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Case Report

Plasmapheresis in a child with cold antibody autoimmune hemolytic anemia: case report

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Abstract

Autoimmune hemolytic anemia is a picture of hemolysis which is caused by autoantibodies against red blood cell surface antigens. It is classified as primary, secondary or warm and cold autoimmune hemolytic anemia according to the temperature at which antibodies react. It is usually an acute and self-limiting condition. Here, we present a three-year-old male patient who presented with malaise, paleness, and dark-colored urine. His hemoglobin level was 5.8 g/dL, and increased indirect bilirubin and lactate dehydrogenase levels and decreased haptoglobulin and reticulocyte levels were noted. A direct Coombs test was positive using anti-C3. Four erythrocyte suspension transfusions were given because the anemia was life-threatening. High-dose steroids (30 mg/kg/ day, methylprednisolone) and intravenous immunoglobulin (1 g/kg/day, two days) treatments were unresponsive. Plasmapheresis was performed and no further transfusions were needed after plasmapheresis. Plasmapheresis treatment can be effective in children with cold type autoimmune hemolytic anemia.

Key words: Autoimmune hemolytic anemia, cold antibody, plasmapheresis

Introduction

Autoimmune hemolytic anemia (AIHA) is a rare disease caused by antibodies binding to the surface of erythrocytes, which is characterized by destruction of erythrocytes. It occurs very rarely in infants and children, and its annual incidence is 2/1,000,000 (1). The diagnosis is made with the presence of anemia, hyperbilirubinemia, reticulocytosis, and a positive DC test (2). The clinical picture ranges between asymptomatic cases to hemolytic anemia and life-threatening acute hemolysis. Underlying diseases, the speed of hemolysis, and the type of autoantibody determine the severity of the clinical picture (1).

There are two types of autoimmune hemolytic anemia including cold-antibody hemolytic anemia and warm-antibody hemolytic anemia. The cold-antibody type constitutes 16-32% of all cases of AIHA and frequently occurs after infections (1, 2). It is generally self-limiting and recovery occurs in a few weeks (1, 2). It has been shown that plasmapheresis may be beneficial in patients who do not respond to steroids and intravenous immunoglobulin (IVIG) treatment (3, 4). In this article, we present a patient with cold-antibody AIHA who recovered with plasmapheresis treatment.

Case

A 3-year-old male patient presented with symptoms of malaise, paleness, and dark-colored urine. In his history, it was learned that he had bronchitis 20 days ago. The physical examination was as follows: temperature: 38.5°C, blood pressure: 80/40 mm Hg, cardiac apical

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beat (CAB): 150 /min, respiratory rate: 40 /min, and peripheral oxygen saturation 90%. His general status was moderate, his skin looked pale, his sclerae were icteric, his liver was palpable 2 cm below the costal margin, and his spleen was nonpalpable. A 1-2/6° systolic murmur was heard in the mesocardiac area. Complete blood count was as follows: hemoglobin: 5.8 g/dL, mean corpuscular volume (MCV): 81.7 fL, mean corpuscular hemoglobin (MCH): 28 pg, mean corpuscular hemoglobin concentration (MCHC): 34.2 g/dL, red cell distribution width (RDW): 13.3%, reticulocytes: 0.75%, white blood cells (WBC): 17,200 /mm³, neutrophil count: 5100 /mm³, and platelet count: 242,000/mm³. Cylinder erythrocytes and hemolysis findings were observed in a peripheral smear (Figure 1). Total bilirubin: 4.62 mg/dL (ref. 0-1.1 mg/dL), direct bilirubin: 0.5 mg/dL (ref. 0-0.2 mg/dL), lactate dehydrogenase (LDH): 2205 IU/L (225-400 IU/L), vitamin B_{12}: 492 pg/mL, folic acid: 10.92 ng/mL, ferritin: 1496 mg/dL, haptoglobulin: 7.56 mg/dL (ref. 30-200 mg/dL), multi-specific DC test (+), DC with anti IgG (-), and DC with anti C3 (+). Hemoglobin electrophoresis, osmotic fragility, and glucose 6-phosphate dehydrogenase activity tests were normal. The immunoglobulin levels were found to be normal for age. Toxoplasma, rubella and cytomegalovirus IgM were (-), IgG (+), anti-HAV IgM (-), anti-HAV IgG (-), HbsAG(-), anti-Hbs (+), anti-HCV (-), herpes simplex Type 1/Type 2 IgM and IgG (-), parvovirus IgM and IgG (-), Epstein-Barr virus VCA IgM and IgG (-), ANA (-), anti dsDNA (-), and lupus anticoagulant (-). C3 and C4 levels were normal.

