Book Chapter

Case Report: First Case of Pemetrexed Plus Cisplatin-Induced Immune Hemolytic Anemia in a Patient with Lung Adenocarcinoma

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the blood samples and conducted the related laboratory tests. HLZ and YTC revised the manuscript. All authors contributed to the article and approved the submitted version.

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Abstract

Background: Drug-induced immune hemolytic anemia (DIIHA) is a rare but potentially life-threatening drug-related complication. There are no previous reports of pemetrexed plus cisplatin as first-line chemotherapy for non-small cell lung cancer resulting in DIIHA.

Case Presentation: In this report, a patient with advanced stage lung adenocarcinoma developed severe immune hemolytic anemia 21days after pemetrexed plus cisplatin chemotherapy. Laboratory findings suggested severe hemolysis, including a rapid decrease in hemoglobin and elevated level of reticulocytes, indirect bilirubin, and lactate dehydrogenase. A workup for possible DIIHA was performed, including direct antiglobulin test (DAT), testing in the presence of the soluble drug, and testing of drug-treated red blood cells (RBCs). It showed a strongly positive (3+) result for anti-C3d but not anti-IgG in DAT. Enzyme-treated RBCs reacted weakly with the patient's serum and pemetrexed when complement was added. Besides, the patient's serum and normal sera were reactive with cisplatin-

treated RBCs. But the eluate from the patient's RBCs and diluted normal sera were nonreactive with cisplatin-coated RBCs. Both untreated and enzyme-treated RBCs reacted with the patient's serum in the presence of soluble cisplatin. In vitro serological tests suggested that complement-dependent pemetrexed antibodies and cisplatin-associated non-immunologic protein adsorption (NIPA) may combine to cause immune hemolytic anemia. The patient's anemia gradually recovered when pemetrexed and cisplatin were discontinued.

Conclusion: This rare case demonstrated that complement-dependent pemetrexed antibodies and cisplatin-associated NIPA might occur simultaneously in a patient with DIIHA.

Keywords

Pemetrexed; Cisplatin; Complement-Dependent Antibody; Non-Immunologic Protein Adsorption; Drug-Induced Immune Hemolytic Anemia

Introduction

Drug-induced immune hemolytic anemia (DIIHA) is a rare but severe complication related to drug application that leads to serious adverse outcomes. The incidence of DIIHA is approximately 1-4 per million per year [1-3]. However, the incidence is likely to be underestimated because many cases are often overlooked and misdiagnosed, often with a diagnosis of warm autoimmune hemolytic anemia [4-6]. In cases of suspected DIIHA, several aspects should be considered: medical history, signs, type of drug, time of drug initiation, the measure of administration, hemolytic features (extravascular or intravascular hemolysis), and co-morbidities [6].

Serologic testing of the associated drug-induced antibodies can be very helpful in verifying and differentiating the diagnosis of DIIHA. Drugs interacting with the immune system can elicit the formation of red blood cell (RBC) antibodies, including drug-dependent and drug-independent. Drug-dependent antibodies react in vitro only in the presence of the drug either bind to the

membrane of red blood cells (RBCs) or dissolve in the patient's serum. The antibodies are directed against the drug only or a combination of the drug and RBC membrane antigen. In contrast, drug-independent antibodies against RBCs can be detected in vitro by the direct antiglobulin (DAT) and the indirect antiglobulin (IAT) in the absence of the drug [2,7]. In addition to drug-induced antibodies and autoantibodies, nonimmunological adsorption of proteins (NIPA) of some drugs is also responsible for the DIIHA [8,9]. These drugs may modify the RBC membrane, and then the proteins are adsorbed nonspecifically onto the modified membrane [10]. NIPA can cause positive DATs and IATs, which may confuse the interpretation of tests to determine the drug-induced antibodies.

Approximately 140 drugs were reported to induce DIIHA [11], of which chemotherapeutic drugs (mainly platinum-based agents) account for a significant proportion [5]. In this study, we report a patient who developed DIIHA after taking an intravenous infusion of pemetrexed plus cisplatin chemotherapy for lung adenocarcinoma.

