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Case Report

Ceftazidime-induced immune hemolytic anemia: a case report

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ABSTRACT

Drug-induced immune hemolytic anemia (DIIHA) is considered a rare condition. Nonsteroidal anti-inflammatory drugs and antineoplastic drugs are the main causes of DIIHA. An 86-year-old male patient with pulmonary infection was admitted to the 960th Hospital of the PLA Joint Logistics Support Force. The patient was treated with ceftazidime in addition to supportive treatment. A history of antibiotics intake and clinical and laboratory hemolysis features were considered to be key bases for DIIHA diagnosis. Clinicians need to be aware of and accurately diagnose this rare complication caused by commonly prescribed drugs to stop the use of causative drugs in time, and therefore, to prevent serious and sometimes fatal consequences.

Keywords: drug-induced immune hemolytic anemia, ceftazidime, blood transfusion

INTRODUCTION

Drug-induced immune hemolytic anemia (DIIHA) is a potentially life-threatening disease that clinicians should be aware of when treating a patient experiencing hemolysis under the treatment of drugs[1]. One particular challenge for clinicians is to distinguish DIIHA from hemolytic anemia caused by other factors, which may lead to delayed diagnosis and treatment[2]. To date, more than 130 drugs have been confirmed as potential causes of hemolytic anemia. Antimicrobials, nonsteroidal anti-inflammatory drugs, and antineoplastic drugs are commonly associated with DIIHA[3]. Ceftazidime is a third-generation cephalosporin administered intravenously or intramuscularly, which exhibits a potent and broad spectrum of *in vitro* activities against most Gram-positive organisms and many Gram-negative organisms[4]. Most importantly, ceftazidime is currently considered to be the most effective cephalosporin against Pseudomonas aeruginosa *in vitro*. In recent years, ceftazidime has been identified as a critically important drug associated with DIIHA[5].

In this report, we discussed a DIIHA case of severe hemolytic anemia in a patient with pulmonary infection after using ceftazidime. It is necessary to raise awareness of this acute life-threatening condition. Antibiotic treatment should be carefully monitored so as to prevent DIIHA.

CASE REPORT

An 86-year-old male with an 8-year history of coronary heart disease and hypertension, as well as a 1-year history of brain injury and anemia, was hospitalized in the emergency department of the 960th Hospital of the Joint Support Force of the People's

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Liberation Army due to a cold and fever. This study was approved by the hospital ethics committee [(2018) scientific research ethics review No. (28)] and obtained the informed consent of the patient and his family.

Blood transfusion and protein supportive therapy was given intermittently due to the patient's history of coronary heart disease and psoriasis for one year. Although the patient remained stable after a series of effective treatments, issues with inhalation led to a more severe pulmonary infection. Examination results taken on the first day of admission showed: hemoglobin, 91.0 g/L; white blood cell count, 17.98×10^9/L; and platelets, 81×10^9/L. Multiple tests showed increased levels of procalcitonin and C-reactive protein, an accelerated erythrocyte sedimentation rate, and the presence of pseudomonas aeruginosa. The patient received ceftazidime (10 mg/day) in addition to supportive treatment, including oxygen and nutritional support.

After 6 days of ceftazidime administration, the patient's hemoglobin (Hb) dropped to 30.3 g/L, indicating a life-threatening complication with persistent hemolysis. Laboratory studies showed that the patient's ABO blood type was B, RhD positive, and samples were negative for irregular antibodies. Direct antiglobulin testing was performed using the standard microtube column agglutination technique according to the manufacturer's instructions (Shanghai Hemo-pharmaceutical & Biological Co., Ltd., China), and the results showed positive IgG (2+) but negative C3d. The suspected DIIHA was proven by reference laboratory analysis, and the presence of 2+ agglutinating ceftazidime-dependent antibody was confirmed (***Fig. 1***). To save his life, two units of red blood cells (RBCs) were prepared, and ceftazidime therapy was discontinued on the same day. Before transfusion, high doses of immunoglobin (0.4 mg/kg) and methylprednisolone (0.5 g/day) were administered. No transfusion reactions were observed, and after several transfusions (a total of 6 units of RBCs), the patient's Hb increased gradually, and he regained consciousness. Transfusion therapy was then stopped, and glucocorticoid was administered with a tapered dose. Before discharge, the patient's Hb level was 112 g/L, and the total bilirubin concentration had returned to a normal level. The patient did not show anemia after discharge. Changes in Hb and red cell indices are summarized in ***Fig. 2*****.**

