time. The co-administration of corticosteroids or the presence of some systemic pathologies such as diabetes or associated inflammatory diseases also has an influence [1,27,28]. Tobacco also has a negative influence, as it produces changes in the epithelium, reduces tissue response to healing, and worsens patients' periodontal status [59,62]. Another important aspect that has been studied is the relative potency of each type of biphosphonate. Non-nitrogen-containing biphosphonates such as etidronate and clodronate have a lower potency and this entails a lower risk of osteonecrosis. These non- nitrogen-containing biphosphonates are those usually used for bone dysplasias and dystrophies like Paget's disease [63]. Those that tend to be prescribed for the treatment of osteoporosis are risedronate, ibandronate and alendronate orally, and their relative potency

and, therefore, their risk of causing ONJ is between 10 and 100 times greater than that of the compounds mentioned above. The prevalence of ONJ in patients in treatment with biphosphonates is estimated to be between 0.1% to 0.12%, with a significant increase if treatment extends beyond 4 years [1,64]. Pamidronate and zoledronate have a potency between 100 and 1,000 times greater than non-nitrogen- containing biphosphonates, and are administered intravenously, mainly in cancer patients. The latter are at highest risk, and published incidence data so far vary between 0.7% and 8.5% [65,66]. In some studies, as is the case published in 2008 by Boonyapakorn T *et al.* [67], with a small sample size, a prevalence of over 23% has been published. Controlled clinical trials carried out to date confirm that cancer patients in treatment with zoledronate have between 50 and 400 times more risk of suffering ONJ than those assigned to placebo groups [68,69].

## Antiresorptives

In this group, denosumab (Prolia®, Xgeva®) is the main antiresorptive agent associated with MRONJ [1,28,67]. It is an IgG2 monoclonal antibody that acts selectively upon the receptor activator of nuclear factor kappa-B ligand (RANKL), and is a key mediator of bone metabolism [70]. Blocking the RANK ligand inhibits osteoclast activity and reduces their survival, giving rise to a reduction in resorption and an increase in bone density [71]. It is related to biphosphonates due to its similarity with regard to indications, but unlike these, denosumab reduces bone turnover and increases bone mineral density presenting several advantages over biphosphonates like improved tolerability, a shorter half-life, and a lower incidence of nephrotoxicity [70]. The medication's action is associated with the dose and pattern of administration and the exposure time; in general, it has a half-life of 25.4 days, producing an effect that lasts up to 5 months, after which it decreases [72]. Its shorter half-life relative to biphosphonates is due to the fact that Denosumab does not integrate into the bone matrix and, therefore, the residual effects in the process of bone remodelling disappear 12 months after discontinuing treatment [1,72]. However, studies that support this data are limited and with very small patient sample sizes [73,74].

Denosumab is a drug indicated for the treatment of osteoporosis and the prevention of associated problems (pathological fracture, compression of the spinal medulla and hypercalcaemia), and in patients with bone metastases [65-69,72-74]. In cancer patients, the recommended dose is higher (120 mg) than in non-oncological cases (60 mg) and, therefore, the risk of these patients developing ONJ increases [61].

The aetiopathogenesis of Denosumab-associated ONJ is not precisely known; there are significant differences with regard to biphosphonates, but in both cases, it is related to the angiogenesis inhibiting and immunosuppressant effects [75]. Clinically, the ONJ lesions produced by Denosumab are practically identical to those of biphosphonates, however, in many cases, they respond better to treatment [74]. It is currently estimated that the risk of developing ONJ in cancer patients treated with Denosumb oscillates between 0.7% and 1.9%, a figure very similar to that of patients treated with zoledronate [62-69,73-75]. This is opposed to patients whose underlying problem is osteoporosis, where the risk of developing ONJ decreases to 0.04% [76,77].

## Antiangiogenics

The antiangiogenic drugs Anti-VEGF (*Vascular Endothelial Growth Factor inhibitors*) and anti-TKI (*Tyrosine Kinase Inhibitor*) are substances capable of inhibiting new formation of blood vessels, used mainly in oncological cases, as angiogenesis is fundamental for tumour growth and the development of the metastasis of some solid tumours [78].

Table 3 shows the various antiangiogenic agents, their route of administration and mechanism of action, as well as their commercial trade name (FDA). They are drugs with a high potential to cause ONJ [3,15,28]. Logic would lead us to believe that the inhibition of angiogenesis negatively affects the ability to regenerate bone tissue, or other tissue, leading to delayed healing, greater susceptibility to reinfection and even necrosis; but the aetiopathogenesis of this ONJ is not currently well-understood [79]. Within this group, there are drugs like Bevacizumab, which is an anti-VEGF with other effects, such as,

for example, the inhibition of chemotaxis of macrophages and the differentiation of osteoblasts [80]; and Sunitinib and other anti-TKIs inhibit the differentiation of osteoclasts and other cells in the monocyte/macrophage slystem, conditioning the local immune response [80].

