Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 08/20/2024
Approved on: 11/11/2024

CASE REPORT

Cold Agglutinin Disease - Case Report

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Keywords:
Anemia, hemolytic, Anemia, hemolytic, Autoimmune, Autoantibodies.

Abstract

Cold antibody autoimmune hemolytic anemia is a rare subtype of hemolytic anemia, mainly in pediatric patients. In this subtype of anemia, the immune system produces antibodies called cold agglutinins, which hemolyze red blood cells, especially in the presence of low temperatures. The disease can have primary or secondary etiology and the main symptoms include pallor, lethargy, jaundice and fever. Treatment varies according to the degree of anemia and severity of symptoms, with thermal control being highlighted. Plasmapheresis can be one of the therapeutic modalities, reserved for refractory cases that did not respond to transfusion; plasmapheresis, although common among adults, is not frequent in pediatrics. This type of hemolytic anemia in children is described as a mild and self-limiting clinical condition, but this report describes the evolution of an 8-year-old patient, who initially presented a frustrating and nonspecific clinical condition. The patient presented an unfavorable clinical evolution with significant anemia, diagnosed with hemolytic anemia due to cold antibodies, refractory to treatment with plasmapheresis and requiring the use of rituximab, reinforcing the importance of this report.

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Resid Pediatr. 2025;15(3). DOI: 10.25060/residpediatr-2025.v15n3-1325

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INTRODUCTION

Autoimmune hemolytic anemia due to cold antibodies is a rare subtype, especially in pediatrics, where the most common type is warm antibodies[1,2]. The annual incidence of cold antibody anemia is estimated at 0.8 cases per 100,000 children[2]. In this subtype, the immune system produces antibodies called cold agglutinins, which hemolyze red blood cells, especially in low temperatures[3].

This type of anemia can be a primary disease of unknown etiology, or a secondary disease triggered by infectious, neoplastic, or autoimmune processes[2,4,5]. Laboratory findings are positive for hemolysis[1]. Commonly described symptoms include pallor, lethargy, jaundice, and fever[6].

Treatment varies depending on the degree of anemia and symptoms, including the need for thermal control – low temperatures are often harmful[1]. Plasmapheresis is indicated for patients with severe conditions and refractoriness to transfusions[1,6]. Rituximab is commonly used in adults, but its use is uncommon in pediatrics[1,7]. There is an increased risk of complications involving thromboembolic events and kidney injury[1,2].

It is noteworthy that in children this type of hemolytic anemia is described as a mild and self-limiting clinical condition, reinforcing the importance of this report given the unfavorable clinical evolution, having been refractory to treatment with plasmapheresis and requiring the use of rituximab[1]. Approval by the Ethics Committee, opinion CAAE 81598824.4.0000.0097

CASE REPORT

An 8-year-old male patient was admitted by direct referral to the emergency room of a tertiary hospital in Curitiba, complaining of earache, runny nose, abdominal pain, vomiting, and presyncope (pallor and hypotonia after emesis). Physical examination revealed only mild pallor and he was oriented and talkative. His sister presented with flu-like symptoms. At the emergency room, he was given expansion, received analgesia, and underwent laboratory tests, which revealed significant anemia, with an erythrogram suggestive of cryoagglutination (a test performed in a hot tube due to the presence of cryoagglutinins).

The patient was transferred to the intensive care unit (ICU) the next day due to behavioral changes, oscillating between agitation, drowsiness, and aggression. Physical examination revealed significant pallor and a normal cranial tomography scan. Based on peripheral blood findings, the patient was investigated for autoimmune hemolytic anemia due to cold antibody, possibly of primary origin. Under hematology-oncology guidance, environmental thermal control (environmental temperature >30°C) was performed, infusion of heated solutions and filtered and phenotyped red blood cells (in small aliquots) was performed, and plasmapheresis (plasma replaced with albumin) was performed if necessary. Before initiating plasmapheresis therapy, the patient developed a decreased level of consciousness, loss of strength in the right upper limb, facial paralysis, and strabismus, associated with pneumonia, requiring orotracheal intubation and initiation of antibiotic therapy with ceftriaxone. Hemolysis, systemic vasculitis due to cold antibody, and encephalopathy associated with the event were investigated. Erythropoietin, folic acid, vitamin B12, and vitamin K were also administered. On the fourth day of hospitalization, the patient developed significant liver abnormalities. On the sixth day, peritoneal dialysis was prescribed due to worsening renal function, oliguria, and anasarca. Furthermore, the patient needed to start a vasoactive drug (norepinephrine). On the ninth day, rituximab was administered once a week for four weeks due to an unsatisfactory response to plasmapheresis.

