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Case Report

J Med Cases. 2018;9(9):284-286

A Five-Month-Old Infant With Severe Autoimmune Hemolytic Anemia Treated Without Blood Transfusions

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Abstract

Autoimmune hemolytic anemia (AIHA) is a rare hematologic disease in children with an incidence of 0.2/100,000 under 20 years of age. This article reports the case of an infant with AIHA in which blood transfusions were not necessary, and performs a brief literature review of this rare disease in children. A 5-month-old infant was with a 9-day fever, progressive and intense pallor, severe hepatosplenomegaly, anicteric, and a history of blood incompatibility in cross-tests. Complementary exams showed hemoglobin 3.3 g/dL with reticulocytosis and erythroblastosis, leukocytosis with left upper shift, elevated lactic dehydrogenase, Coombs direct reactive with predominance of IgG. The child evolved with important improvement after pulse methylprednisolone therapy and treatment with folic acid and ceftriaxone, without performing any blood transfusion. The clinical features of AIHA include anemic and hemolytic signs. Mainly, diagnosis is done by laboratory tests showing anemia, hemolysis and positive direct antibody test. In children, it tends to an acute course and to an excellent response to corticosteroids, but erythrocytes transfusions are often used in critical hemoglobin levels.

Keywords: Autoimmune; Hematology; Pediatrics; Anemia, Hemolytic; Transfusion; Blood

Introduction

Autoimmune hemolytic anemia (AIHA) is an immune-hematological disorder with premature hemolysis caused by autoantibodies action against erythrocyte surface antigens. In children, it predominates in males, and it is a rare disease with an estimated annual incidence of 0.2 new cases/100,000 inhabitants under 20 years of age. Also, it has a tendency for an intense and transient anemia [1].

Manuscript submitted February 6, 2018, accepted February 26, 2018

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doi: https://doi.org/10.14740/jmc3019w

AIHAs are classified per the antibodies activity temperature. Warm AIHA (wAIHA) is named after the predominance of antibodies which have maximum activity at 37 °C. Usually, they are IgG that opsonize the red blood cells causing phagocytosis by splenic macrophages recognition of the IgG. In cold AIHA (cAIHA), the maximum activity of the antibodies occurs below human body normal temperature, most at 0 - 5 °C; so, they are called cold agglutinins, and in adults, most of them are IgM, as in children, IgG is more common. When recognizing erythrocyte antigens, cold agglutinins strongly activate the complement, mainly the C3b fraction, with higher hepatic hemolysis and intravascular hemolysis by membrane attack complex formation. The mixed forms are characterized by IgG and IgM antibodies that act between 4 and 37 °C [2]. Paroxysmal cold hemoglobinuria (PCH) is a rare form of cAIHA, more common in children, in which anti-P IgG (Donath-Landsteiner antibody) binds to red cells surface at cold temperatures along with complement fractions, and, when in warmer body parts, the complement cascade is activated causing hemolysis [3].

The aim of this article was to report the case of a child diagnosed with severe wAIHA and treated without any blood transfusions, reviewing the literature on this subject.

This case report was authorized by the legal guardian of the patient and it was approved by the institution's research ethics committee.

Case Report

A previously healthy 5-month-old male infant was admitted by the Pediatric Intensive Care Unit with a history of 9-day fever of 38 °C, adynamia, poor feeding, abdominal swelling, severe and progressive mucocutaneous pallor, and blood incompatibility in cross-tests. There was negative history for urinary, respiratory or gastrointestinal symptoms, trauma, or contact with drugs and toxins. Personal history revealed vaginal premature labor at 36 weeks of gestational age, exclusive breastfeeding only until 2 months old. Family history was negative for immunological or hematological illnesses. At physical examination, it presented a critical general condition, hypoactive, pallor (4+/4), tachycardia, painful hepatosplenomegaly with palpable liver 4 cm from the right costal border and spleen 4 cm from the left costal border, anicteric and afebrile. The first diagnostic hypothesis was visceral leishmaniasis due to the history of fever, pallor and visceromegaly without jaun-

dice. Then, complementary tests showed severe anemia with hemoglobin 3.3 g/dL, macrocytosis (mean corpuscular volume 98.1 fL), peripheral smear with anisocytosis, and poikilocytosis with schizocytes, dacrocytes, crenated erythrocytes and 29 erythroblasts in 100 counted leukocytes, leukometry of 20,400/mm^3 with lymphocytosis (58%) and left upper shift (segmented 17%, bands 12%, metamyelocytes 2%, myelocytes 1%), 175,000/mm^3 platelets. Hemolysis tests showed high reticulocytes (5.80%), high LDH (4,690 U/L), but total bilirubin normal, direct antiglobulin test (DAT) strongly positive with predominance of IgG and cross-tests with agglutination. Electrolytes, creatinine, AST and ALT were normal. K39 was negative. Imaging exams (echocardiography, chest radiography and abdominal ultrasonography) were without alterations.