**Table 3:** Types of antiangionenic agents and characteristisc.

| Active ingredient | Route administration | Mechanism of action | Brand Name |
|---|---|---|---|
| Bevacizumab | IV | Anti-VEGF | Mvasi® Avastin® |
| Aflibercept | IV | Anti-VEGF | Zaltrap®, Eylea® |
| Pazopanib | PO | Anti-VEGF | Votrient® |
| Cabozantinib | PO | Anti-VEGF | Cometriq®, Carbometyx® |
| Sunitinib | PO | Anti-TKI | Sunitinib malate, Sutent® |
| Axitinib | PO | Anti-TKI | Inlyta® |
| Dasatinib | PO | Anti-TKI | Dasatinib, Sprycell® |
| Imatinib | PO | Anti-TKI | Imatinib mesylate, Glivec®, Gleevec® |
| Erlotinib | PO | Anti-TKI | Erlotinib hydrochloride, Tarceva® |
| Sorafenib | PO | Anti-TKI | Sorafenib, Nexavar® |

Although this group of medications does not have strong scientific support or even solid prevalence or incidence numbers for the risk of ONJ, given that many have only begun to be associated with this pathology in the last 5 years, all of them should be considered medications at risk of causing osteonecrosis. Another problem we find related to the short time period over which these have been studied with regard to ONJ, is that it is still unknown how long the risk remains once treatment is discontinued, in the case of needing to carry out a surgical procedure involving bone tissue on the patient [76]. What we do know, however, is that in the same way that occurs with the rest of medications described to date, ONJ associated with antiangiogenics can appear spontaneously or after surgical intervention, and is more common in the mandible than the

maxilla. The time that elapses between starting treatment and the appearance of osteonecrosis is extremely variable (again, this is also related to the scarce evidence for it) from a couple of weeks to up to 15 months [81,82].

## Biologic Immunomodulators

Biologic immunomodulators are medications, generally monoclonal antibodies, designed to bind to mediators of the inflammatory response. They have represented an improvement in the quality of life of patients with inflammatory diseases such as Crohn's disease, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, or psoriasis, among others, and have made it possible to reduce the adverse effects of the other therapeutic options for these types of diseases [83]. They are also prescribed as treatment for some cancerous processes. Their history in the group of medications at risk of causing ONJ is very recent. Since 2017 cases associated with compounds like Infliximab (anti- TNFα), Adalimumab (anti-TNFα) or Rituximab (anti-CD20), have been published [84- 86]. Similarly, to the situation with antiangiogenic agents, there is no solid scientific evidence of this risk of immunomodulator-associated ONJ, given that there are insufficient data on prevalence and/or incidence that show a statistically significant association. We do not have an estimate of objective risk, and the knowledge available on the aetiopathogenic mechanisms that could cause this adverse effect is scarce [84-86]. In the case of anti-TNFα agents, it is thought that the inhibition of bone remodelling could be secondary to the inhibition of RANKL. This process would induce monocyte apoptosis and would facilitate reinfection of the affected area as a result of local immunosuppression [86-88]. Though we do not have solid scientific evidence, considering the possibility that new cases may arise and in a few years a strong association between this type of medication and ONJ may be definitively established, it goes without saying that we should be cautious with these patients and apply similar prevention protocols to those we would apply to a patient in treatment with biphosphonates, antiresorptive agents or antiangiogenic agents [17].

Within this group, we also include corticosteroids, as it has been demonstrated that prolonged treatment of systemic corticosteroids significantly increases the risk of suffering osteonecrosis or avascular necrosis, which involves the death of bone tissue and its matrix due to reduced blood flow. The latter is most common in the femur, tibia, or humerus [88,89]. Corticosteroids also have an effect on osteoblasts, reducing their production and on osteoclasts by extending their half-life; in addition, they induce osteocyte apoptosis, and this is associated with a reduction of VEGF, angiogenesis, interstitial fluid, and tissue resistance [88]. In the jaw bones, corticosteroids do not produce osteonecrosis on their own, but they do in patients in concomitant treatment with biphosphonates or denosumab, presenting a higher risk of developing ONJ in these cases [90,91]. In 2019 Veszelyné *et al* [92] published a study in which one of the groups studied was patients in treatment with biphosphonates and corticosteroids. In this group, the incidence of osteonecrotic lesions was significantly greater than in the group that only received treatment with biphosphonates ($p < 0.01$). This risk also depends on other factors such as the dose and duration of the corticotherapy, intra-articular administration, and the underlying pathology of the patient such as renal insufficiency, graft-versus-host disease, chronic inflammatory disease, HIV, lymphoblastic leukaemia [87].