The patient showed gradual clinical improvement and was discharged. Follow-up at the hematology clinic revealed a normal physical examination upon return, with complete remission of symptoms.

DISCUSSION

Autoimmune hemolytic anemia is characterized by the destruction of red blood cells caused by autoantibodies. It can be subdivided into warm antibody hemolytic anemia, cold antibody hemolytic anemia, mixed subtype, and paroxysmal cold hemoglobinuria. The most common subtype in children is caused by warm antibodies, accounting for 90% of cases; however, in the reported case, cold antibody hemolytic anemia was diagnosed[2,7].

The average age of onset of cold antibody anemia is 76 years, while the report presented refers to the pediatric age group[8]. Hemolytic anemias can occur at any time between childhood and adolescence, with a peak incidence being more common in children under 5 years of age[5].

Autoimmune hemolytic anemia can be primary (idiopathic) or secondary. Secondary forms, accounting for approximately 50% of cases, are generally related to autoimmune diseases, lymphoproliferative disorders, infections, tumor masses, and solid organ transplantation[2,4,5]. An association between hemolytic anemia and Mycoplasma pneumoniae, Epstein-Barr virus, influenza, chickenpox, measles, and other atypical bacteria has been described in the literature[2,5,9,10]. The patient in question had positive IgG serology for Epstein-Barr virus.

The clinical presentation is quite variable in severity, with the most common clinical course being chronic or recurrent[2,4,7]. In this report, the disease presented acutely and to date has not recurred, although the time period analyzed is quite limited[4]. Symptoms are generally related to changes in temperature, and cold can trigger hemolysis[4,5]. Cryoagglutinins are responsible for hemolysis and typically agglutinate when exposed to temperatures <37°C[3].

Most cases present with pallor, jaundice, fatigue, and choluria, less commonly with abdominal pain and fever[5]. On admission, the reported patient presented with abdominal pain and other nonspecific symptoms (not suggestive of hemolysis). The clinical presentation is related to the degree of anemia; in approximately 77% of cases, the disease is self-limited[4,5]. The anemia is usually not as severe as that reported in this report; in the literature, the mean hemoglobin level on admission was 8.9 g/dL, while in the presented report it was 5 g/dL[8]. Hemoglobin <8 g/dL on admission is an important risk factor for ICU admission and mortality[11].

Although uncommon, the clinical picture can include massive hemolysis, leading to organ failure and death[11]. Intravascular hemolysis releases high levels of hemoglobin into the bloodstream to be filtered by the kidneys, which can result in hemoglobinuria and loss of renal function[2]. Some risk factors, such as hospitalization, infection, acute renal failure, and the need for transfusion, indicate an unfavorable outcome[11]. In this case, a transfusion was required upon hospital admission and renal replacement therapy was required due to worsening renal function. The most common causes of death include infection, myocardial infarction, pulmonary embolism, and multiple organ failure[11].

Laboratory diagnosis is made by the presence of autoantibody adhesion to erythrocyte cells (visualization of agglutinated red blood cells under a microscope) and, indirectly, by the presence of a positive Coombs test and other signs of hemolysis such as reticulocytosis, spherocytosis, increased unconjugated bilirubin and lactic dehydrogenase (LDH)[2,5,10,12]. The patient reported had laboratory tests with a positive direct Coombs test, reticulocytosis, increased LDH, and the presence of cryoagglutinins in a peripheral blood slide (Figure 1). A bone marrow biopsy should be performed in all patients demonstrating red cell hyperplasia[10].

It is important to emphasize that there are no well-established criteria for defining autoimmune hemolytic anemias, with diagnosis being made through typical clinical manifestations and laboratory findings[13].

Paroxysmal cold hemoglobinuria should be among the main diagnostic hypotheses in the evaluation of patients under 18 years of age with hemolysis associated with infection and cold. However, in these cases, patients commonly present with hemoglobinuria, which was not found in the reported case[4].

