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A Rare Case of IgA-mediated Autoimmune Hemolytic Anemia in a Young Adult

Majid Alameri[1*] and Abdullah Alnuaimi[1]

[1]Department of Internal Medicine, Medicine Institute, Sheikh Khalifa Medical City (SKMC), UAE.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

A 21-year-old previously healthy male presented with unexplained intravascular hemolysis. Patient had anemia, elevated serum indirect bilirubin, elevated LDH, reticulocytosis, decreased haptoglobin and spherocytosis. Initial Laboratory investigations revealed a negative direct antiglobulin test (DAT), suggesting a Coombs-negative hemolytic anemia. Additional testing with monospecific anti-IgA was strongly positive. Autoimmune hemolytic anemia due to warm-reacting IgA autoantibodies is very rare and presents with "Coombs negative" autoimmune hemolytic anemia. A diagnosis of idiopathic IgA-only-associated warm AIHA was made after extensive investigations. Treatment included transfusion of multiple ABO/RH-D compatible typed red cell concentrates and administration of high-dose steroids. This case report will highlight the initial clinical presentation, panel of investigations for diagnosis; course of treatment and follow up with a brief literature review of the pathophysiologic mechanism and suggested treatment modalities for this rare IgA-induced warm AIHA.

Keywords: Intravascular hemolysis; autoimmune hemolytic anemia; IgA autoantibodies.

**Corresponding author: E-mail: majameri@seha.ae;*

1. CASE REPORT

A 21-year-old male previously healthy was admitted to the hospital because of progressive sensation of fatigue, left upper quadrant abdominal discomfort and unexplained acute onset hemolytic anemia. Prior to current presentation he has been always in excellent health. Prior to the admission by 2 weeks he noticed a change in the color of his urine to dark brown and yellowish eyes. Family history, surgical history, drugs history, social and occupational history were all negative. Systemic review was unremarkable apart from presenting symptoms.

On physical examination he appeared pale and icteric. The blood pressure was 133/61 mmHg, regular pulse of 103/min, temperature 37 Celsius. Lymph nodes were not palpable. Chest and cardiovascular examination were normal. Abdominal examination showed non tender splenomegaly only, the liver was not enlarged. No skin rash or edema noted.

The blood count revealed anemia with a hemoglobin (Hb) concentration of 7.9 g/dL, a high mean corpuscular volume (120 fL), mean corpuscular hemoglobin (MCH) of 34 picograms (pg)/cell (N:27-34), Corpuscular Hemoglobin Concentration (MCHC) of 333 g/dl (N:320-370), normal platelet count of 180 $x10^9$/L (N:140-400), corrected reticulocyte count noted to be high 15.6 percent (N:0.5-1.5 percent). Lactate dehydrogenase was significantly elevated (1566 IU/L), while haptoglobin was undetectable in the serum. White blood cell count (WBC) came back within normal range with normal differential counts. The blood group was O, Rhesus positive. Peripheral blood film examination did not show any schistocytes, but spherocytes, Howell-Jolly bodies and polychromasia were observed (Fig. 1). Osmotic Fragility test was negative for spherocytosis. Laboratory tests performed to rule out metabolic disorders and nutritional deficiencies; in particular serum levels of iron, ferritin, copper, folic acid, vitamin B12, methylmalonic acid and homocysteine were all within the normal ranges. Glucose-6-phosphate dehydrogenase (G6PD) came back within normal levels. The direct polyspecific antiglobulin test (DAT) gel test was negative. The thermal amplitude testing and cold agglutinin was not performed as DAT was negative for C3, IgM and IgG. DAT using monospecific anti-human IgA reagent (DiaMed/BioRAD, Switzerland) was used and came back strongly positive for IgA (+3). Serologic tests for HIV and hepatitis panel was negative. The antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) and Anti-neutrophil cytoplasmic antibodies (ANCAs) were negative. Tests for coeliac disease including anti-gliadin (AGA) and anti-endomysium (EMA) antibodies were negative .Urine toxicology and metabolic screen was negative. Flow cytometric analysis did not show any evidence of a Paroxysmal nocturnal hemoglobinuria (PNH) clone based upon analysis of a variety of GPI-linked antibodies on red blood cells, monocytes and granulocytes.

