Autoimmune Hemolytic Anemia Without Overt Signs of Hemolysis

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Abstract

Autoimmune hemolytic anemia (AIHA) is a common cause of acquired hemolysis where the immune system targets antigens found on the body's red blood cells. This eventually leads to the activation of the complement system, manifesting the clinical signs of anemia. A methodical approach is required to assess anemia including laboratory studies and, in some cases, imaging. However, the studies vary in clinical sensitivity and specificity, especially in AIHA. Patient is a 35-year-old morbidly obese female with a past medical history significant for Roux-en-Y gastric bypass, hepatic steatosis, alcohol use disorder, and Guillain-Barré syndrome who presented to the Emergency Department for altered mental status, dyspnea, and a productive cough. She was found to have normocytic anemia with a hemoglobin level of 3.5 g/dL. Previous immunological panels were negative at an outpatient appointment less than two months prior to the admission. During her admission, the standard anemia evaluation did not suggest hemolysis or reveal the underlying cause of the anemia, which proved to be refractory to transfusions. Repeat immunological testing provided evidence of autoimmune hemolytic anemia, which was further supported by the patient's response to empiric steroid therapy. Determining the etiology underlying anemia presents a challenge requiring a systematic approach. AIHA presents with evidence of hemolysis and a positive direct antiglobulin test (DAT); however, it is often a diagnosis of exclusion necessitating a complete workup. It is important to recognize that DAT is not completely sensitive or specific. Additionally, AIHA may be DAT-negative or acquired after previously negative immunologic evaluations. These are important considerations in refractory anemia in which all other causes of anemia have been thoroughly evaluated.

Introduction

Autoimmune hemolytic anemia (AIHA) is a common cause of acquired hemolysis in which a patient's immune system targets antigens found on the body's red blood cells destroying the cell. This immune response eventually leads to the activation of the complement system, manifesting the clinical signs of anemia including pallor, fatigue, tachycardia, and tachypnea (1). Those patients with evidence of anemia should undergo a stepwise evaluation to assess hemolysis with both clinical evaluation and laboratory studies. Laboratory studies including complete blood count (CBC), haptoglobin, lactate dehydrogenase (LDH), and peripheral smear yield evidence of hemolysis; however, some of the studies vary in clinical sensitivity or specificity, especially in AIHA. The case detailed below presents a 35-year-old female who presented with signs of anemia but no significant indicators of hemolysis.

Case Presentation

Patient is a 35-year-old morbidly obese female with a past medical history significant for Roux-en-Y gastric bypass, hepatic steatosis, alcohol use disorder, and Guillain-Barré syndrome. Of note, she was diagnosed with iron deficiency anemia after her bariatric surgery in 2018 and was started on folate and iron supplementation with a new hemoglobin baseline around 11 g/dL. Her hemoglobin remained stable until two months before her admission. During that time, she underwent an anemia evaluation including iron studies, blood smears, and an immunologic assessment with DAT, antinuclear antibody (ANA) test, and C-reactive protein, all of which were consistent with her baseline or negative.

The patient presented to the Emergency Department for altered mental status, dyspnea, and a productive cough. Upon initial evaluation, she was found to have normocytic anemia with a hemoglobin level of 3.5 g/dL. She received 6 units of packed red blood cells (PRBC) over the next 12 hours, improving her hemoglobin to 5.4 g/dL. Another unit of PRBC and platelets was transfused, increasing her hemoglobin to 7.0 g/dL, at which time she was hemodynamically stable. Concurrently, the patient was diagnosed with septic shock secondary to *E. coli* urinary tract infection and pneumonia, requiring initiation of vasopressor support with norepinephrine, IV ceftriaxone, and Intensive Care Unit (ICU) admission. Her septic status improved, but she developed anasarca and her anemia remained refractory even after an additional 3 units of transfused PRBCs. She was subsequently transferred to the Progressive Care Unit (PCU) for continued close monitoring.

