Autoimmune hemolytic anemia in a preoperative patient: a case report and literature review

Pande Tiara Maharani1*, I Gusti Ayu Wiradari Tedja2, Dewi Catur Wulandari3

ABSTRACT

Background: In patients undergoing elective surgery, it is known that as many as one-third have preoperative anemia. Preoperative anemia is associated with an almost five-fold increase in the likelihood of postoperative mortality. So, it is essential to know the cause of anemia so that the management is appropriate so that surgery can be performed safely and prevent patients from dying on the operating table or postoperatively. This case report aims to describe the pathogenesis of the laboratory findings in a patient with autoimmune hemolytic anemia (AIHA) who was accidentally diagnosed during preoperative screening and the management performed.

Case: A 65-year-old man with an enlarged prostate was scheduled for elective surgery. Preoperative examination revealed anemic right and left conjunctiva, decreased erythrocytes, hemoglobin, hematocrit, and increased MCV, MCH, and MCHC, peripheral blood smear dominated by red cell agglutination and positive direct Coomb’s test. The patient was given methylprednisolone 62.5 mg intravenously before transfusion and given a transfusion of 2 units of slow drip packed red cells (PRC) under close supervision. There were no transfusion reactions during and after transfusion. There was an increase in Hb after transfusion so that the patient could be operated on.

Conclusion: The patient in this case was diagnosed with AIHA based on preoperative laboratory findings. Laboratory results showed evidence of autoimmune hemolytic anemia with decreased erythrocytes, hemoglobin, hematocrit, spherocytes, and agglutination on peripheral blood smear and positive Coomb’s test. Rapid identification and treatment of anemia help improve preoperative conditions.

Keywords: AIHA, anemia, Coomb’s test, hemolytic, preoperative


INTRODUCTION

Anemia is a state of decreased concentration of circulating hemoglobin in the blood that results in a reduced amount of oxygen delivered to the tissues.1 In patients undergoing elective surgery, it is known that as many as one-third have preoperative anemia. Although the anemia found before surgery is mild, it still increases the risk of red blood cell (RBC) transfusion.2 Anemia in preoperative patients increases in prevalence in the elderly.3 This anemia is found with different causes and is almost asymptomatic beforehand. A retrospective study of 8000 noncardiac surgery patients found that the prevalence of preoperative anemia was nearly 40%. Preoperative anemia is associated with an almost five-fold increase in the likelihood of postoperative mortality.4 Even in noncardiac surgery patients, mild preoperative anemia (Hb 10-12 g/dL in women; 10-13 g/dL in men) is associated with a 41% increase in mortality and a 31% increase in morbidity.5 So, it is essential to know the cause of anemia so that the management carried out is appropriate, surgery can be performed safely, and patients can be prevented from dying on the operating table or postoperatively. Several examinations are needed to be carried out to find out the cause of anemia.6

Anemia can be classified based on the size of red blood cell morphology, microcytic, normocytic, and macrocytic, through basic red blood cell examination parameters such as mean corpuscular volume (MCV). Each of these erythrocyte sizes can lead to the most likely differential diagnosis.7 Autoimmune hemolytic anemia (AIHA) during complete blood count (CBC) examination usually finds either normocytic or macrocytic erythrocyte morphology. The autoantibody-mediated destruction of red blood cells causes this anemia. The hallmark of AIHA is a positive direct Coomb’s test result. AIHA can be classified based on the triggering temperature, warm and cold, and
autoimmune hemolytic anemia. Warm autoimmune hemolytic anemia (WAH) accounts for 50-70% of all AIHA patients, with red blood cell destruction occurring at temperatures above 37°C. In contrast, cold autoimmune hemolytic anemia (CAHIA) is caused by IgM autoantibodies that bind to erythrocytes at temperatures below 37°C so that red blood cells are agglutinated and complement, and hemolysis occurs. We present a case of a patient with AIHA accidentally diagnosed during preoperative screening and describe the pathogenesis of the patient’s laboratory findings and management. This case report is expected to provide an understanding of preoperative conditions such as hemolytic anemia and its management.