Bone marrow sampling and analysis showed a normal erythroid hyperplasia secondary to peripheral hemolysis, no blast cells seen. Computed Tomography (CT) of chest, abdomen and pelvis was done and did not show any enlarged lymph nodes and showed only splenomegaly, measured with 15.6 x 10.6 cm in cross sectional direction at the level of the hilum without any other pathology (Fig. 2). Screening Oesophago-gastro duodenoscopy (OGD) and colonoscopy were done and did not reveal any pathology.

Based on the clinical presentation, history, examination and extensive investigations a diagnosis of idiopathic IgA-mediated autoimmune hemolytic anemia (IgA AIHA) was made.

During admission the patient received 2 units of packed RBCs (ABO type O) and was initiated with prednisone treatment at a daily dose of 1 mg/kg. Hb concentration increased to 10.2 g/dL within a week. However, the patient had another episode of hemolysis during admission despite treatment with prednisone and was treated with another blood transfusion of 2 units of packed RBCs. The dose of prednisone initially was 1 mg/kg/d, was gradually tapered thereafter.

During the follow up and after 3 months since discharge patient had viral flu which triggered hemolysis and was treated with prednisone and blood transfusions.

Our patient responded well to high-dose steroids, but due to repeated exacerbations this treatment could not be tapered completely. Rituximab and splenectomy were discussed and offered but declined by the patient as he preferred to stay in steroids for now. The direct antiglobulin test continued to be positive for IgA at 6 months of follow up.

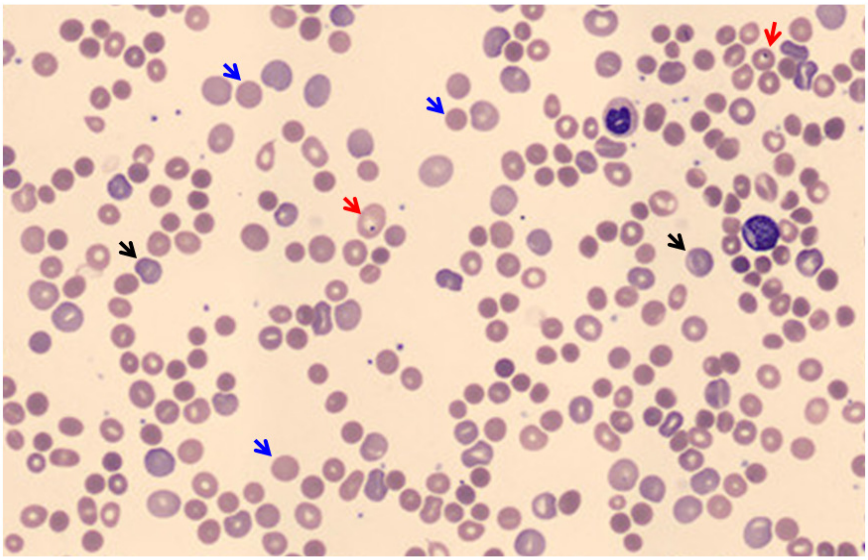

Fig. 1. Peripheral blood smear

Peripheral blood smear showing several characteristic findings of hemolytic anemia: Spherocytes (blue arrows), Polychromasia (black arrows), and Howell-Jolly bodies (red arrows)