Another immunomodulating drug is methotrexate, which is prescribed for the treatment of rheumatoid arthritis or other autoimmune and chronic inflammatory disorders, as well as some tumours and malignant haematological processes [93]. The association between methotrexate and the risk of osteonecrosis is controversial, as in many described cases, it occurred in patients undergoing concomitant treatment with biphosphonates or corticosteroids, and in addition, these patients could develop a lymphoproliferative disorder secondary to treatment with methotrexate, which could be the cause of the necrotic process in the bone. Nevertheless, very recent studies have published case series of patients in treatment with methotrexate, but no other medication, having risk of osteonecrosis without having developed lymphoproliferative disorder. Although it is a start, these are studies with a very small sample size [93]. In the case by

Henien *et al* [94] is presented 2 cases of patients with rheumatoid arthritis in treatment with low-dose methotrexate, but over a very prolonged time. In this article they argue that the aetiopathological mechanism for methotrexate-associated osteonecrosis is unknown, but there are many factors that could be responsible such as, for example, the inhibition of DNA synthesis, cell replication, and that at high doses it is cytotoxic and at low doses it inhibits the function and proliferation of B and T lymphocytes, as well as the release of IL-1, TNFα and other cytokines, and the inhibition of osteoblast proliferation [91-94].

## Other Medications

In the literature, we find other medications with cases that have developed osteonecrosis. In this group we include Everolimus, Temsirolimus, Ipilimumab or Azacitidine.

The first two compounds are mTOR (mammalian Target of Rapamycin) inhibitors, and have antiangiogenic and immunosuppressant properties. They are primarily used in transplant patients, but at high doses, they are also prescribed for advanced stage kidney or breast cancer, and some types of leukaemia [95]. As occurs with immunomodulators, the majority of documented cases of osteonecrosis associated with mTOR inhibitor treatment arise in patients treated simultaneously with biphosphonates, denosumab or antiangiogenic agents. Though they are few and very recent, there are publications of cases of ONJ associated with Everolimus as monotherapy, but they do not constitute solid scientific evidence that supports their role in MRONJ development, and we do not have sufficient data or reliable prevalence/incidence figures [96-98].

In the case of Ipilimumab (anti-CTLA-4 monoclonal antibody) used in the treatment of advanced melanoma or Azacitidine (chemotherapeutic agent) used in the treatment of myelodysplastic syndromes and leukaemias, there are very isolated cases of ONJ that have been described which may be related to the therapy, but there is no clarity as to the aetiopathological mechanism of the process [17].

More studies are needed with larger samples to strengthen the scientific evidence associated with those drugs, but, as has been occurring throughout the years with the other medications that are currently considered to be involved in developing ONJ, time and consistency will help us compile more cases and understand their relationship with osteonecrosis and the mechanisms of action involved in its development [17].

## Treatment

The treatment of ONJ lesions is very complex and presents a challenge for professionals as there is still controversy today [58]. The majority agree that treatment must be customised for each case, as it depends on the patient's underlying condition and the stage of progression of the process [1]. Within the parameters proposed and, as we have already said, depending on each case, going from conservative treatment, surgical debridement (sequestrectomy), resection of the affected tissues, and other alternative therapies like hyperbaric oxygen, laser therapy or, more recently, treatment with stem cells in order to regenerate damaged bone [58,59].

For the AAOMS, the aim of treatment is to eliminate symptoms, control infection, avoid progression of osteonecrosis and prevent the appearance of new lesions [36]. For this, as first line of treatment, the recommendations are irrigation of the lesions with antiseptics, antibiotic therapy, and patient follow-up [36,59]. This consists of conservative management, in which 70% of cases achieve improvement or elimination of symptoms, but a small percentage of very mild lesions are cured [58]. Nevertheless, a recent review indicates that the majority of lesions (still in early stages) are not resolved through this strategy and, therefore, concludes that surgical resection of the lesion and part of the surrounding healthy bone tissue is the treatment with best results [100]. Hyperbaric oxygen, used in post-operative recovery following surgical resection of ONJ lesions improves the success rate [58]. Another recent study, in this case a multicentre study, concludes that resective surgical treatment is successful for stage 2 lesions, but not all lesions are susceptible to the same treatment, as there are many cases that do

not heal after the intervention [58,100]. Therefore, over the years, other less invasive and more successful therapeutic options have been sought, even for high severity cases [59,101].

The team of Kuroshima et al. published a study in 2014 showing that the use of parathyroid hormone (PTH) intermittently considerably reduces the appearance of ONJ lesions. However, the administration of PTH is very restricted in patients with cancer, who are also those with the greatest risk of developing osteonecrosis [102]. On the other hand, there are other medical therapies like activated vitamin D3, vitamin K12 or some modulators of oestrogen receptors that have been studied as preventive therapies in patients in treatment with antiresorptives, but without yielding very good results [59].

The combination of Pentoxifylline and Tocopherol is a formula whose preventive and therapeutic effect on ONJ has been studied extensively in recent years. Pentoxifylline is a non-selective inhibitor of phosphodiesterase and Tocopherol is Vitamin E. There are multiple effects produced by this combination that serve as reasons for which it has been proposed as treatment for ONJ: anti-inflammatory effect through inhibition of neutrophil action, inhibition of vasoconstriction and platelet aggregation promoting blood circulation, stimulation of the release of plasminogen activator, regulation of growth factor release, induction of differentiation of mesenchymal cells in the chondro-osteogenic line promoting osteogenesis, etc. [103]. Studies have been published in which treatment with Pentoxifylline (400 mA) and Tocopherol (500 mg) leads to the disappearance of bone exposure and associated symptoms, without adverse reactions, in 70% of patients with ONJ. Authors today generally agree that the results are promising, but more studies are needed to be able to confirm that it is effective in preventing and treating ONJ [104,105].