It was initiated pulse methylprednisolone therapy for 3 days (30 mg/kg/day) associated with folic acid (5 mg/day). On the fourth day, prednisolone (1 mg/kg/day) was started. Due to the fever without a focus, ceftriaxone was given intravenously (100 mg/kg/day) for 7 days. It was difficult to find a compatible blood bag due to agglutination in all cross-tests performed. A "least incompatible" cross-matching donor was found in the second day of hospitalization, but blood transfusion was not required due to the early clinical-laboratory response to corticosteroids, as seen in the rising levels of hemoglobin on the second day (4.20 g/dL). This blood bag was held in reserve. During the hospitalization, the patient evolved afebrile, with an important general condition improvement and presented a reduction of cutaneous-mucous pallor, and a regression of hepatosplenomegaly. At hospital discharge, after 9 days of hospitalization, his liver was impalpable, while his spleen was palpable 2 cm from the left costal border, both painless. Complementary exams showed hemoglobin 7.80 g/dL with anisocytosis, macrocytosis and polychromasia, leukogram with 22,800/mm^3 leukocytes, 75% of which were lymphocytes, without left shift, 252,000/mm^3 platelets. Prednisolone and folic acid were prescribed. He continues in an outpatient follow-up at this hospital to elucidate secondary etiology, which the complementary tests have not been able to rule out.

Discussion

Typical wAIHA presents with anemia syndrome (with weakness, fatigue, pallor, dizziness, poor feeding, tachycardia, tachypnea, and headache) and hemolytic signs (hepatosplenomegaly and jaundice), generally acute and intense. If critical, can be associated with intravascular hemolysis signs (dark urine related to hemoglobinuria and hemosiderinuria, and pink plasma). The cAIHA is generally insidious and chronic, presents with a crisis of exposure to cold, leading to hemolytic anemia, acrocyanosis and Raynaud's phenomenon. PCH causes intravascular hemolysis after cold exposure [4].

In AIHA, jaundice will occur only when hemolysis causes blood elevated unconjugated bilirubin levels that overcome the liver glucuronidation capacity, so, is not always present. In a patient with strong hemolysis evidences, even with normal bilirubinemia, the investigation must proceed to causes of hemolytic anemia.

Laboratory tests generally exhibit normocytic or macrocytic anemia due to reticulocytosis. Peripheral blood smear demonstrates anisocytosis and poikilocytosis, with variable forms as young erythrocytes forms and spherocytes. Associated autoimmune thrombocytopenia leads to Evans syndrome diagnosis. Increased LDH, unconjugated hyperbilirubinemia, and reduced haptoglobin are hemolysis evidences. While the direct Coombs test or DAT detects antibodies on the surface of red blood cells, monospecific reagents will differentiate the antibodies: classically, wAIHA is IgG positive and C3d positive or negative, whereas cAIHA is C3d positive and IgG negative. PCH is diagnosed by the presence of the Donath-Landsteiner antibody [3].

However, in the strong suspect of AIHA, a negative DAT cannot exclude it. According to the literature, 3-11% wAIHA cases have negative DAT, and this can be explained by: erythrocyte-bound IgG titles under the detectable for the disponible reagent, IgG with low affinity that can be removed by preparatory washes, or AIHA caused by IgA, monomeric IgM or natural killer cells. Then, it is possible to improve DAT results through enhanced tests: using column agglutination, or repeat DAT after 4 °C or low ionic strength saline red cell wash to elevate the IgG antibodies sensibility, or test with IgA, IgM or natural killer cells reagents, or using polybrene or flow cytometry. Also, it is recommended that, if these tests are not disponible, the patient must be treated for AIHA according to the clinical-laboratory correlation [5, 6].

There are remarkable differences between AIHA in children and in adults: 1) AIHA is more common in adults; 2) children AIHA often follows a common viral infection, while adult AIHA is frequently secondary to an underlying disease (especially lymphoproliferative or autoimmune); 3) children wAIHA has generally a good prognosis with an acute and self-limited course, with a better response to corticosteroids, as adult wAIHA tends to a recurrent and chronic course. In children, the mortality ranges 10-30% and prognosis is worse in Evans syndrome and chronic wAIHA [1, 2].