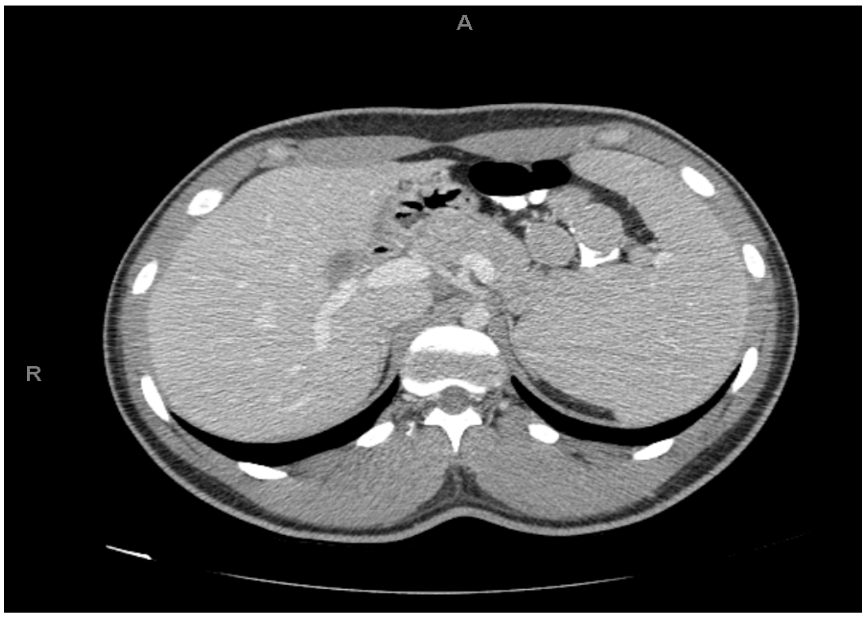

Fig. 2. CT of the abdomen

CT of the abdomen showing splenomegaly, measured with 15.6 x 10.6 cm in cross sectional direction at the level of the hilum

2. LITERATURE REVIEW

Autoimmune hemolytic anemia (AIHA) due to IgA autoantibodies is rare. AIHA has a spectrum of clinical presentations depending on the rate of hemolysis and the underlying co-morbidities. This spectrum can range from gradual minor hemolysis and mild anemia, or may be with life-threatening anemia. IgA class antibodies are present in about 14 percent of patients with warm-type autoimmune hemolytic anemia (WAIHA) [1]. The reported cases of AIHA due to IgA alone as a sole cause are very rare, representing 0.1 percent to 0.2 percent of AIHA

cases [2]. A negative DAT test has been always reported in almost all cases of IgA autoimmune hemolytic initially regardless of the severity of the hemolytic anemia [3]. When such DAT is negative and autoimmune hemolytic anemia is suspected, a second DAT using monospecific anti-human IgA antibodies must be performed [3]. Furthermore, IgM warm AIHA often have more severe hemolysis and more fatalities (up to 22 percent) than patients with other types of AIHA [4]. The degree of anemia also depends on the efficacy of the erythroblastic response [5]. In a case series of 52 patients with AIHA, reticulocytopenia reported to occur in some 25 percent of adults diagnosed with AIHA which mandate a very strong transfusion support and represent a clinical emergency [6]. Presence of reticulocytopenia during the hemolytic episode of AIHA carries significantly higher mortality rate (up to 70 percent) [7].

Warm AIHA has been noted to be associated with number of lymphoproliferative disorders, infections, autoimmune diseases and rarely as a paraneoplastic phenomenon in solid tumors [8,9,10]. Therefore, patient with initial presentation of AIHA should undergo extensive investigations to search for other possible causes of hemolytic anemia, as well as possible underlying disease [11]. A recent study suggested a novel Western immunoblotting as a new tool for investigating direct antiglobulin test–negative autoimmune hemolytic anemia [12].

Corticosteroids are the mainstay of therapy for warm AIHA. Majority of patients with warm AIHA successfully treated with corticosteroid therapy alone (response rate up to 70 percent). Patients with refractory warm AIHA should be offered a second line treatment with rituximab (response rate up to 60 percent) and splenectomy. Patients with warm AIHA refractory to second line treatments should be considered for immunosuppressive drugs such as azathioprine, cyclosporine and mycophenolate mofetil [13]. Our patient had a rapid and sustained response to oral steroid therapy. His clinical course improved with infrequent need for packed red blood cell transfusions, with an increase in hemoglobin concentration as well as decreased serum lactate dehydrogenase levels.

3. CONCLUSION

This case highlights the importance of the IgA monospecific DAT test in cases of negative routine DAT in patients presenting with hemolytic anemia. A negative direct antiglobulin test does not completely rule out the diagnosis of autoimmune hemolytic anemia especially in the rare case of IgA mediated immune hemolysis. Additional testing may be necessary in patients with an unusual presentation of hemolytic anemia and negative DAT to identify the presence of IgA autoantibodies, which may lead to clinically significant hemolytic anemia that require specific treatment modalities that can save patients' lives.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

This case study has been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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