Recently, animal studies have shown that the infusion of mesenchymal stem cells from bone marrow in ONJ lesions allows wound closure and tissue healing [106]. The same results are obtained from studies in rats, in which systemic transplants are performed of the vascular fraction of the stroma of adipose

tissue [107]. However, cell therapy could become the treatment of choice in a not too distant future.

Other treatments like laser therapy [17] or the infusion of autologous platelet concentrate [108], do not have clinical data concluding they are effective [101].

## Prevention

There is currently no treatment that is 100% effective for all cases of MRONJ and precisely for this reason, authors agree that prevention is essential.

Ideal prevention would be dental evaluation prior to starting treatment and care in the oral cavity with periodic visits to the dentist during the time the medication is taken[1,4]. It has been demonstrated that with something this simple, the risk of developing ONJ is reduced considerably, up to 77.3% [1-3,53,61].

The specialist should ensure that the patient who will start taking biphosphonates, antiresorptive drugs, or others with a potential risk of osteonecrosis have no infected sites or periodontal sacs or caries that could provoke bone processes, and some authors even argue for the need to remove areas potentially exposed to trauma or irritation such as tori, due to their demonstrated relationship to osteonecrotic lesions [53,58,61].

Patients who will start treatment with intravenous biphosphonates are considered patients at high risk of developing osteonecrosis, and when surgical treatment is necessary (extractions, periodontal surgery, periapical surgery, cystectomy, ostectomy, etc.) it should be performed 4 to 6 weeks before starting treatment [53,58].

It is also important to treat the patient's mouth, and educate them on oral hygiene, and impress upon them the importance of carrying out periodic follow-ups [56,61].

In patients who are already in treatment, each case must be looked at individually, but the specialist should have some general guidelines in mind [53]:

Low risk patients: are those who have received oral treatment at low doses, for less than 4 years, and who do not have any other associated systemic or local risk factor (e.g. tobacco, periodontal disease, diabetes, etc.) (Figure 2). In those patients we can perform any conservative and/or surgical treatment with no need to withdraw the medication, as discontinuing the medication would not have benefits in these patients [61]. It is necessary that the patient be informed at all times of the risks entailed, such that every procedure is carried out after having signed an informed consent. Antiseptic use is always recommended prior to any intervention, and if performing surgery, an antibiotic regimen should be prescribed before and after [58,61]. If the intervention is to emplace implants, the patient must also be informed more specifically, as the rate of failure of implants in patients in treatment with biphosphonates or antiresorptives is higher, though not significantly [61,109].

| Patient on treatment with antiresorptive agents | Dose | | Therapy (years) | | Presence of associated risk factors (Concomitant treatmen with corticosteroids, antiangiogenic or immunosuppressive drugs, Mellitus Diabetes) | |
|---|---|---|---|---|---|---|
| | Low | High (or BF IV) | <4 years | > 4 yeras | None | ≥ 1 |
| *Low risk* | X | | X | | X | |
| *High risk* | X | | X | | | X |
| | X | | | X | X | |
| | | X | X | | X | |

**Figure 2:** Scheme for identifying low or high risk patients base don doce, therapy time and associated risk factors.

High risk patients: patients in treatment with drugs by intravenous route, or orally at high doses, associated with corticosteroids or antiangiogenics, for more than 4 years or with associated systemic or local risk factors. (Figure 2) Conservative treatments such as the elimination of caries or non-surgical dental treatment may be carried out [59,61]. Cases of ONJ lesions have been reported after a root canal, although some

authors argue that the instrumentation of colonised root canals and even the trauma that can result from the clamp during treatment can be the cause of osteonecrosis. For this reason, specialists recommend that before performing endodontics, rinse with antiseptics, avoid anaesthesia with a vasoconstrictor, avoid trauma of the soft tissues with the clamp, avoid extrusion of the instruments and irrigant around the apex, and administer an antibiotic regimen before and after treatment [61,110]. In these patients, we should always avoid surgical treatments as much as possible. We should keep in mind that dental extraction is the local factor involving the highest risk of developing ONJ. In teeth indicated for extraction, less invasive alternatives to extraction like root canals and coronectomy should always be considered. Atraumatic extraction with orthodontics is also recommended [61]. One way or another, teeth with inflammatory/infectious pathology must be treated, as a process of this type, even if asymptomatic, could also be a significant risk factor [28]. Therefore, in some cases, surgery is inevitable, and in these cases, we must plan and treat with greater caution. There are several factors that can help us manage patients with risks for ONJ. Among these: levels of serum C-terminal telopeptide (sCTX) as a predictive value, the suspension of the drug for a set time before and after the treatment (drug holiday) and thorough infection control before carrying out surgery [59.61,109].

sCTX is a marker for bone resorption, and indicates osteoblastic and osteoclastic activity, which can therefore serve as a reflection of the pharmacological effect of antiresorptive therapy [61]. Marx et al. [60] already indicated at the time of their publication that this marker might tell us the degree of risk that existed, with a value equal to or greater than 150 pg/mL meaning that there was a low risk of ONJ, and that as the value decreased, the risk increased. However, subsequent studies do not find a significant relationship between the sCTX value and the development of ONJ, lessening its strength as a predictive value, as they affirm that it is greatly affected by other factors like age, tobacco, alcohol consumption, sex, ovulation, circadian rhythm, corticotherapy or pathologies like diabetes [111,112].

