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(CASE REPORT)

Warm autoimmune hemolytic anemia with anti-e specificity: A case report

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Abstract

Warm autoimmune hemolytic anemia is a rare condition characterized by warm autoantibody destruction of red blood cells. Antibody specificity cannot be determined in most cases and an apparent autoantibody specificity to a specific antigen is rarely seen. Here we present a case of a 43-year-old female patient presenting with acute small bowel obstruction and requiring an exploratory laparotomy. However, laboratory investigations showed evidence of intravascular hemolysis with normocytic normochromic anemia, reticulocytosis, elevated bilirubin and lactate dehydrogenase levels, and low haptoglobin level. Two units of packed red blood cells were requested. Blood bank investigations including antibody screening, antibody identification panel, direct coombs testing with polyspecific and monospecific anti-human globulin, extended rhesus phenotype, and confirmatory elution testing revealed an IgG autoantibody with anti-e specificity. No compatible units with Rh (e) - positive units were found. However, Rh (e) - negative units' transfusion was associated with a risk of alloimmunization and a decision of two least incompatible units was taken. So, an anti-e IgG autoantibody was identified which is a rare and challenging clinical condition in terms of diagnosis and transfusion.

Keywords: Hemolytic Anemia; Autoimmune; Anti-e; Autoantibody

1. Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disorder characterized by autoantibody-mediated red blood cells (RBCs) destruction, with an incidence rate estimated to be approximately 1-3 per 100,000 per year and a mortality rate of 11% [1]. Depending on the temperature at which the autoantibody reacts, AIHA can be classified into warm, cold, and mixed types [2]. AIHA is further sub-classified as primary or secondary to an underlying disease [3]. In warm autoimmune hemolytic anemia (w-AIHA), the responsible autoantibodies bind RBCs' surface optimally at 37°C. Typically, autoantibodies are polyclonal, reacting with all tested RBCs where no autoantibody specificity can be identified [4]. A clear-cut specificity is rare to be seen in w-AIHA, with only a few reports describing autoantibodies against "e" antigen [5-7]. Moreover, transfusion, in this case, is a challenge since ''e'' antigen is prevalent among the Lebanese population [8-10].

2. Case presentation

A 43-year-old female gravida 3 para 3, presented to the emergency department (ER) for severe abdominal pain radiating to the back associated with abdominal distention, constipation, nausea and multiple episodes of non-bloody non-bilious vomiting. The patient had a history of small bowel obstruction one year before that resolved spontaneously with non-operative management. There was no history of prior blood transfusion or drug intake. On examination, she was icteric

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and pale and tachycardic. Abdominal examination showed a distended abdomen with diffuse tenderness. The other examinations were within normal limits. An MRI done before admission showed evidence of moderate small bowel obstruction with edema of the mesentery in the right lower quadrant. However, an abdominal computed tomography scan done in the ER showed evidence of small bowel obstruction.

Her initial laboratory workup showed anemia with a hemoglobin level of 8.2g/dl, hematocrit of 24.9%, leukopenia with a white count level of $1.7*10^3/mm^3$ and normal platelets count ($283*10^3/mm^3$). The peripheral blood smear showed normocytic normochromic RBCs, numerous polychromatophils, and spherocytosis. The reticulocyte count was elevated (16%) with an absolute reticulocyte count of $0.45*10^6/mm^3$. Lactate dehydrogenase level was high (488 IU/L). Serum bilirubin was elevated (direct: 1.78 g/dl, indirect: 2.37 g/dl). Liver enzymes and renal profile were normal. Other findings showed elevated CRP level being 7.73 mg/L, low haptoglobin level (<0.762 g/l), and elevated D-dimer level (2.99 µg/ml). The coagulation profile tests were normal. Based on the above findings, a diagnosis of adhesive small bowel obstruction with sepsis and hemolytic anemia was made. The patient was planned for an exploratory laparotomy.

Requests for packed red blood cells (PRBC) preparation were received in the blood bank. Forward and reverse blood groups were O-positive. Antibody screenings using the 3-cell panel (ID-Dia cell I-II-III) showed positivity with I and III cells but was negative with II cells (R2R2). Antibody identification using 11-cell panel (ID-DiaPanel, Bio-Rad) was done. The panel showed positivity with all cells except R2R2 cell phenotype (the only cell negative for the "e" antigen) (figure 1). Auto-control (patient own RBCs and plasma) showed reactivity to polyspecific anti-human globulin (AHG). DAT was performed using column agglutination technology (CAT) (Biorad). DAT was 4+ positive. An extensive direct coombs test was done using monospecific AHG reagents using CAT (Biorad) and showed positivity for IgG (figure 2). In order to confirm the anti-e specificity of the antibody, an elution test using chloroform technique was done and the eluate showed reactivity with the "e" antigen cell phenotype, while no reactivity was seen with cells negative for the "e" antigen (figure 3). The extended Rhesus (Rh) phenotype using CAT (Bio-Rad) indicated that the patient was C+/c- and E-/e+. Moreover, there was an absence of any history of prior blood transfusion or drug intake with the ongoing hemolysis. In addition, serology testing (HIV, EBV, CMV and Hepatitis C) and antinuclear antibody (ANA) were negative. Serum protein electrophoresis was normal. Hence, a diagnosis of w-AIHA with anti "e" specificity was established. Cross matches done with all blood bags were incompatible. Only 4 units were found to be least incompatible.

