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CASE REPORT

# Finding the elusive and causative autoantibody: An atypical case of autoimmune hemolytic anemia

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### Key Clinical Message

An isolated IgA-mediated autoimmune hemolytic anemia can present a diagnostic challenge. When a routine direct antiglobulin test (DAT) is negative but clinical suspicion remains high, further testing with monospecific antisera should be performed. As with IgG-mediated WAIHA, steroids are first-line treatment, though splenectomy is often required to achieve a durable treatment response.

### Keywords

Anemia, autoimmune hemolytic anemia, blood bank, erythrocyte, hemolytic anemia.

## Introduction

A 77-year-old Caucasian female was transferred from a referring hospital to the inpatient medical floor for evaluation of refractory hemolytic anemia. The patient initially reported several days of fatigue, jaundice, and darkening of her urine, approximately 1 month prior to her current presentation. At the referring hospital, she was found to have hemolytic anemia, thrombocytopenia, and acute kidney injury. She was first thought to have thrombotic thrombocytopenic purpura and plasmapheresis was implemented. It subsequently was discontinued when the ADAMSTS13 level came back as normal. On review of her peripheral blood smear, spherocytes were noted and a diagnosis of autoimmune hemolytic anemia was made, despite a negative Coombs test. The patient was started on corticosteroids and weekly rituximab. She was discharged after a several week admission on a steroid taper and with a plan for her to complete four weekly doses of rituximab.

Within a few days after discharge, however, her fatigue and jaundice recurred. She was noted to have blood in her urine by a visiting nurse. She was again admitted to the referring hospital where she was found to have worsening of her anemia and thrombocytopenia. She received three doses of IVIG, with subsequent improvement of her hemoglobin and platelet levels. Her labs revealed ongoing hemolysis, however, and a splenectomy was recommended. She then requested transfer to our institution for a second opinion.

The patient's initial presentation with fatigue, jaundice and dark urine is concerning for anemia secondary to a hemolytic process. A microangiopathic process, including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation, should be considered. Autoimmune hemolytic anemia (AIHA) can be idiopathic or secondary to many disease processes, including infection, rheumatologic conditions, drug exposure, and lymphoproliferative disorders. Paroxysmal nocturnal hemoglobinuria presents with hemolytic

anemia, although it is also associated with thrombosis and pancytopenia. Other causes of Coomb's negative hemolytic anemia include hereditary spherocytosis, RBC enzymopathy, and Wilson's disease.

## Case History

The patient complained of significant fatigue and dyspnea on exertion. She also reported night sweats throughout the month prior to her presentation. The patient had a 15 lb. weight loss over the course of a few months and was prescribed an appetite stimulant. She denied any recent history of infection. The patient had no joint complaints. Her past medical history was significant for colorectal cancer, which was diagnosed 9 years ago and treated with surgical resection, chemotherapy, and radiation. She also had a history of idiopathic thrombocytopenic purpura (ITP) approximately two decades prior to her current presentation. She was treated with steroids which resulted in normalization of her platelet count. Since her diagnosis of ITP, she had been followed by a hematologist regularly. The patient's home medications included amlodipine, levothyroxine, vitamin D3, albuterol, mirtazapine, atenolol-chlorthalidone, raloxifene, lisonopril, furosemide, and potassium supplementation. Her family history was notable for pancreatic cancer in her mother. She lived with her husband and was retired.

On examination, she appeared pale and fatigued, but she was in no acute distress. Her temperature was 36.9°C, pulse 69, respiratory rate 22, blood pressure 135/64 mm Hg, and oxygen saturation 94% on 4 L nasal cannula. The patient had scleral icterus and trace peripheral edema. She had no splenomegaly, lymphadenopathy, petechiae, or purpura on examination.