While in the PCU, she continued to have frequent drops in her hemoglobin prompting evaluation (Figure 1). Her iron studies remained suggestive of anemia of chronic disease with a total iron-binding capacity of 79 ug/dL and transferrin saturation of 15%, but she also had mild reticulocytosis (122.6 K/uL). Additionally, her urinalysis contained urobilinogen, but no bilirubin. Throughout her admission, she was jaundiced with an elevated total (7.5–11.9 mg/dL) and direct (4.4–7.2 mg/dL) bilirubin; however, she had a known history of hepatic steatosis and was found to have transaminitis with an elevated gamma-glutamyl transferase (118 U/L) on admission. Her haptoglobin and lactate dehydrogenase remained within normal limits. She received an upper endoscopy, excluding gastric ulcerations. She was given another 2 units of PRBC, improving her hemoglobin, but its level did not remain stable. Subsequent CT and tagged red blood cell scans did not show any evidence of extravascular bleeding. Previous outpatient antibody testing demonstrated that she was direct and indirect Coombs negative; however, on repeat testing during the admission, she tested positive for direct Coombs with immunoglobulin and C3. A peripheral blood

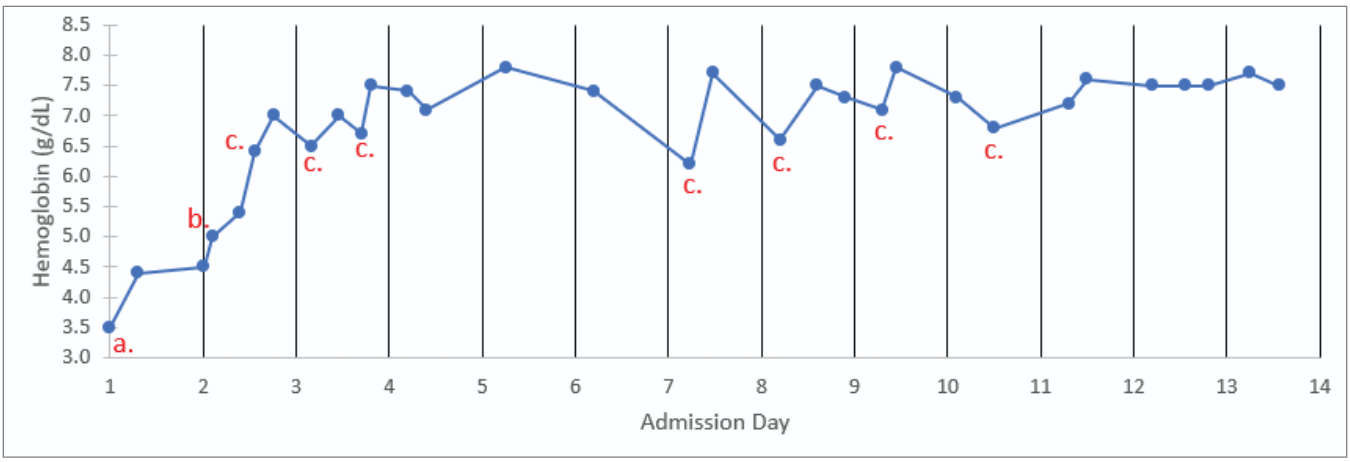

Figure 1. Trend of patient's hemoglobin (g/dL) during the 11-day admission. Red letters indicate points at which packed red blood cell (PRBC) units were transfused. a.= 4 units PRBC transfused; b.= 2 units PRBC transfused; c.= 1 unit PRBC transfused.

Admission Day	1	2	3	4	5	6	7	8	9	10	11	12	13
Ferritin (ng/mL)	1,610 1,480	-	-	-	-	-	-	3,112	-	-	4,406	-	-
Total Bilirubin (mg/dL)	8.4	9.1 10.3 11.0	11.5 11.9	11.9	11.3	9.8	8.2	8.3	8.7	-	-	-	7.5
Direct Bilirubin (mg/dL)	4.5	4.4 5.0 5.7	6.6	7.2	6.6	5.6	4.9	4.9	-	-	-	-	3.6
Reticulocyte Count (K/uL)	122.6	-	-	148	-	-	-	-	-	-	-	-	-
Haptoglobin (mg/dL)	46	-	-	-	-	-	-	89	-	-	-	-	-
LDH (U/L)	223	-	209	-	-	-	-	215	-	-	-	-	-

Table 1. Laboratory values throughout the patient's 14-day admission. Repeat labs within a 24-hour period are listed in chronological order.

smear demonstrated macrocytic (MCV 107.3 fL) red cells with typical granular platelets, no white cell atypia, and no evidence of dysplasia or malignancy.