There is currently tremendous controversy regarding the suspension of treatment. The FDA, AAOMS, Korean Association of Oral and Maxillofacial Surgeons and other groups suggested the suspension of medication for at least 2 months prior to surgical intervention for those patients in oral treatment with a high risk of ONJ, so long as systemic conditions allow [1]. The risk of fracture in patients with a history of fracture or unfavourable densimety can increase if we withdraw medication for 6 months [61,77,78]. On the contrary, a recent study in Japan has demonstrated that the suspension of medication prior to extraction does not reduce the risk of ONJ in these patients. This occurs with biphosphonates, which are retained long-term in the bone matrix, so interruption for several weeks or months does not significantly affect the bone remodelling process [113]. Denosumab is considered to have some reversibility. For this reason, numerous studies affirm that the suspension of denosumab or other compounds with similar action over RANKL entails much quicker resolution compared to bisphosphonates [78,110,113].

We conclude that it makes more sense and has more positive outcomes to interrupt antiresorptive treatment than biphosphonates. However, the suspension of oral biphosphonates for 2-3 months prior to the intervention continues to be a justified and endorsed guideline at present [61,76-78].

The control of any infectious process is fundamental prior to subjecting a patient at risk to surgical intervention [28,78,114]. Recent studies show that an inflammatory-infectious periodontal or periapical process is one of the most potent and influential risk factors for the development of ONJ [61,110]. The only way to reduce this concrete risk is to control the process with medication, hygiene measures, use of antiseptics, and prior treatments are also recommended such as tartar removal or root canal, in teeth with periodontal or periapical infection that have an indication for extraction [61].

Figure 3 shows a flow chart for a patient in treatment with any of the medications with potential to cause ONJ.

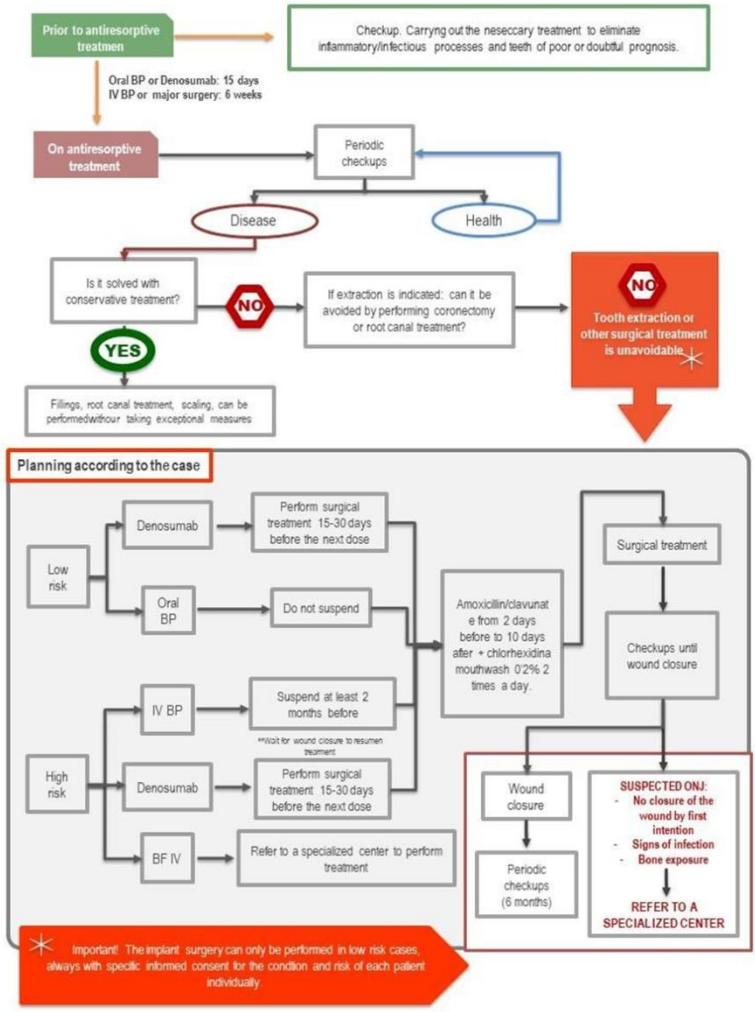



**Figure 3:** Performance diagram.

## Clinical Case

We present the case of a 50 year old woman with no known drug allergies or toxic habits. Her relevant medical-surgical history includes depression, cataracts, and breast cancer in 2010 overcome by a right mastectomy and radiotherapy, and a relapse

in 2013 with metastasis in the pleura, liver, and bone involvement.