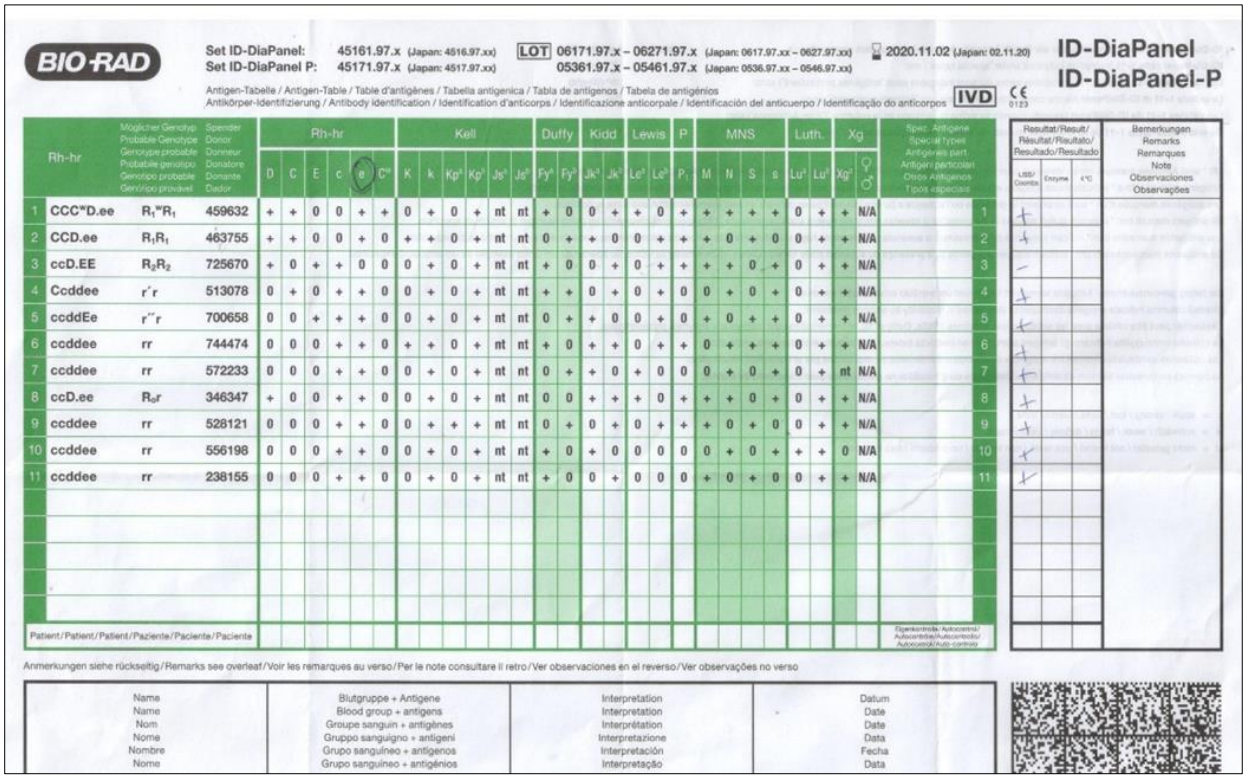

Figure 1 Antibody identification using 11 cell panel (ID-DiaPanel, Bio-Rad), Panel shows positivity with all cells except R2R2 cell phenotype