Due to the presence of antibodies and anemia refractory to transfusions (13 total units) with no overt signs of hemolysis, hematology was consulted for additional recommendations. Transfusions were held until the patient became symptomatic, and a prednisone taper was started. She remained anemic, but her hemoglobin did not decrease to the threshold necessitating transfusion or to the level of becoming symptomatic. Since discharge from the hospital, the patient remains anemic (average hemoglobin 8 g/dL) and follows closely with hematology outpatient for continued treatment of suspected warm autoimmune hemolytic anemia.

Discussion

Autoimmune hemolytic anemia is a rare condition with a heterogeneous clinical presentation leading to diagnostic challenges. The symptomatology is similar to other cases of anemia with pallor, fatigue, tachycardia, dyspnea, and potentially jaundice. In these patients, the laboratory assessments are essential to discerning the type and cause of the anemia. These tests are especially important in cases where the patient remains refractory to transfusions with continued decreases in hemoglobin, as a source of the bleeding needs to be controlled.

Tests such as a CBC, reticulocyte count, blood smear, and LDH yield certain results expected in AIHA, a hemolytic anemia. This patient is unique in that she did not demonstrate the typical laboratory findings expected in patients with AIHA (Table 1). For instance, she had direct hyperbilirubinemia with normal haptoglobin and LDH levels. For learning purposes, an elevated *indirect* hyperbilirubinemia, decreased haptoglobin levels, and increased LDH levels are typical (1, 2). LDH is found intracellularly, therefore, when RBCs rupture, we expect LDH to be released into the bloodstream. Haptoglobin typically binds free hemoglobin after rupture of RBCs. There were no spherocytes or red blood cell fragments present on the patient's peripheral blood smear, another common finding of AIHA. Being that the patient did not have these findings, it is difficult to say that she was in a true state of hemolytic anemia (3, 4). Further complicating the diagnosis was her previously diagnosed hepatic steatosis, which can lead to elevated LDH and reduced haptoglobin (1).

Admittedly, a repeat antibody test was not conducted at the time of admission given her outpatient assessment, which was negative for any abnormality. Imaging and endoscopic evaluations were the next steps to identify the source of bleeding. These were also negative, which necessitated repeat antibody testing. The direct Coombs test or direct antiglobulin test (DAT) is the most sensitive and specific test in diagnosing AIHA, especially when distinguishing warm, cold, and mixed

forms (3–5). Although considered the gold standard laboratory test, DAT is not completely sensitive or specific so alternative causes of anemia should be investigated (3). DAT detects the presence of IgG or C3d complement, but monoclonal antibodies specific for IgM, IgA, and complement C3c can be utilized to broaden the results (2). In 5–10% of cases, AIHA is DAT-negative, further complicating diagnosis and delaying treatment. After other causes are ruled out, diagnosis is established based on response to empiric treatment with steroids, which is an effective treatment for any classification of acquired AIHA (3).

Conclusion

The multitude of potential etiologies underlying anemia present a diagnostic challenge for any clinical team, requiring a methodical approach including physical exam, laboratory assessments, and imaging. Typically, autoimmune hemolytic anemia presents with evidence of hemolysis and a positive DAT; however, it is often a diagnosis of exclusion necessitating a complete hematological workup. In some cases, as in this patient, signs of hemolysis beyond a low hemoglobin may not be evident, completing the clinical presentation. Although DAT is the gold standard test for AIHA, it is important to recognize that the test is not completely sensitive or specific. Additionally, AIHA may be DAT-negative in a small cohort of patients and patients may acquire AIHA despite previously negative immunologic evaluations. These considerations are especially essential in cases refractory to transfusions in which all other causes of anemia have been thoroughly evaluated.

Disclosures

The authors declare there is no conflict of interest regarding this article's publication.

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