The patient's current medication is Clexane®, Hidroferol®, Xeloda®, Natecal® and Mirtazapina®.

In January 2019, she comes to the Master of Medicine, Surgery and Oral Implantology at the Dental Hospital of the University of Barcelona, referred by a primary care dentist to carry out an extraction of the residual root of 3.8. The patient indicates that the area oozes and that the antibiotic regimen prescribed by her doctor no longer has an effect.

The patient indicates having been in treatment with Denosumab® after the recurrence of the cancerous process. Her specialist had indicated its suspension 8 months prior to presenting at our department. She was receiving a dose of 120 mg per month by intramuscular route for 5 years.

In Figure 4, we show the panoramic radiograph and a clinical image of the first visit.

Given that the imaging test shows an area of bone rarefaction at 3.8 and the angle and mandibular branch involved with the lower dental nerve, with poorly defined radiotranslucent and radiopaque areas, we decide to perform a CBCT of the area for better analysis. We also see that the infectious process also involves 3.7.

In the CBCT (Figure 5), a large bone sequestrum is identified of 1.5 x 1 cm, associated with the infectious process that concerns the mandibular angle and extends through the mesial zone of 3.7, with a fracture of the vestibular cortical layer of the residual root of 3.8 without directly contacting the lower dental nerve.

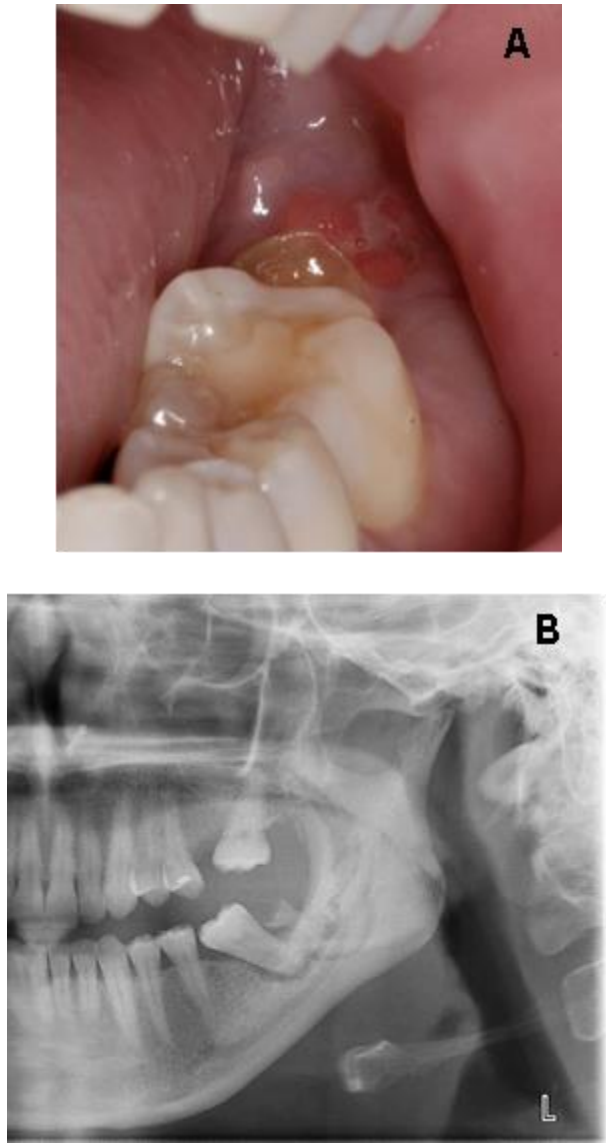



**Figure 4: A)** Clinical image. **B)** Orthopantomography.

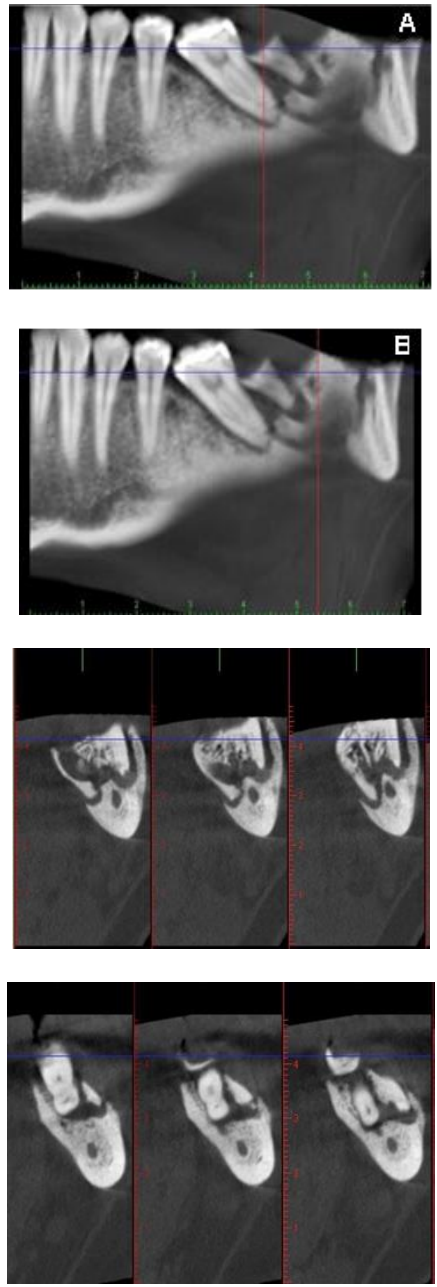
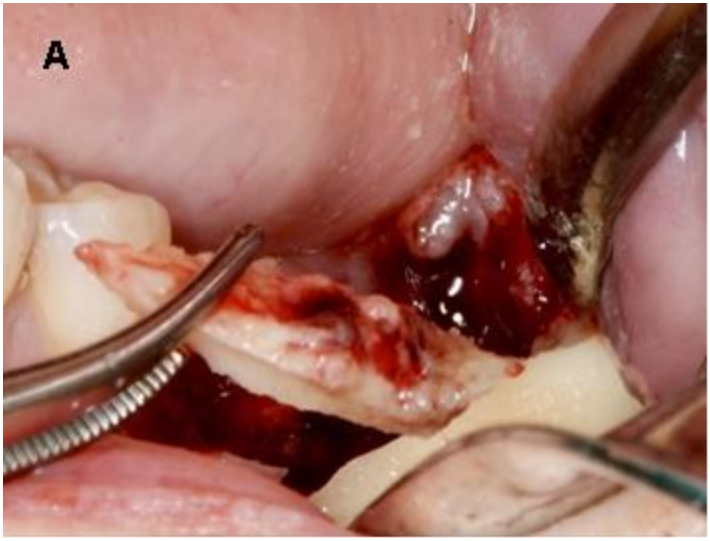



**Figure 5:** Tomographic cuts. A) infectious process periapice zone of 3.7. B) Bone sequestration at the 3.8 level with fracture of the vestibular cortical.

Based on the data, the patient was told of the situation and possible risks arising from it and from the intervention, and signed an informed consent. The surgical intervention was scheduled under an antibiotic regimen, to extract 3.7 and 3.8 and, taking into account the size of the sequestrum and the posibility that the lesion was a recurrence of the cancerous process, it was planned to take a tissue sample for histopathological analysis.

