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Case Report

Autoimmune Hemolytic Anemia Induced by Anti-D Injection

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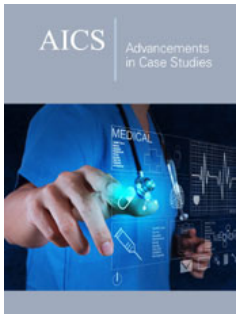
ISSN: 2639-0531



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Submission: January 03, 2023

Published: January 09, 2023

Volume 3 - Issue 4

How to cite this article: Mariana Boulos, Elias Saad, Nimer Assy. Autoimmune Hemolytic Anemia Induced by Anti-D Injection. Adv Case Stud. 3(4). AICS.000570. 2023.
DOI: 10.31031/AICS.2023.03.000570

Abstract

Anti-D immunoglobulin can cause acute hemolysis when used in the treatment of Rh(D) positive patients with immune thrombocytopenic purpura (ITP). The use of Anti-D immunoglobulin to prevent Rh(D) alloimmunization during pregnancy is quite safe. Although drug induced immune hemolytic anemia have been described during pregnancy, hemolytic anemia was not described as adverse event of Anti-D immunoglobulin administered as a prophylaxis for Rh(D) negative pregnant women. Herein we present an unusual case of warm type autoimmune hemolytic anemia induced by Anti-D immunoglobulin in O Rho(D) negative pregnant women.

Keywords: AIHA (Autoimmune hemolytic anemia); Anti-D; Pregnancy

Case Report

A 32 years old women, in her third pregnancy at 16 weeks period of gestation, presented to the hospital with a history of fatigue, malaise, dyspnea, nausea and syncope. Her first and second pregnancy were uneventful although she was at risk of alloimmune hemolytic disease of the fetus and newborn because her blood type was O Rho(D) negative and this risk was minimized by passive immunization using Rho(D) immunoglobulin. There was no history of cough, skin rash, fever, hematuria, chest pain or neurologic symptoms. 3 days prior to the development of her symptoms the patient was given a passive immunization by an intra-muscular injection of 150μg of Rho(D) immunoglobulin (Kam RhoD I.M., KAMADA, IL).

In the emergency department, the patient appeared very pale, blood pressure and respiratory rate were normal. No tachycardia reported. Her physical examination revealed no pathologies. The Hemoglobin level was 4.4 with increased serum levels of indirect bilirubin (total, 9.9mg/dL; direct 4.5mg/dL), and lactate dehydrogenase (LDH) (635mg/dL), while platelet count was normal (417 x 109/L). These results were consistent with acute hemolytic anemia, so we issued a direct antiglobulin test (DAT) which was positive to warm antibody IgG (2+), C3d (4+) and C3c (3+). on her ER stay hemoglobin dropped to 3.8g/dL so she was rushed to the intensive care unit, where she received 5 blood units a treated with systemic glucocorticoids (Prednisone) 80mg once a day. After hemoglobin increased to 8g/dl she was admitted to our internal medicine department to workup and treat her situation.

On our department, she was in a good condition, in her examination she looked very pale, her vital signs were stable. On her physical examination spleen was palpable with no other findings. She was treated with Prednisone 80mg once a day. A Workup for secondary causes of Autoimmune hemolytic anemia was established. Autoimmune factors (anti CPP, RF, ANA, ANCA P , ANCA C) were all negative, viral causes were excluded (EBV,CMV , Influenza A+B). Hepatic serology was positive for HBc and negative HBs indicating past infection with HBV,

other hepatic viruses were all negative. The patient denied any autoimmune or inflammatory diseases in her family, she reported no previous chronic diarrhea, weight loss or decreased appetite, arthritis or extra-intestinal manifestation of inflammatory bowel disease, she also denied receiving new drugs, antibiotics or herbal substances. During her hospital stay, she reported vaginal bleeding, gynecological ultrasound performed revealed a fetus with no pulse, so she was transmitted to gynecology department, there she went through curettage and transmitted back to our yard. Since lymphoproliferative disorders may trigger autoimmune hemolytic anemia, Chest and abdominal Computed Tomography (CT) scan was performed, revealing no lymphadenopathy or tumors suspected.

In summary, we report a previously healthy 15th weeks pregnant woman which was admitted to our department with Warm type Autoimmune hemolytic anemia following an Anti-D injection, serological evaluation to connective tissue disorders, ANA were negative, with no criteria meeting Systemic lupus erythematosus and lymphoproliferative evaluation including a chest and abdominal CT scan were normal.