Treatment is guided by the severity of anemia and symptoms presented[4]. Red blood cell transfusion should be limited to cases of severe anemia (hemoglobin <6 g/dL) or hemodynamic instability[4,5]. It is recommended that blood components be warmed and that the environment also have a controlled temperature in order to minimize the chance of hemolysis[5].

Symptomatic patients should be treated with folic acid and other vitamin supplements as needed[4]. Corticosteroid therapy presents a limited clinical response in less than 15% of cases and is not indicated[3,12]. Splenectomy is also not indicated[2,3].

Plasmapheresis is used in cases of severe hemolysis to remove intravascular autoantibodies in critically ill patients. In an attempt to avoid activation of the complement system, plasmapheresis with albumin is indicated, as was done in the case described[4,7].

Rituximab is described as first-line treatment for severe cases, but it is rarely necessary in children, unlike what was reported in this report[3,4,7,14]. This medication acts on the classical pathway of the complement system[3]. The literature reports that 60% of patients treated with rituximab have a satisfactory clinical outcome; however, it has been shown that the medication is generally effective for a limited period of 6 to 11 months[14]. The response to this medication is independent of age, previous treatment, or combination with other drugs[12]. A recent study involving rituximab demonstrated an increase in hemoglobin levels of 4.5 g/dL; in the case presented, there was also a gradual increase in hemoglobin levels after the initiation of therapy (see Figure 1)[10].

Autoimmune hemolytic anemia due to cold antibodies in pediatric patients is generally self-limiting. Management is supportive, involving optimized hydration, effective diuresis,

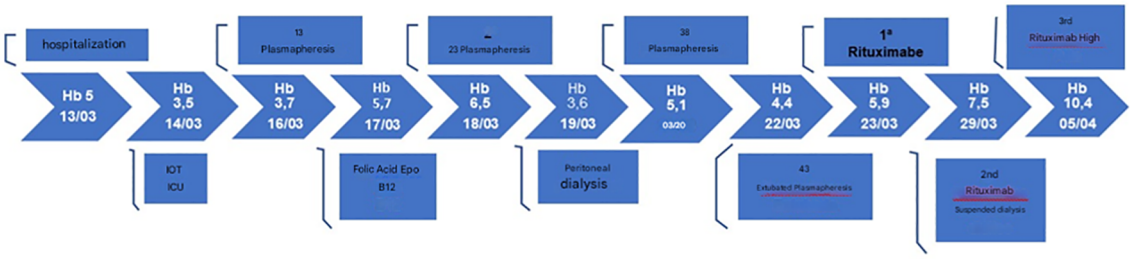


Figure 1. Flowchart with hemoglobin levels demonstrating variability throughout hospitalization and progressive increase in levels according to the therapy used. Acronyms: Hemoglobin (Hb), intensive care unit (ICU), orotracheal intubation (OTI), folic acid (folic acid), erythropoietin (Epo), Vitamin B12 (B12).

and adequate renal hemoglobin excretion[2]. Therefore, the unfavorable outcome of the clinical case presented here is even more significant, as several interventional measures were required, in addition to rituximab and plasmapheresis. After these measures were instituted, the patient showed complete regression of symptoms and normalization of the peripheral blood profile (Figure 2).

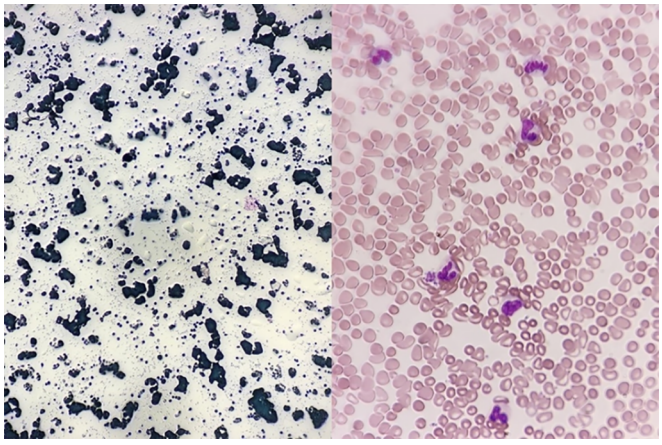


Figure 2. Left: Admission blood count slide with 10x magnification, showing agglutinated red blood cells; right: slide after 3 plasmapheresis sessions and start of rituximab with 40x magnification, showing normocytic and normochromic red blood cells homogeneously distributed across the slide, without agglutination.

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