CASE DESCRIPTION

A 65-year-old man came to the hospital polyclinic complaining of stagnant urine for the last few months. The patient admitted that he had been lacking energy for the past few days. Fever, dizziness, or other complaints were denied, and a history of previous transfusions was also denied. The patient has a history of diabetes mellitus since the last 15 years of routine control and using insulin drugs. It is known that the patient also has a history of allergy to amoxicillin. The physical examination found blood pressure 108/64 mmHg, pulse 73 times/min, respiratory rate 20 times/min, temperature 36.5°C, SpO₂ 99%, and right and left conjunctiva anemia. To support the patient’s complaints, a urological ultrasonography examination was performed, and the results showed an impression of an enlarged prostate with calcification and a Prostate-specific antigen (PSA) examination with a value of 4.72 (reference value <4). The patient was planned for elective surgery and had a preoperative examination.

The results of the hematology examination can be seen in Table 1. From the peripheral blood smear examination, a suspicious impression of hemolytic anemia was obtained, with differential diagnosis of AIHA cold agglutinin and warm AIHA, and it was recommended to do LDH, indirect bilirubin, and Direct Coombs test. The patient underwent a direct Coombs test, which resulted in a positive (4+); the indirect Coombs test was negative. The patient was also known to have blood type O with positive rhesus. Crossmatch results for several donors’ blood were incompatible with 4+ agglutination. The patient was diagnosed with autoimmune hemolytic anemia, benign prostatic hyperplasia, and type II diabetes mellitus.

The therapy given to the patient was fast-acting analog insulin 6 IU every 8 hours (subcutaneously), long-acting analog insulin 12 IU every 24 hours (subcutaneously), and a slow drip washed red cell (WRC) transfusion with premedication of methylprednisolone 62.5 mg and furosemide 20 mg intravenously. Clinical and laboratory examination improved after the treatment, and the surgery was done without any transfusion reaction.

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Hematologic examination of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Before transfusion (17-09-2023)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>8.15 x 10³/ul</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>0.25 x 10⁶/ul</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.7 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>2.9 %</td>
</tr>
<tr>
<td>MCV</td>
<td>116.0 fl</td>
</tr>
<tr>
<td>MCH</td>
<td>348.0 pg</td>
</tr>
<tr>
<td>Platelets</td>
<td>198 x10³/ul</td>
</tr>
<tr>
<td>NEUT%</td>
<td>80.4 %</td>
</tr>
<tr>
<td>LYMP%</td>
<td>9.9 %</td>
</tr>
<tr>
<td>MONO%</td>
<td>5.3 %</td>
</tr>
<tr>
<td>EOS%</td>
<td>4.2 %</td>
</tr>
<tr>
<td>BASO%</td>
<td>0.2 %</td>
</tr>
</tbody>
</table>

Figure 1. Image of peripheral blood smear stained using write solution at 100 times magnification. Agglutination of red blood cells (black arrow), and spherocytes (blue arrow).
DISCUSSION

Anemia is a decrease in hemoglobin (Hb), hematocrit (HCT), or red blood cells in the blood circulation. One of the causes of anemia is autoimmune hemolytic anemia (AIHA). Two criteria must be met to diagnose patients with AIHA: serologic evidence of autoantibody and clinical findings or laboratory evidence indicating hemolysis. Serological findings can be proven by a positive direct Coomb’s test or direct antiglobulin test (DAT). Laboratory findings that prove the presence of hemolysis include normocytic/macrocytic anemia, elevated reticulocytes, increased unconjugated bilirubin, decreased haptoglobin, and peripheral blood smears with more specific features such as spherocytes or agglutination. The hematological examination in the patient’s case above showed a decrease in erythrocytes, hemoglobin, and hematocrit, which is evidence of anemia, an increase in MCV (macrocyes), MCH, and MCHC, which can lead to differential diagnoses, one of which is AIHA. The peripheral blood smear showed spherocytes of red blood cells and directed Coomb’s test 4+ (positive), so the patient could fulfill the diagnosis of AIHA.

Autoimmune hemolytic anemia is the occurrence of red blood cell destruction faster than usual (120 days) due to the presence of autoantibodies (IgG and/or IgM) and/or complement attached to the surface of red blood cells thus activating faster red blood cell destruction by the complement system and reticuloendothelial system. Autoimmune hemolytic anemia is a rare disease whose incidence is 0.8 to 3/100,000 people per year occurring more at the age of over 40 years but also in early childhood. As per this patient, she was 65 years old when diagnosed with AIHA.

Symptoms in AIHA may vary depending on age and comorbidities. In primary AIHA, symptoms of anemia, such as fatigue, predominate. There are no diagnostic findings on physical examination of patients with AIHA. In general, the findings of anemia seen are pallor, jaundice, palpable spleen, and hepatic enlargement. The patient’s symptoms in the case showed general symptoms of anemia, namely easy fatigue, and on physical examination, the right and left conjunctiva were found to be anemic.