## Differential Diagnosis

Given the patient's age, history of carcinoma, and prior episode of ITP, a secondary AIHA due to an underlying malignancy or rheumatologic condition, is possible. Secondary causes of AIHA are determined in 20–80% of cases, depending on the patient population being studied [1]. Lymphoproliferative disorders, including chronic lymphocytic leukemia (CLL), Hodgkin's disease, non-Hodgkin's lymphoma, and Waldenström's macroglobulinemia, are the most common causes of secondary cases of warm antibody autoimmune hemolytic anemia (WAIHA) [1]. The patient's history of malignancy and recent weight loss raises suspicion for recurrence. In the setting of solid tumors, both a warm or cold antibody autoimmune hemolytic anemia (CAIHA) are possible, though warm antibodies are more common [2]. Review of patient's medication list revealed no clear source for a drug-induced immune hemolytic anemia (DIIHA). Medications most commonly associated with DIIHA include ceftriaxone, piperacillin, and cefotetan [3].

## Laboratory and Imaging Evaluation

The patient's white blood cell count was 16,100 per cubic millimeter, with 96.7% neutrophils, 0.3% lymphocytes, 1.0% monocytes, 0% eosinophils, 0.3% basophils, and 1.7% immature granulocytes. The hemoglobin level was 7.5 g per deciliter, with a mean corpuscular volume of 100.9 fL. At the referring hospital her hemoglobin was 6.4 g per deciliter for 2 days prior to transfer despite transfusion of 6 units of packed red blood cells. The platelet count was 145,000 per cubic millimeter. The prothrombin time and partial thromboplastin time were both normal. The serum sodium, potassium, and bicarbonate were all within normal limits. The serum creatinine was 0.8 mg per deciliter and the blood urea nitrogen was 36 mg per deciliter. The patient's liver enzymes were normal. The bilirubin was 1.9 mg per deciliter. LDH was 940 (normal range 120–240) and haptoglobin was <10 mg per deciliter.

The peripheral blood smear revealed >5 spherocytes per high-power field. Schistocytes were not identified. White blood cell number and morphology were normal. Flow cytometry was sent to evaluate for paroxysmal nocturnal hemoglobinuria (PNH) and cold agglutinin titers were obtained.

The decreased haptoglobin, elevated LDH, and reticulocytosis, are all consistent with hemolytic anemia. A microangiopathic process is unlikely given the lack of schistocytes. The spherocytes seen on peripheral blood smear could be consistent with hemolytic anemia or secondary to recent transfusion at the referring hospital. In order to further investigate potential secondary causes of AIHA, including lymphoma, solid tumors, and clonal immunoglobulins, a computed tomographic (CT) scan and bone marrow evaluation should be obtained.

A CT scan of the chest, abdomen, and pelvis was obtained and revealed fluid within the endometrial canal. There were no enlarged abdominal, retroperitoneal, or pelvic lymph nodes. In the chest, there were small to moderate layering right and small left pleural effusions. Flow cytometry revealed no evidence of a PNH clone. ADAMTS13 activity returned at 47%. Cold agglutinins were <1:10. Bone marrow biopsy from the referring hospital was reviewed and exhibited a normocellular marrow with erythroid hyperplasia and stress dyserythropoiesis. There was no evidence of neoplasia. Direct antiglobulin test (DAT) returned negative for IgG and C3.

The patient was continued on prednisone 50 mg daily and transfused two units of packed red blood cells. Rituximab was held while further evaluation was completed.

She initially responded appropriately to the transfusion with her hemoglobin increasing from 7.0 to 10.4 g per deciliter. Within 3 days, her hemoglobin had decreased to 8.8 g per deciliter.

Given the finding of fluid within the endometrial canal on CT scan, a gynecologist was consulted and a transvaginal ultrasound was obtained. Ultrasound revealed multiple endometrial masses and moderate pelvic ascites.

Despite a negative DAT, there was still strong suspicion for an AIHA. Further testing is required in such cases in order to determine the pathogenic autoantibody and to confirm the diagnosis. The DAT is a screening test and only detects the presence of IgG and/or complement (C3) on the surface of erythrocytes [4]. If the initial screen is positive with a negative albumin control, then testing with monospecific antisera (anti-IgG, anti-C3d) is performed [5]. Approximately 1–10% of patients diagnosed with AIHA have been reported to have a negative DAT [6]. Few of the DAT negative cases of AIHA are due to IgA autoantibodies, which are not detected with typically available antisera. At this time, there are no FDA-approved anti-IgA (or anti-IgM) reagents for use in patient transfusion testing. These cases must be sent to a handful of outside immunohematology reference laboratories, using unlicensed reagents.