Amoxicillin/clavulanic acid was prescribed 875 mg/125 mg once every 8 hours for 10 days, explaining that the patient should start the regimen 2 days prior to the intervention. The surgery was carried out under local anaesthesia of articaine 4% with epinephrine 1:100,000, after a 0.2% chlorhexidine rinse for 1 minute. The extractions were performed without complications, and a full thickness incision was performed with flap detachment from the socket of 3.7 to the retromolar area and a sample of bone tissue was taken with a rotary instrument encompassing healthy bone cortex and an area of bone tissue with necrotic appearance and associated granulation tissue. (Figure 6) After careful curettage, the wound was closed without tension using silk sutures 4/0. (Figure 7)



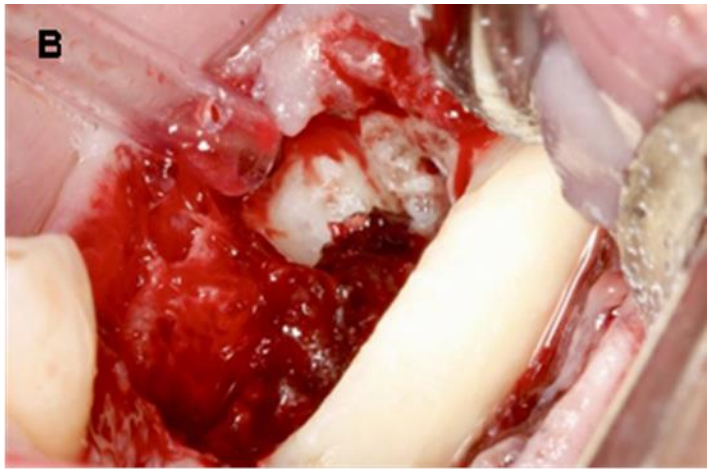



**Figure 6**: **A)** Tissue sampling. **B)** Clinical appearance of the wound before curettage.

After the above, a check-up was performed at 7 days, verifying that there was no bone exposure and the patient was asymptomatic, and the suture was removed. (Figure 8A)

At the 15 day check-up (Figure 8B) the patient appeared with a bone exposure of 2.5 x 1 cm in size, asymptomatic. Due to the size of the exposure, risk of mandibular fracture, and not yet having the pathology results, the patient was referred with a report and all additional exams performed to the maxillofacial surgery department for assessment and treatment.
After 15 days (Figure 8C) the patient returned to our department with discomfort on the left side of the tongue because she felt something was rubbing it. A clinical examination observed a second exposure at the tongue in the retromolar zone with a bony spicule of necrotic appearance. Irrigation of the zone was carried out with chlorhexidine and not seeing mobility, it was decided to polish the spicule with a rotary instrument to avoid rubbing. The patient already had her visit scheduled with the maxillofacial surgery department.