Case Presentation

A 65-year-old male patient was admitted to the hospital with a chief complaint of cough and hemoptysis for two months. Cheat computed tomography (CT) suggested a mass in the right lung with mediastinal adenopathy. The diagnosis of lung adenocarcinoma ($cT_4N_2M_0$, Stage IIIB) was established based on histopathology obtained from transbronchial biopsy and endobronchial ultrasound-transbronchial needle aspiration. The patient then underwent the first cycle of pemetrexed (500mg /m^2, Day 1) combined with cisplatin (75mg /m^2, Day 1) chemotherapy on November 7th, 2021, after the preparation with folic acid, vitamin B12, and glucocorticoids. On November 26th, 2021, the patient developed amaurosis, weakness, and icteric sclera and was admitted to the hospital again. Laboratory tests showed a rapid drop in hemoglobin (HGB) and elevated levels of reticulocytes (Rets), indirect bilirubin (IBIL), and lactate dehydrogenase (LDH). There were no schistocytes in the peripheral blood smear. The count of white blood cells and

platelets was all normal. A possible diagnosis of bone marrow suppression or thrombotic thrombocytopenic purpura has been ruled out. Chest CT did not show any signs of lung parenchymal hemorrhage. Repeated occult blood tests of stool were negative. There was no evidence of bleeding from the lung or gastrointestinal tract. Additionally, anti-nuclear antibodies were negative. Peripheral $CD55^{-}CD99^{-}$ monoclonal red blood cells were not detected with flow cytometry assay, which ruled out the diagnosis of paroxysmal nocturnal hemoglobinuria. The DAT showed strongly positive with anti-C3d (3+) but not with anti-immunoglobin G (IgG). The patient's medication history and main symptoms are displayed in Figure 1 (Case report timeline). And the detailed results of related laboratory tests of blood samples collected at 2 weeks (October 25th, 2021) pre chemotherapy and 3 weeks (November 27th, 2021), 4 weeks (December 4th, 2021), 6 weeks (December 18th, 2021), 8 weeks (December 31st, 2021), 11 weeks (January 21st, 2022) and 14 weeks (February. 11th, 2022) post chemotherapy are listed in Table 1:

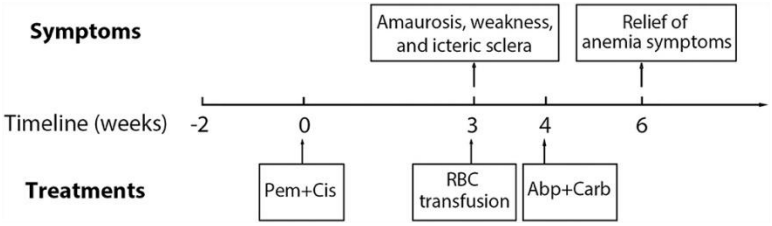

Figure 1: Timeline of patient's clinical course. Pem, pemetrexed; Cis, cisplatin; Abp, albumin-bound paclitaxel; Carb, carboplatin; RBC, red blood cells.

Table 1: Laboratory test results and changes of the patient before and after pemetrexed plus cisplatin chemotherapy.