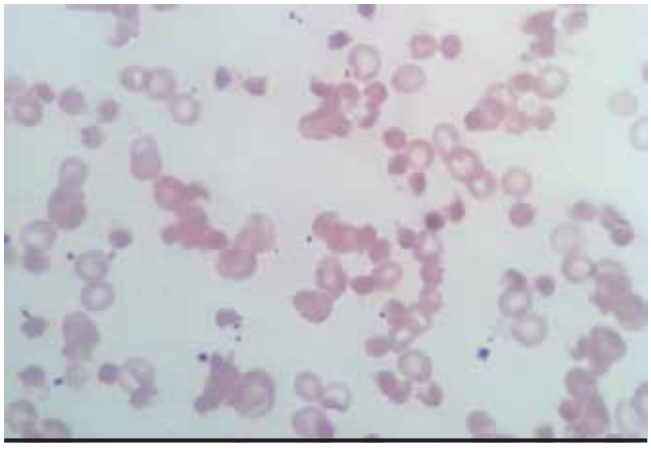

Figure 1. Peripheral smear appearance

Abdominal ultrasonography revealed no findings except for hepatomegaly (11 cm). An erythrocyte suspension (ES) was transfused at a dose of 10 cc/kg because of hypoxemia, hypotension, and heart failure. Antibiotic treatment (cefoperazone-sulbactam/IV, clarithromycin/oral) was initiated because the body temperature was 38.5°C and above. A second (ES) was transfused because the severe hemolysis and findings of reduced blood pressure, hypoxemia, and heart failure continued. Following transfusion, the hemoglobin level was between 5 and 6 g/dL. The DC test was repeated in the patient whose hyperbilirubinemia continued. Multi-specific DC was found as (++++) (Anti IgG (-), anti C3 (++++)). The fact that visible agglutination was present inside the tube when the patient's blood was incubated at +4°C and agglutination disappeared at room temperature supported the presence of cold-antibody. In addition, red urine color (blood reaction was found as +++ on complete urinalysis) and absence of splenomegaly supported intravascular hemolysis.

Autoimmune hemolytic anemia secondary to infection was primarily considered because of the presence of previous history of infection and continuing fever during hospitalization. Methylprednisolone at a dosage of 30 mg/kg/day was initiated as high-dose steroid treatment. Treatment was given as a single intravenous dose. The patient's hemoglobin level was reduced to 4 g/dL following the first dose of steroid. IVIG was given at a dose of 1 g/kg for 2 days because the reduction in hemoglobin levels continued despite high-dose steroid treatment. ES transfusion was given for one more week because heart failure, hypotension, and hypoxemia continued. Previously warmed ES was given because of the presence of positive cold antibody. Hemolysis continued with a high rate despite IVIG and high-dose steroid treatment.

Table 1. Laboratory data of the patient and treatment methods applied

	Hb (g/dL)	Bilirubin (mg/dL)	LDH (IU/L)	Haptoglobulin	Ret %	Treatment
At presentation	5.8	4.6	2205	7.56	0.75	ES
First day	5.8	4.5	2834	7.56		ES
Second day	6.8	4.5	2750	7.56	0.84	Steroid+ IVIG
Third day	5.1	4.4	2497	7.56		Steroid+IVIG+ES
Fourth day	4.4	4.4	2450	7.56		Steroid+Plasmapheresis+ES
Fourth day (12 hours later)	8.2	3.5	1643	7.56		Steroid
Eighth day	11.3	0.28	1385	46.9	14.5	Steroid

ES: erythrocyte suspension; IVIG: intravenous immunoglobulin; Ret: reticulocyte

On the fourth day of hospitalization, plasma exchange was performed with one unit of fresh frozen plasma (with Fresenius device). Previously warmed ES was transfused before the procedure to prevent the development of hypovolemic shock. On the fourth day following plasmapheresis, the reticulocyte percentage was found as 14.5% and there was no need for further ES. The patient's laboratory data and therapies applied are shown in Table 1. On the 11th day of hospitalization, the patient was discharged with a hemoglobin level of 12.1 g/dL. Steroid treatment was discontinued by tapering the dose by 50% with 2-day intervals. The DC test became negative in the follow-up visit one month later and the patient is being followed up without any further problems. Written informed consent was obtained from the patient's parents.