Hemolysis begins when autoantibodies bind to the red blood cell membrane and recruit complement, the pathogenesis of which is differentiated based on the adhering autoantibodies. Immunoglobulin G autoantibodies are monomers that have weak avidity to activate the complement system and do not cause spontaneous agglutination, then will destroy red blood cells through antibody-dependent cellular cytotoxicity (ADCC), driven by the macrophage monocyte system that phagocytizes blood cells through the Fc fragment of IgG (or complement fraction C3b). This underlies the extravascular hemolysis that mainly occurs in the spleen in the case of macrophage-mediated ADCC and destruction in the liver in the case of C3b-mediated ADCC. Immunoglobulin M is a 1-million-Da molecule that can span the distance between red blood cells and overcome the natural repulsive forces between red blood cells, thus allowing spontaneous in vitro agglutination. In the body’s core, circulating IgM is not bound to the surface of red blood cells, but when the blood moves to the peripheral circulation and cools, IgM transiently binds to the red blood cell membrane. In addition, IgM autoantibodies are pentamers with high avidity to activate the complement cascade from the beginning (C5) to the end (C9) so that MAC is formed on red blood cells, which results in the lysis of the blood cells, causing intravascular hemolysis.

Agglutination in red blood cells will cause analysis errors on hematologic equipment. Hematocrit (%) is usually three times the hemoglobin value (g/dL). The patient in the case had a discrepancy between the hemoglobin value and hematocrit. The hemoglobin value in the patient was 8.7 g/dL, and the hematocrit value obtained was 2.9%. This was caused by the inability of the hematology analyzer to measure the number of red blood cells and related indices. Hematology equipment will analyze CBC and cell count based on cell diameter. Still, in the agglutination state, red blood cells stick to each other, so the equipment will misinterpret the resulting aggregates as single erythrocytes (macrocytic). This results in an error of low red blood cell count and red blood cell size that appears to be enlarged. The device cannot evaluate massive aggregates. As hematocrit and erythrocyte indices are also calculated using red blood cell counts, there will also be errors in assessing very low hematocrit. Unlike erythrocytes and hematocrit, hemoglobin is measured directly through lysis of erythrocytes in another channel. To avoid analysis failure, move or warm the sample to 37°C before analysis. The above explanation also supports the CBC results in the case. In addition to the inconsistency of Hb values with hematocrit, shallow erythrocyte values, and high MCV and MCHC were also obtained.

Autoimmune hemolytic anemia should be suspected in patients with macrocytic anemia, and changes in hematologic markers such as increased serum lactate dehydrogenase (LDH) and unconjugated bilirubin, decreased haptoglobin, increased absolute reticulocytes, and in peripheral blood smears found reticulocytosis and spherocytosis. The Gold standard for diagnosing AIHA is the Coombs or direct antiglobulin test (DAT). With monospecific antisera (anti-IgG, anti-IgA, anti-IgM, anti-complement (anti-C)) that can differentiate disease classification.

Hemolytic anemia is generally classified based on red blood cell autoantibodies’ immunological and chemical nature. These consist of WAIHA, C/AIHA and MAIHA. Warm AIHA accounts for 50-70% of all AIHA patients, caused by warm autoantibodies that are mostly IgG1 or IgG3 subclasses or associated with complement fractions. Anemia is macrocytic due to marked reticulocytosis. Blood smear examination often shows anisocytosis, polychromasia, and obvious spherosis. A positive DAT (anti-IgG or anti-IgG + anti-C3) indicates the presence of RBC autoantibodies and/or complement proteins that bind to circulating red blood cells in vivo. C/AIHA is caused by antibodies that react optimally at 4°C, including cases of cold agglutinin disease (CAD) and paroxysmal cold hemoglobinuria (PCH). CAIHA is relatively rare when compared to WAIHA. The diagnosis of CAD is determined by the patient’s blood autoagglutination, which
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CASE REPORT

worsens at 4°C and normalizes at 37°C. Patients with CAD show positive DAT with anti-C3 or anti-C3d but negative with anti-IgG reagents. If confirmed by cold agglutinin titer examination, a titer of >1:40 is obtained. Mixed autoimmune hemolytic anemia represents about 6%-8% of all AIHA in adults.22,23