Detection items	2 weeks pre chemotherapy	3 weeks post chemotherapy	4 weeks post chemotherapy	6 weeks post chemotherapy	8 weeks post chemotherapy	11 weeks post chemotherapy	14 weeks post chemotherapy	Reference Range
Hemoglobin (g/L)	127.00	68.00	69.00	86.00	104.00	111.00	91.00	130.00-175.00
RBC count ($\times 10^{12}$)	4.54	2.30	1.79	1.58	3.53	3.65	3.11	4.30-5.80
MCV (fL)	85.10	82.20	97.20	94.30	92.10	89.30	87.50	82.00-100.00
MCH (pg)	28.00	29.60	38.50	54.40	29.50	30.40	29.30	27.00-34.00
MCHC (g/L)	328.00	360.00	397.00	577.00	320.00	340.00	335.00	316.00-354.00
Reticulocyte proportion (%)	NT	2.93	9.58	1.25	NT	NT	NT	0.50-1.50
Platelet count ($\times 10^{9}$)	274.00	781.00	445.00	310.00	185.00	192.00	139.00	100.00-350.00
WBC count ($\times 10^{9}$)	7.24	21.77	13.14	3.83	2.75	3.23	4.27	3.50-9.50
Total bilirubin (μmol/L)	6.84	36.21	9.31	8.97	NT	10.05	8.39	5.00-21.00
Indirect bilirubin (μmol/L)	4.56	27.96	5.86	6.90	NT	9.12	6.50	3.40-17.00
LDH (IU/L)	185	593	318	245	NT	NT	210	100.00-250.00
Folic acid (nmol/L)	NT	19.42	NT	NT	NT	NT	NT	7.00-45.10
Vitamin B12 (pmol/L)	NT	304.00	NT	NT	NT	NT	NT	133.00-675.00
Serum ferritin (ng/mL)	NT	1561.00	NT	NT	NT	NT	NT	23.90-336.20
EPO (mIU/mL)	NT	56.87	NT	NT	NT	NT	NT	2.59-18.50
Irregular red cell antibodies	Negative	3+	Negative	Negative	Negative	Negative	Negative	Negative
DAT for anti-IgG	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
DAT for anti-C3d	Negative	3+	3+	3+	3+	2+	1+	Negative

RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean red blood cell hemoglobin concentration; LDH, Lactate dehydrogenase; EPO, erythropoietin, DAT, direct anti-globulin test; NT, not tested.

Diagnosis Based on Serological Tests

The venous blood samples were collected 3 weeks (November 27th, 2021), 4 weeks (December 4th, 2021), 6 weeks (December 18th, 2021), 8 weeks (December 31st, 2021), 11 weeks (January 21st, 2022) and 14 weeks (February. 11th, 2022) post chemotherapy of pemetrexed plus cisplatin. Serological analysis of the patient's blood samples was performed, including DAT for anti-IgG and anti-C3d, acid elution test, and irregular RBC antibody screening IAT in Coombs card. The methods and materials used are described in detail in the supplementary materials.

The DAT results for anti-C3d were positive but negative for anti-IgG for all the blood samples collected from 3 to 14 weeks after chemotherapy of pemetrexed plus cisplatin. But the reaction of DAT for anti-C3d became weaker over time from 8 to 14 weeks after chemotherapy. The results of irregular RBC antibody screening were positive at 3 weeks, but negative at 4 weeks and 6 weeks after the chemotherapy. The detailed results of DAT and irregular RBC antibody screening are shown in Table 1.

Testing in the Presence of Soluble Drugs

The patient's serum was incubated with untreated and enzyme-treated RBCs in a solution with pemetrexed or cisplatin. Results of the tests performed with the drug solution are summarized in Table 2. The patient's serum reacted only with enzyme-treated RBCs in the presence of both pemetrexed and fresh sera from 3 to 8 weeks after chemotherapy. This result indicates that anti-pemetrexed antibodies may be present in the patient's serum, and the response may require the involvement of complement. However, pemetrexed-induced antibodies disappeared after 11 weeks post-chemotherapy. This suggested that the antibodies were gradually cleared from the patient's circulation after a single dose of the drug. Interestingly, the patient's serum and normal sera reacted with both untreated and enzyme-treated RBCs with cisplatin from 3 to 14 weeks post-chemotherapy. These results may be due to the occurrence of NIPA in the presence of cisplatin.

Table 2: Testing the reaction in the presence of soluble drugs.