Direct antiglobulin test polyspecific interpretation was positive 1+ and a warm autoantibody was detected. Testing at the LA American Red Cross laboratory performed with an anti-IgA reagent revealed strong reactivity (3+) and confirmed the presence of an IgA autoantibody.

## Treatment and Follow-up

The patient's hemoglobin decreased to 6.7 g per deciliter 4 days after transfusion with 2 units packed red blood cells. She received a fourth dose of Rituximab and was transfused once again with 2 units of PRBCs. Her hemoglobin increased appropriately to 9.2 g per deciliter.

The patient developed gross hematuria with a foley catheter in place. The Foley catheter was initially placed at the referring hospital due to episodes of acute urinary retention. Urology was consulted and upon irrigation, there were several blood clots removed. She ultimately underwent cystoscopy and hysteroscopy which revealed radiation changes of the urothelium and benign endometrial polyps.

One week after her second transfusion, the patient's hemoglobin decreased to 7.7 g per deciliter. Her ongoing anemia was thought to mainly be secondary to the hematuria and not due to ongoing hemolysis. LDH decreased to 342, down from 940 at admission. She was continued on prednisone 40 mg daily with a plan for a 3-month long taper. If she relapsed while on steroid therapy, it was discussed with the patient that she would be referred for splenectomy. The patient completed the steroid taper under the supervision of her local hematologist, without evidence of relapse as per our last communication.

Initial treatment of WAIHA is with glucocorticoids. Typically, 15–20% of patients will have complete remission and be able to discontinue steroids, however, most patients will require maintenance dosing [1]. Steroid refractoriness is often seen in patients with underlying malignant tumors, benign ovarian teratomas, or with warm IgM antibodies [1]. In case reports of IgA-AIHA, patients have been responsive to steroids at least initially, but there are several reports of splenectomy ultimately being required [7, 8]. After splenectomy, steroid therapy was able to be discontinued in each case [7, 8]. In patients who have contraindications to splenectomy or decline surgery, rituximab is another second-line treatment option [9]. In a retrospective study of 11 patients with primary WAIHA treated with rituximab, eight patients had a complete response and three patients had a partial response [10].

## Discussion

The majority of AIHA cases are caused by warm antibodies, with IgG being the most commonly involved. IgA antibodies in the context of WAIHA are rare, occurring alone or with complement in <2% of patients, thus routine screening with serum containing anti-IgG and anti-C3d is diagnostic in most cases of WAIHA [7]. An analysis including 5,177 patients with AIHA included only 5 cases (<0.1%) due to autoantibodies which were exclusively of the IgA isotype [11]. Case reports of IgA-mediated WAIHA include an infant, a woman with superficial thrombophlebitis, a patient with Hodgkin lymphoma, and a patient with a history of renal transplant [4, 7, 9, 12].

The pathogenesis of IgA-mediated hemolysis was revealed through the identification of specific Fc receptors for IgA on lymphocytes, granulocytes, and monocytes [13]. IgA autoantibodies cause hemolysis by adherence of antibody-coated erythrocytes to Fc receptors of phagocytic cells [13]. There has also been suggestion of the activation of complement by IgA autoantibodies leading to a C3 coating of erythrocytes with subsequent-enhanced trapping by macrophages [4]. Thus, both complement-independent and complement-mediated processes are thought to be involved in the pathogenesis of IgA-mediated AIHA.

An isolated IgA-mediated AIHA is a rare clinical entity. When a routine DAT is negative but clinical suspicion remains high for AIHA, further testing with monospecific antisera should be performed. As with IgG-mediated WAIHA, steroids are first-line treatment, though splenectomy is often required to achieve a durable treatment response.

 

## Conflict of Interest

None declared.

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