Direct Coombs’s test or DAT can differentiate immune or non-immune hemolysis. The test can be used initially with a polyclonal anti-human globulin (AHG) reagent (Coomb’s serum) containing anti-IgG and anti-C3d. It may also contain antibodies to other C3 determinants (C3dg, C3b, C3c) and other immunoglobulins (IgA, IgM). If positive with polyclonal reagents, the sample can be retested with monospecific anti-IgG and anti-C3d/C3dg reagents to characterize the reactivity further. The principle of this test is that red blood cells coated with IgG and/or complement will agglutinate when these reagents are added. Usually, the negative charge found on red blood cells keeps blood cells suspended in a saline solution separately. Still, the presence of antibodies that coat red blood cells makes red blood cells cross-link with adjacent red blood cells, resulting in clumping of red blood cells.20 Indirect Coombs’s test is used to detect the presence of incomplete immunoglobulin (IgG) and or complement in the patient’s serum.34 The patient obtained a positive Direct Coomb’s test result (4+), but the Indirect Coomb’s test was negative. This means some antibodies coat the patient’s red blood cells, but there is no free irregular alloantibody in the patient’s serum. Coombs test was performed using polyclonal AHG reagent, and it is impossible to retest using monospecific AHG and cold agglutinin titer examination. Therefore, the patient could not be classified as a type of AIHA.

First-line treatment for WAIHA patients is agreed to be corticosteroids, although their use is based on experience and substantial evidence. Little published information on their effectiveness, and clinical trials do not support this. The mechanism of action of steroids is probably down-regulation of Fc receptors on phagocytes and reduced IL-2 production. The most crucial early effect of steroids is to suppress the uptake of red blood cells opsonized by macrophages in the spleen. Another proposed early impact is reducing the binding affinity of autoantibodies for the patient’s red blood cells. The corticosteroid administered is usually prednisone given at an initial dose of 1.0-1.5 mg/kg/day for 1-3 weeks until a hemoglobin level of more than 10 g/dL is achieved.35,36 CAIHA often does not require treatment at Hb >10 g/dL.15 The disease is usually self-limited, what can be done is avoidance of cold temperatures and the use of pre-warmed IV fluids and warm blankets to minimize exacerbation of hemolysis during hospitalization. Transfusion can be done according to the patient’s needs, and pre-warming techniques can reduce autoantibody reactivity.37,38 The choice of infusion site in the extremities should be warmer, and the use of blood products with high plasma should be avoided.35 The blood that can be given is packed red cells (PRC) or washed red cells (WRC).39 Transfusion should be given at a slow rate.40

Before transfusing a patient, one of the procedures performed is a crossmatch test. This test looks for unexpected antibodies in the recipient’s plasma against red blood cells in the erythrocyte concentrate. A positive result is referred to as incompatible. An incompatible crossmatch means the recipient has antibodies against the red blood cells in the erythrocyte concentrate. What needs to be determined if there is an incompatible result is whether it is an autoantibody (against the patient’s red cell antigens) or an alloantibody (against non-self red cell antigens, i.e., foreign red cell antigens from pregnancy or transfusion), or both. If there is no previous history of transfusion or pregnancy and there is a positive DAT result, the diagnosis is AIHA. If the patient needs a transfusion, there is no need to waste time on crossmatch examination because autoantibodies will react to every red blood cell from every erythrocyte concentrate. Therefore, the risk of transfusion should be conveyed to the patient, and transfusion should be done under close monitoring.41

CONCLUSION
The case patient was diagnosed with AIHA based on preoperative laboratory findings. Laboratory results showed evidence of anemia with decreased erythrocytes, hemoglobin, and hematocrit. Hemolytic was evidenced by spherocytes and agglutination in the peripheral blood smear, and autoimmune evidence was indicated by a positive Coombs’s test. The type of AIHA could not be determined as Coombs’s test performed on the patient was not specific for any anti-human globulins, and cold agglutinin titer was impossible. As the patient required surgery, the decision was made to correct the anemia by transfusion. Methylprednisolone 62.5mg was given before transfusion, followed by 2 units of slow drip PRC under close supervision. There were no transfusion reactions during and after transfusion. There was an increase in Hb after transfusion so that the patient could be operated on.

CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
The author PTM conceptualized, searched for literature, collected data, was the principal author, and edited the manuscript. Authors IGAWT and DCW reviewed and proofread the manuscript.

REFERENCES
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