Sample tested	Pemetrexed or PBS (3, 4, 6, 8 weeks post chemotherapy)		Pemetrexed or PBS (11, 14 weeks post chemotherapy)		Cisplatin or PBS (3, 4, 6, 8, 11, 14 weeks post chemotherapy)	
	Untreated RBCs	Enzyme-treated RBCs	Untreated RBCs	Enzyme-treated RBCs	Untreated RBCs	Enzyme-treated RBCs
Patient's serum + drug	0	0	0	0	2+	3+
Patient's serum + PBS	0	0	0	0	0	0
Patient's serum + C + drug	0	1+	0	0	2+	3+
Patient's serum + C + PBS	0	0	0	0	0	0
Normal sera + drug	0	0	0	0	2+	3+
Normal sera + PBS	0	0	0	0	0	0

PBS, phosphate buffer saline; C, compliment; RBC, red blood cell

Testing of Drug-treated RBCs

The reaction of the patient's serum pooled normal sera, and drug-treated RBCs are shown in Table 3. The tests results at all follow-up dates were identical. The patient's serum didn't react with pemetrexed-treated RBCs. The patient's serum, diluted serum, and normal sera were all reactive with cisplatin-coated RBCs. In contrast, elution prepared from the patient's RBCs and diluted normal sera failed to react with cisplatin-coated RBCs. Combined with the previously mentioned results of the reaction with cisplatin, as shown in Table 2, it suggested that NIPA may be present on the membrane of cisplatin-treated RBCs.

Table 3: Testing the reaction with drug-treated RBCs.

Sample tested	Pemetrexed-treated RBCs (3, 4, 6, 8, 11, 14 weeks post chemotherapy)	Cisplatin-treated RBCs (3, 4, 6, 8, 11, 14 weeks post chemotherapy)	Untreated RBCs (3, 4, 6, 8, 11, 14 weeks post chemotherapy)
Patient's serum	0	2+	0
Patient's serum diluted 1 in 20	0	1+	0
Eluate	0	0	0
Last wash	0	0	0
Normal sera	0	2+	0
Normal sera diluted 1 in 20	0	0	0
PBS	0	0	0

PBS, phosphate buffer saline; RBC, red blood cell

The reason why the patient's serum, diluted serum, and normal sera were all reacted consistently with the RBCs in the presence of the soluble cisplatin, as well as with the cisplatin-treated RBCs, may be due to the concentration of cisplatin added in the in vitro serological tests is much higher than that in vivo. While the intensity of the DAT reaction is weakening over time, implying that cisplatin-associated NIPA is also weakening over time, as less and less cisplatin adsorbed non-specifically on the membrane of RBCs. Therefore, we confirmed by serological methods that pemetrexed and cisplatin might cause DIIHA in two distinctive ways.

Assessment, Treatment Modification, and Follow-up

According to the clinical symptoms, laboratory test results, and related medication history of the patient, the diagnosis of DIIHA was made. Due to severe anemia, the patient received 2 units of suspended RBCs on November 7th, 2021. Then the chemotherapy regimen of pemetrexed plus cisplatin was discontinued. The patient was not treated with glucocorticoids. For further treatment of lung adenocarcinoma, the chemotherapy regimen (every 3 weeks, 4-6 weeks) was converted to albumin-bound paclitaxel (200mg /m^2, Day 1) plus carboplatin (Area Under Curve 5, Day 1) from December 2nd, 2021. The level of HGB gradually increased, and the level of Rets, IBIL, and LDH returned to normal. The timeline of the patient's major clinical symptoms, the entire course of the disease, and therapy is demonstrated in Figure 1.

Discussion

DIIHA diagnosis requires a definite manifestation of hemolytic anemia, a temporal relationship to drug administration, a positive DAT after drug application, and an attenuated hematologic reaction in the patient's serum after cessation of drug [6,12]. The patient reported having clinical features such as immune hemolysis, negative eluate, positive DAT, presence of pemetrexed-induced complement-dependent antibodies, cisplatin-associated NIPA, and a gradual recovery of anemia, supporting the diagnosis of DIIHA.