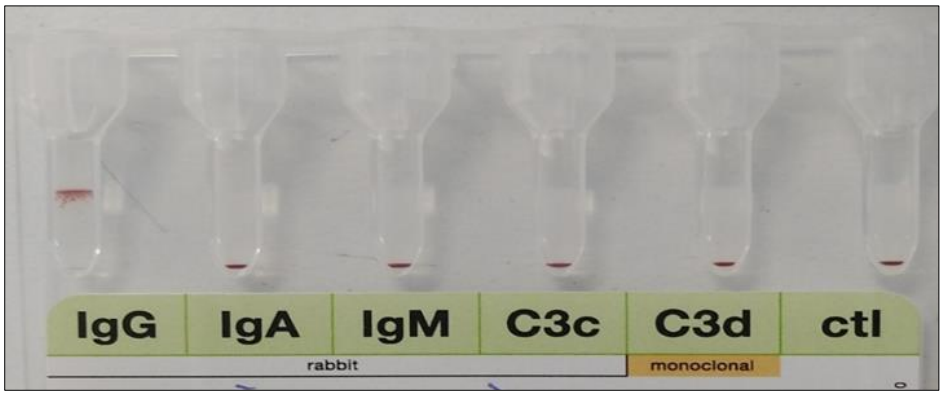

Figure 2 Extensive direct coombs test showing positivity to IgG monospecific AHG

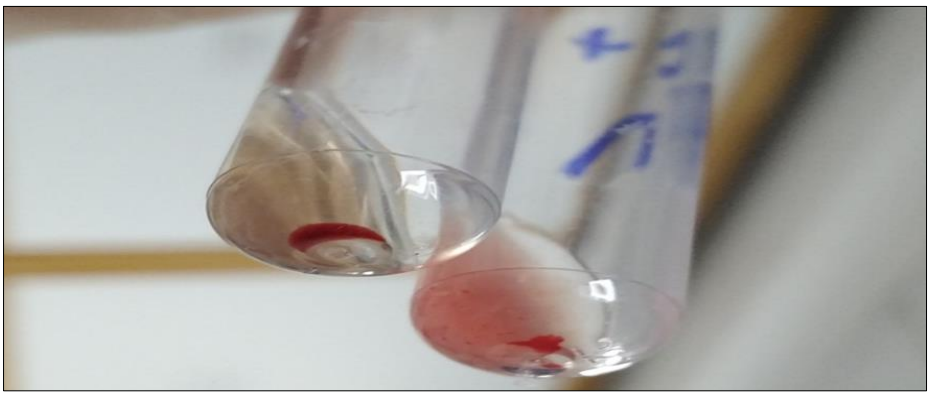

Figure 3 Eluate reacting with "e" antigen positive cells and non-reacting with "e" negative cells

Surgery was postponed and non-operational management including IV Hydration (Crystalloid fluids), NPO diet, and bowel decompression where a nasogastric tube was inserted, and IV antibiotics were administered. The patient's condition did not improve since she had bilious vomiting after 3 days of admission with intermittent episodes of abdominal pain and nausea relieved by analgesics and anti-emetics.

After 3 days of admission, the patient started on a 4-day course of dexamethasone (40 mg/day). Parenteral nutrition (Oliclinomel N4-550) was started on day 5. A CT scan done on day 7 showed increased small bowel dilation and increased abdominal ascites. Due to the deterioration of the patient's clinical condition, an exploratory laparotomy was planned, and 2 least incompatible O-positive units were prepared. During and following surgery, the patient's hemoglobin remained stable and did not require PRBC transfusion.

3. Discussion

Destruction of RBCs before their normal life span is defined as hemolytic anemia [11]. There are numerous etiologies for hemolysis including hemoglobinopathies, inherited protein deficits, enzymopathies, immune-mediated hemolytic anemia, and extrinsic nonimmune causes (microangiopathic hemolytic anemia (MAHA), infections, direct trauma, and drug-induced hemolysis). Notably, in Immune hemolytic anemias, antibodies directed against antigens on the RBC's surface are the main cause of the disease. There are three types of immune hemolytic anemia: autoimmune, alloimmune, or drug-induced [12].

One of the most important RBC antigens is the Rh blood group system, which is expressed only in RBC's membrane as a part of a protein complex. Rh complex consists of approximately 45 antigens involved in maintaining the erythrocyte membrane integrity. In fact, the most significant and screened Rh antigens are D, C, E, c, and e. These antigens form a complex that consists of 2 RhCcEe protein (carries either C or c antigens together with E or e antigens) or RhD (expresses the D antigen) protein molecules and two molecules of Rh-associated glycoprotein (RhAG) [8,9].

Lebanese erythrocyte phenotype was demonstrated to be similar to the Caucasian population in a study conducted by Baz *et al* [10]. The most frequent Rh haplotype in the Caucasian population is *DCe* [8, 9]. Therefore, the “e” antigen is highly prevalent among the Lebanese population.