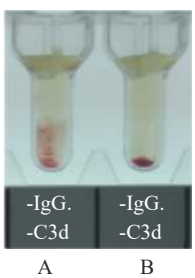

Fig. 1 **Serological investigation of the ceftazidime-dependent antibody using the gel card technique.** A: The result showing 2+ agglutination of the patient's plasma and eluate in the presence of the drug. B: The negative result without ceftriaxone.

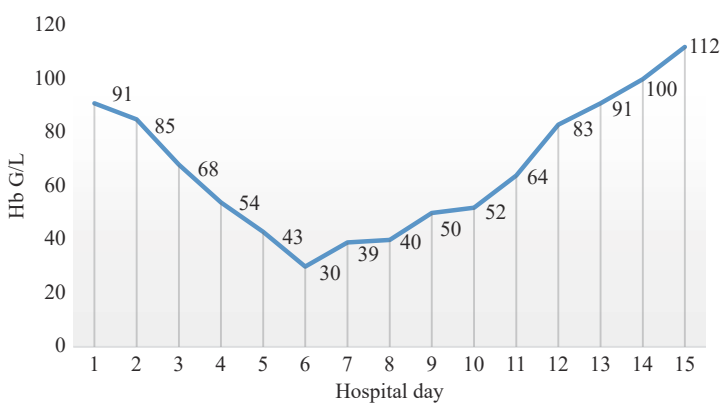

Fig. 2 **Hb levels of the patient on the hospital day.**

DISCUSSION

DIIHA is estimated to have an incidence rate of approximately 1/1 000 000 individuals in the population, but has potential life-threatening complications; hence, early and accurate diagnosis is necessary[6]. There are three mechanisms causing DIIHA[2], including drug adsorption, immune complex mechanism, and autoantibody production. The first mechanism is drug absorption, also known as hapten

induction, in which the drug covalently binds to the erythrocyte membrane and stimulates the production of IgG antibodies. The second is immune complex, in which the drug covalently or non-covalently binds RBCs to produce new antigens and induces IgM antibodies. When the antibodies bind to the erythrocyte membrane, complement activation occurs, leading to intravascular hemolysis. The third mechanism is nonimmunologic protein adsorption. Drug changes the structure of the cell membrane and causes the non-specific adsorption of membrane proteins (such as IgG, IgM, complement, albumin, *etc*.), which result in a positive Coombs test without hemolysis.

In this study, hemolysis resulting from ceftazidime was an example of hapten-induced hemolytic anemia. The adverse reactions of the patient were attributed to ceftazidime due to the time and dose relationships between drug usage and the development of the disease. In addition, there were no other risk factors for developing hemolytic anemia and the patient had no underlying evident etiology. An abundance of ceftazidime present on the RBC membrane is thought to stimulate IgG antibody production, which in turn binds to the cell membrane, ultimately resulting in intravascular hemolysis. The patient's presentation was typical of that of "hemolytic syndrome", including fever, a decrease in hemoglobin, and the presence of IgG antibody 2+. More attention should be paid to the identification of DIIHA drugs, as a failure to do so can result in the continued administration of the offending agent and a worsening of the patient's hemolytic anemia. When hemoglobin is extremely low and life-threatening, blood transfusions should be administered to save lives, while all related antibodies should be detected and monitored to distinguish drug antibodies and auto-antibodies. It is appropriate for adults to receive no more than 2 U washed RBCs per transfusion, with a slow infusion and constant observation.

DIIHA is underestimated and under-reported because most cases are not likely to lead to dramatic hemolysis or require intervention. Patients suffering from pulmonary infection are at an increased risk of DIIHA; therefore, it is critical to recognize susceptible patients, terminate treatment if hemolysis occurs, choose suitable blood products, and advise them against any further ceftazidime exposure and make a clear note on the patient's records.

Acknowledgments

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