Anemia is one of the most frequent side effects of chemotherapy. There are two leading causes of anemia: insufficient RBC production due to bone marrow suppression and excessive RBC destruction due to various reasons. Pemetrexed is a dose-dependent, multitargeted folate analog that suppresses tumor growth by impeding DNA synthesis and folate metabolism(13). Supplementary folic acid and vitamin B12 during the chemotherapy reduce the RBC toxicities while maintaining antitumor activity [14,15]. The antineoplastic activity of cisplatin is mainly due to its ability to cross-link with DNA, thus blocking

transcription and replication [16]. Cisplatin-based therapy often has a disproportionate effect on erythropoiesis compared with other blood cells, resulting in a cumulative, clinically significant anemia [17]. Besides, long-term application of cisplatin may lead to renal tubular damage, resulting in a decreased level of erythropoietin (EPO) produced by peritubular interstitial cells, leading to renal anemia [18,19]. Although both pemetrexed and cisplatin can affect erythropoiesis, the process is chronic and cumulative in its onset. Our patient was supplemented with folic acid and vitamin B12 before chemotherapy. And the patient had a normal renal function and urinalysis pre- and post-chemotherapy and was adequately hydrated during chemotherapy to reduce renal toxicity. Moreover, the average lifespan of erythrocytes is about 120 days. Thus, a decrease in erythropoiesis due to bone marrow suppression or EPO reduction after the first cycle of chemotherapy with pemetrexed plus cisplatin is unlikely.

Pemetrexed-induced antibodies were detected in the serum of the patient. Moreover, the reaction is complement-dependent, as confirmed by positive anti-C3d in DAT. These results were similar to previous cases of DIIHA induced by pemetrexed treating non-small cell lung cancer. In one of the reports, the DAT test was positive for anti-C3d [20], while in another report, the DAT test was positive for both anti-IgG and anti-C3d [21]. The antibodies are probable IgM, and there is a possible secondary switch to IgG, IgA, or even IgE through a recombination/deletion process termed immunoglobulin heavy chain class switch recombination [22,23]. The unique feature of our patient is that the pharmacologic antibodies induced by pemetrexed were complement-dependent. C3d component is the inactivated form of C3b, which is involved in phagocytosis, formation of C3 convertase, and stimulation of complement [10,24,25]. C3d-coated RBCs helped us to understand that cells survive complement activation either by the classical pathway, i.e. due to drug-dependent antibodies to RBCs or due to activations of the alternative pathway in the presence of nearby RBCs [6]. We speculate that the immune complex formed by the antibody-pemetrexed-complement-RBC membrane resulted in hemolysis.

NIPA on the RBC membrane has been observed for many drugs, including cisplatin. These drugs have a β-lactam moiety to bind to RBCs via a chemical moiety that is not a β-lactam moiety, resulting in the exposure of β-lactam moiety that covalently binds to other proteins (immunoglobulins, complement, albumin, etc.) [26]. The absorbed protein can react with receptors on macrophages and cause RBCs destruction, though they are not antibodies against the drug or RBCs. Although it is not an antibody-mediated process, RBCs are damaged by a distinct immune response, similar to RBCs coated with drugs and drug-specific antibodies [27]. Two previous studies investigated that cisplatin-associated DIIHA was due to NIPA instead of cisplatin-induced antibodies [8,28]. Besides, the pooled normal sera had a reaction in the IAT, but normal sera diluted 1 in 20 didn't react, which is consistent with our study.

The essential treatment of DIIHA is to stop using the suspected drug. In some severe cases, transfusion and plasma exchange may be necessary [4,29,30]. The role of glucocorticoids in DIIHA treatment remains unclear [4]. In our case, we administered a blood transfusion promptly, and the patient gradually recovered from anemia after discontinuation of pemetrexed and cisplatin. Considering the effect of glucocorticoids on lung cancer, we didn't apply glucocorticoids to the patients.

Tube testing is a classic method of detecting drug-dependent or drug-independent antibodies. The advantages of tube testing are convenience, rapid, and low expenses. In the early studies, most scholars used the tube method for DIIHA-related serological testing. In 2020, Tan Ngoc Nguyen's team confirmed that the gel method was more sensitive, reliable, and reproducible than the conventional tube method for detecting all the drug-dependent antibodies investigated in their studies [26,31]. Hence, we performed all our serological testing in the gel method.

In summary, we reported a case of DIIHA that may be induced by complement-dependent pemetrexed antibodies and cisplatin-induced NIPA. To our knowledge, this is the first case of two possible mechanisms of DIIHA in a single patient. Although

rare, DIIHA is a potentially life-threatening complication that requires careful monitoring when chemotherapy or other medications are administered.

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