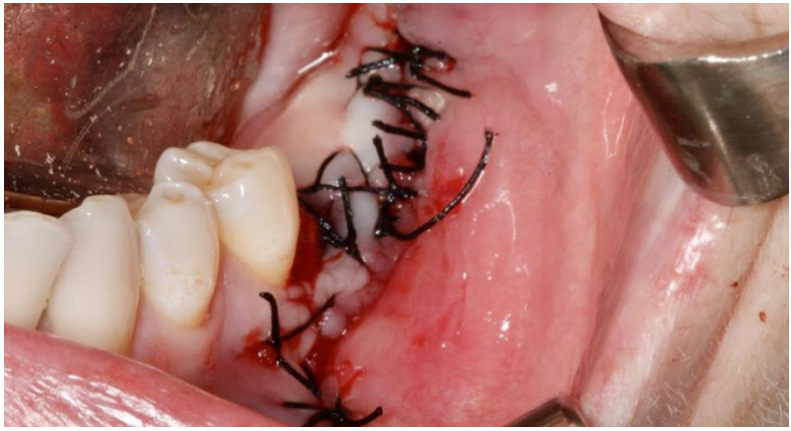
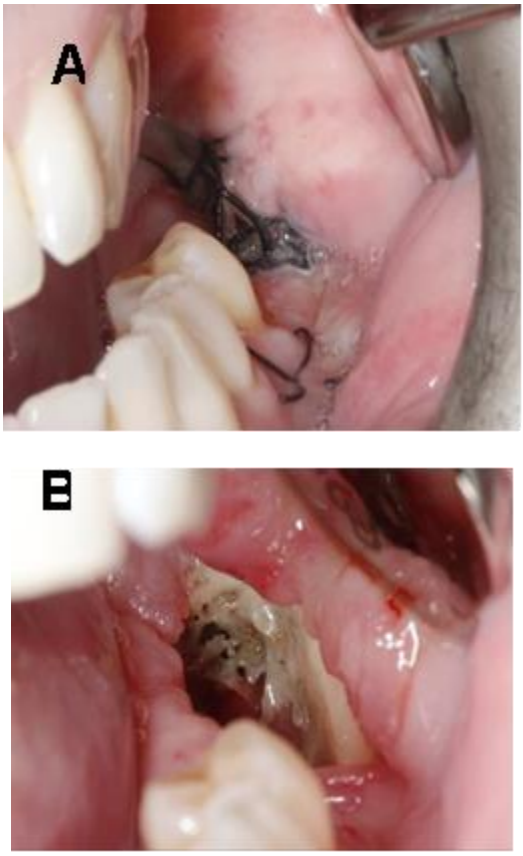


**Figure 7**: Wound closure, immediate postoperative.



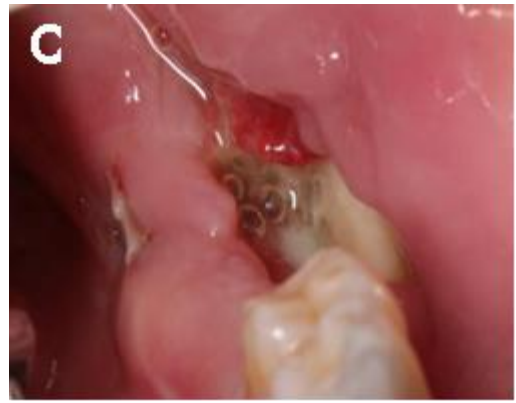



**Figure 8:** A) control after 7 days before removing the sutura, B) after 14 days with bone exposure and C) after 30 days with bone spicule in the lingual área.

The pathology report confirmed that it was an MRONJ lesion, showing granulation tissue, necrotic bone tissue with signs of resorption in the absence of osteoclasts, and no signs of malignancy.

## Conclusions

The list of medications that can provoke ONJ was compiled very recently in the 21st Century and is ever-growing. Despite the fact that biphosphonates are the best-known and most-studied in this regard, today, cases of osteonecrosis are still elevated due to an over- prescription of these types of medications and due to errors in prevention and diagnosis.

A good clinical history and thorough interview is fundamental in dental consultation to avoid these types of errors and instill essential preventive measures in these patients and, in complicated high-risk cases, refer them to a specialised department. All these measures do not make the risk of osteonecrosis disappear, but they do help diminish or reduce the severity of cases if we apply appropriate follow-up.

It is very important to inform the patient of their situation and the risks entailed by the ensuing treatment, of the importance of maintaining good oral hygiene and attending periodic dental

check-ups, as well as communicating any anomaly in their mouth such as pain, mobility or inflammatory signs to their specialist.

In these patients, when confronted with the need for surgical treatment, it is essential to carry out a thorough interview and to plan treatment in accordance with the established protocols, controlling the infectious process, if any, following the least traumatic technique possible, under antibiotic guidelines and rigorous aseptic measures, and performing post-operative controls.

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