A recent study with 35 children diagnosed with AIHA showed its predominance for males (65.7%) and for wAIHA (80.0%). Of the children, 45.7% had secondary AIHA (14.3% viral and 31.4% autoimmune). Evans syndrome was present in 20.0% of cases. Jaundice occurred in 28.8% cases. At the treatment, 62.8% patients needed erythrocytes transfusion, and 82.7% responded to corticosteroids [7]. Similar findings are related in another recent study with 68 children with AIHA: 57.1% were males, 60.3% had associated diseases (97.6% of them due to infections), and Evans syndrome was present in 29.4% cases. Jaundice occurred in 41.2% cases, 88.9% cases had good response to corticosteroids, and erythrocytes transfusion was performed in 64.7% due to severe anemia [8].

wAIHA is classified as primary when is idiopathic or secondary when clinical evolution is related to another condition. Possible etiologies of secondary forms include viral infections, autoimmune, chronic inflammatory or lymphoproliferative diseases, non-lymphoid malignancies and drugs [9].

The first step of the case in question was: how to suspect an AIHA? The syndrome of fever, pallor and hepatosplenomegaly raised two main differential diagnoses: visceral leishmaniasis and hemolytic anemia. Visceral leishmaniasis, very common in this Brazilian region, leads to bicytopenia and/or pancytope-

nia on the hemogram, with reticulopenia and K39 positive test, which was not the case. Although bilirubin levels were normal, anemia plus positive hemolysis tests led to hemolytic anemias. Among hereditary hemolytic anemias, hereditary spherocytosis (HS) is an important differential diagnosis because the spherocytes can be present both in HS or AIHA, but, in this case, familial history was negative and peripheral blood smear had not spherocytes. Also, case history was negative for other etiologies of acquired hemolytic anemias. Finally, anemia plus hemolysis plus DAT positive diagnosed AIHA.

The second step was to classify the AIHA. In children, wAIHA makes up most of the cases, there was a febrile syndrome at the beginning of the case, no intravascular hemolysis signs (more common in cAIHA) were found, as well as acrocyanosis and/or Raynaud's phenomenon. Finally, the monospecific DAT showed the predominance of IgG, allowing wAIHA diagnosis.

The third step was to search underlying disease in AIHA. For this, clinical examination and imaging exams were performed, but they were negative.

Currently, there is not a standard guideline for AIHA treatment in children. Evidences show that first-line treatment for primary wAIHA is corticosteroids at 1 - 2 mg/kg/day (prednisolone or equivalents), but pulse steroid therapy may offer faster results than standard doses. Refractory wAIHA treatment comprises immunosuppressors (azathioprine, mycophenolate mofetil or cyclophosphamide) isolated or associated to corticosteroids. Rituximab, splenectomy, erythropoiesis-stimulating agents and intravenous IgG are possibilities which may be used in wAIHA resistant to immunosuppressors and corticosteroids [6]. Prophylactic folic acid prevents megaloblastosis due to hemolysis and is recommended for all cases.

Erythrocytes transfusion should be performed in cases of asymptomatic patients with hemoglobin levels < 7 g/dL or in hemodynamic instability or hypoxic anemia despite hemoglobin levels. However, the autoantibodies cause agglutination during cross-tests and hemolysis. Still, delaying transfusion in critical anemic patients because of serologic incompatibility can be mortal [6]. Therefore, "least incompatible" red blood cells transfusion should be carried out and under appropriate medical supervision.

Transfusion goal is to provide an increase in oxygen-carrying capacity, though transitory due to hemolysis by panreactive antibodies. In an urgent situation, ABO-RhD group matched erythrocytes can be used, even if there is cross-matching panagglutination. Although, red cell extended phenotype determination reduces the risk of evoking alloantibodies and provides a safer red cells transfusion, especially in non-urgent cases or when there is great suspect of high risk of alloimmunization. Fulminant hemolytic crisis is a rare but feared side effect that causes elevated morbidity and mortality. Once the decision of transfusion has been secured, careful management transfusion must be done, as the initial transfusion of small aliquots of red blood cells to reduce the risk of fluid overload or massive hemolysis. Then, if there is no reaction, planned transfusion may be continued [10].

In this case, transfusion was not performed due to the fast increase in hemoglobin levels and clinical response after pulse therapy.

So, in a child with hemolytic anemia syndrome, especially when sudden and intense, and/or there is incompatibility in multiple cross-tests, AIHA must be searched, despite its rarity, owing to its morbidity and mortality, and potential prompt response to corticosteroids. AIHA can be the first clinical presentation of an underlying disease, and this makes necessary a good complementary investigation of its etiology. Even with risks, transfusion should not be avoided when it is indicated.

Grant Support

None.

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