Discussion

Autoimmune hemolytic anemia (AIHA) is an immune disease leading to red blood cell destruction by autoantibodies directed against autologous RBC antigens [1]. Those antibodies may be classified into 3 types: a warm type which causes agglutination at 37 °C (80-90) % , a cold agglutin that reacts optimally on 0-5 °C and a mixed type that displays both features [2]. Warm type AIHA is suspected in patients with specific morphologic findings on peripheral smear defined as micro spherocytes. This disease may occur in primary and secondary settings, which requires inquiry of potential underlying etiologies essential. The ultimate diagnosis must be confirmed by a positive Direct Antiglobulin Test (DAT) identifying an anti-RBC autoantibody. Most cases of warm AIHA is associated with positive DAT for Immunoglobulin G (IgG) and/or the complement component C3 [2,3].

Although drugs are a rare cause of inducing hemolytic anemia, it should be taken into account inquiring the presence of drug antibody when evidence of hemolytic event is found. Both immune and non-immune events describe the pathogenesis of the disorder [4]. Drug induced immune hemolytic anemia (DIIHA) is roughly estimated around 1 in 1 million of the population [5], the mechanism and type of drugs leading to the disorder was up to some changes in the last 50 years [6], the number of drugs have increased through the years, it is estimated by reviewing updated literature that the number is up to 130 types of drugs causing DIIHA [7]. The most common drug responsible for causing DIIHA were cephalosporin , cefotetan in particular accounting for 54% of the cases reported in the last 30 years [5].

Although anemia in pregnancy is considered somehow a part of normal pregnancy, it is estimated that 40% of pregnant women have anemia [8] it have serious consequences for the fetus and the mother. Iron deficiency anemia and physiologic anemia are the most common type of anemias in pregnancy. The WHO defines severe anemia in all persons as a Hb of <7g/dL and very severe anemia as a Hb of <4g/dL [9]. It is estimated that the prevalence of severe anemia in pregnant women is 0.9% [10]. Hemolysis occurs also in pregnancy conditions, HELLP syndrome occurs in approximately 1 out of 500 pregnancies, acute fatty liver of pregnancy in 1 of 1000 pregnancies and Thrombotic thrombocytopenic purpura/ Hemolytic-uremic syndrome in 1out of 100000 pregnancies. On the other hand, the incidence of this rare disorder have not been widely reported, it is estimated to be low at 0.8 – 3 cases per 100000 person/years with overall prelevance of 17 cases per 100000 individuals.

Rh immune globulin (RhIG) contains high-titered immunoglobulin (Ig)G D antibodies and is used to prevent maternal alloimmunization to the D blood group antigen. The use of Anti-D immunoglobulin has dramatically reduced the incidence of Rh (D) alloimmunization from 16% to less than 0.1% [11]. Anti-D immunoglobulinis is also used for the treatment of immune thrombocytopenic purpura (ITP) [12]. Anti-D immunoglobulin induced hemolytic anemia is the main adverse reaction reported when the immunoglobulin is used as the treatment ITP and these cases of hemolysis developed exclusively in patients who are Rh(D) positive and the hemolysis is extravascular and the mean decrease in hemoglobin is 1 to 2.0g/dL [13]. The mechanism of action of anti-D in ITP depends mainly on extravascular hemolysis of anti-D–sensitized red blood cells by splenic macrophages, which does not occur in individuals who are Rh(D) negative so they will not develop hemolytic anemia. Anti-D immunoglobulin can also induce intravascular hemolysis [14] and even case of disseminated intravascular coagulation (DIC) have been reported. The incidence of severe hemolytic reactions is 1 in 1115 patients, and most of the reactions (94% of cases) occurred within 4 hours. The mechanism of this reaction is not well understood, but some can be explained by a contamination of the anti-d regimen by alloantibodies which cause sensitization of a critical mass of circulating RBCs, resulting in complement activation and acute intravascular hemolysis [15].

This patient's adverse reaction of warm type hemolytic anemia can be attributed to the anti-D immunoglobulin for many reasons. First is the temporal relationship between use of the drug and the development of the illness, second is the absence of risk factors for developing hemolytic anemia, and third no underlying etiology was evident. The reaction is not explained by lysis of anti-D–sensitized red blood cells because the patient is Rh(D) negative, and it is not explained by a contamination of the anti-D regimen by blood group alloantibodies because the reaction occurred 3 days after the anti-D injection, the patients hemolysis was extravascular, and an autoantibody was detected by DAT.

Conclusion

Anti-D induced warm type auto-immune hemolytic anemia is rare in individuals whose blood group is Rh(D) negative with no cases published. Health care providers should be aware of the serious and life-threatening hemolytic anemia, not only in Rh(D)

positive ITP patients, but also in Rh(D) negative pregnant women who are treated with anti-D immunoglobulin to prevent Hemolytic disease of the newborn.

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