On the other hand, antibodies against Rh antigens can be due to either alloimmunization (antibody against D, C, c, E, and e) or autoantibodies found in w-AIHA [8,13]. Regarding autoantibody, and based on the optimal temperature to which it binds on the patient’s RBCs in vivo, AIHA is classified into three categories: warm antibody AIHA (w-AIHA), cold agglutinin syndrome (CAS), and paroxysmal cold hemoglobinuria (PCH). “Mixed AIHA" is an unusual case where laboratory data show mixed serologic criteria for both categories: w-AIHA and CAS [4]. More importantly, w-AIHA is the most common type, accounting for approximately 70% to 80% of all adult cases and approximately 50% of pediatric cases [3]. W-AIHA may occur at any age with a median age of 52 years with a slight female predominance in most cases [14]. Moreover, w-AIHA is subclassified into primary and secondary. Primary w-AIHA occurs in the absence of an underlying disease; however, secondary w-AIHA occurs as a complication of an underlying disease [4]. Autoantibodies in w-AIHA are IgG antibodies directed against self RBC antigens that result in phagocytosis of RBCs and extravascular hemolysis by hepatic Kupffer cells or splenic macrophages [15]. Patients with w-AIHA present with symptoms related to the anemia itself. The onset of symptoms can be insidious over months or sudden with symptoms of acute hemolysis with severe anemia and jaundice over a few days [3].

Laboratory workup should initially include a complete blood count, a reticulocyte count, lactate dehydrogenase (LDH), indirect bilirubin and haptoglobin levels, and a direct antiglobulin test (DAT) [14]. Diagnosis depends mainly on direct antiglobulin test (DAT) results, which show reactivity with anti-IgG [1]. It is important to differentiate between w-AIHA and cold agglutinin disease, which is caused by an IgM and shows reactivity for anti-C3d and negative reaction with anti-IgG [14]. Laboratory evidence of hemolysis (anemia, reticulocytosis, high LDH, increased indirect bilirubin, and low haptoglobin levels) and positive anti-IgG DAT make the diagnosis of w-AIHA [1,14].

In fact, antibody specificity in w-AIHA cannot be determined in most cases where all tested red cell samples show positivity with autoantibody [16]. An absolute or relative specificity for blood group antigens can be occasionally seen, and the Rh blood group accounts for most of these cases [7]. In saline or LISS indirect antiglobulin tests, antibody specificity is infrequently seen apparent for simple Rh antigens (D, C, E, c, e) [17] as it was shown in our case. However, Willer *et al* reported autoantibodies on RBCs directed against "D", "e", "E", and "C" in 10 out of 30 patients having autoantibodies and out of a total of 100 patients presenting with warm autoantibodies [7]. Interestingly, only a few cases of w-AIHA with an antibody specifically directed against “e" antigens were reported [5-7].

Treatment of w-AIHA is based on hemolysis severity and whether the bone marrow is compensating for RBC destruction. If bone marrow is compensating, monitoring of the patient with no treatment is considered. However, if anemia develops, medical treatment should be initiated [18]. Treatment options include corticosteroid, immunosuppressive drugs, and most recently, rituximab [1].

Furthermore, in w-AIHA, when no apparent specificity to a blood group antigen is seen, autoantibodies have specificity to common RBCs antigen and are pan-reactive that will result in incompatible cross-match to all units tested [2]. RBCs transfusion in w-AIHA patients is not a contraindication [18]. Transfused RBCs will have a decreased survival and the benefit provided to the patient will be temporary where the destruction of these RBCs will be at the same rate as patient RBCs [8,16]. Therefore, transfusion should be limited to patients with severe anemia or at high risk for cerebrovascular or cardiac events [18]. Consequently, transfusion in w-AIHA depends on the clinical situation, where risks and benefits need to be assessed [17]. Alloantibody should be excluded before transfusing RBCs using auto-adsorption methods when no specificity and pan-reactive panel is present. Transfusion of the least incompatible unit should be considered if transfusion is needed [18].

On the other hand, if autoantibody specificity is apparent, units lacking that specific antigen should be transfused. However, alloimmunization risk when transfusing patients with antigen-negative units is increased. Namely, patients with antigen profile $E^{-}e^{+}$ transfused with "e" negative units will be exposed to “E” antigen and will further be at increased risk for alloimmunization. Units selected for transfusion should not have an antigen not present in the patient due to alloimmunization risk [5]. As previously mentioned, ‘’e’’ antigens are highly prevalent among the Lebanese population [8-10], and finding ‘’e’’ negative units is a challenge. Yet, in our case no compatible unit was found, so based on a recent study that demonstrated safety and effectiveness of transfusion of least incompatible RBC’s [19], two least incompatible units were prepared for the patient before surgery.

4. Conclusion

W-AIHA is a rare condition characterized by the presence of typically pan-agglutinin autoantibody, and an apparent specificity to simple Rh antigens is occasionally seen. RBC's transfusion in such patients is challenging and should only be considered in severe and life-threatening conditions. Consequently, alloantibody exclusion, determining antibody specificity when available, and avoidance of alloimmunization should be considered. When no compatible units are available, transfusing the least compatible units is safe.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have declared that no competing interests exist.

Statement of ethical approval

Ethical approval from the IRB committee at Makassed General Hospital was obtained.

Statement of informed consent

Informed Consent was obtained from the patient.

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