Discussion

In AIHA developing secondary to infection, symptoms generally occur 2-3 weeks after the onset of infection and recover spontaneously in 2-3 weeks (2). In most patients, the multi-specific DC test and DC test with anti-C3 are positive and the DC test with anti-IgG is negative (1). In our patient, the DC test performed with anti-IgG was negative at the time of presentation. A 4+ reaction was found on the complement DC test, which was repeated because severe hemolysis continued and the patient was considered to have cold-antibody AIHA. Reticulocytopenia has been reported in 39% of pediatric patients with AIHA (5). Potential mechanisms including suppression of the bone marrow secondary to infection and immune-mediated apoptosis of erythrocyte precursor cells in the bone marrow have been proposed as the cause of reticulocytopenia (6). Marked reticulocytosis (14.5%) was found in our patient on the eighth day of immunosuppressive treatment and on the fourth day after plasmapheresis. It was thought that the reticulocyte count might have increased because both antibody production was reduced and immune-mediated destruction of erythrocyte precursor cells in the bone marrow was reduced by way of removal of antibodies that were present in the circulation.

The diagnosis of cold-antibody AIHA is made with the presence of hemolytic anemia, reticulocytosis, hyperbilirubinemia, increased LDH level, and classically, a negative Coombs test with anti-IgG and a positive Coombs test with anti-C3 (7). In the study by Swiecicki et al., (7) in which 89 adult patients who were diagnosed as having cold agglutinin disease were evaluated retrospectively, it was reported that more than 90% of the patients had a positive Coombs test with anti-C3. In our patient, the presence of a positive Coombs test with anti-C3, visible agglutination inside the tube when the blood sample was incubated at +4°C, and disappearance of agglutination at room temperature in addition to hemolysis findings supported the diagnosis of cold-antibody AIHA. Our patient had a history of infection 20 days ago and symptoms of fever from the time of hospitalization. Therefore, cold-antibody AIHA secondary to infection was considered. In children, cold-antibody disease is most commonly observed in association with infections including mycoplasma and Epstein-Barr virus infections (2). In our patient, Epstein-Barr virus serology was found negative and mycoplasma serology could not be studied. Investigations related with connective tissue diseases, which were requested in terms of other diseases that could lead to secondary AIHA, revealed no pathology. Bone marrow aspiration was not performed because physical examination and laboratory findings supporting hematologic malignancy were not accompanying.

Treatment of AIHA varies according to the etiology and severity of the clinical picture (1). Antibiotics may be beneficial in the treatment because cold-antibody disease secondary to infections other than viral infections is generally transient (2). In these patients, immunosuppressive treatment and plasmapheresis are rarely needed (2). In our patient, high- dose steroid treatment as immunosuppressive treatment was initiated in addition to antibiotics because life-threatening AIHA was present. It was reported that use of high-dose IVIG (0.5-1 g/kg/day) for five days might be effective in patients with marked splenomegaly (8). According to guidelines published in subsequent years, use of high-dose IVIG is recommended only in life-threatening conditions (9). IVIG treatment was administered in addition to steroid treatment in our patient because life-threatening anemia was present. However, the patient was considered to be unresponsive to treatment because rapid reduction in hemoglobin levels continued after IVIG treatment and plasmapheresis was performed.

Plasma exchange is efficient in the treatment cold-antibody disease by way of elimination of related circulating antibodies in the plasma (1, 10). Plasmapheresis in AIHA is recommended as third-line treatment in patients who need urgent transfusion until the effects of immunosuppressive treatment appear and in patients who are unresponsive to immunosuppressive treatment and splenectomy and have relapse (1). The American Society for Apheresis Applications Committee divided diseases into four categories by efficiency of apheresis. According to the 2010 guidelines, life-threat-

ening cold-agglutinin disease is included in category II. In category II diseases, plasmapheresis is recommended alone or in combination with other therapies as second-line treatment (10). Clinical outcomes of cases of AIHA treated with plasmapheresis have been reported as case reports. On such report noted that a patient with severe cold-antibody AIHA was unresponsive to steroid and IVIG treatment and persistent remission was obtained following plasmapheresis (3). In a five-year-old female patient who developed cold agglutinin disease after acute gastroenteritis, recovery could not be achieved with steroid and IVIG treatment and need for transfusion was eliminated following a single application of plasmapheresis (4).

In a study by Aladjidi et al., (5) in which 265 children with AIHA were evaluated retrospectively, it was shown that 37% of patients had primary AIHA, 63% had secondary AIHA, previous infection was present in 10% of the cases of secondary AIHA, and immunologic causes were present in 53%. It has been shown that immunologic diseases develop subsequently in approximately half of patients who report infection initially and these patients show a chronic prognosis. Therefore, investigators have emphasized that a full immunologic investigation and long-term follow-up is needed in cases of secondary AIHA, even if there is a well-defined infection.

Although cases of cold-antibody AIHA secondary to infection are mostly mild and self-limiting, they may rarely present with a severe clinical picture, as in our case. With this case report, we wish to emphasize that plasmapheresis is an efficient treatment method in patients who present with a severe clinical picture and long-term follow-up is appropriate in terms of immunologic diseases that may occur subsequently.

Informed Consent: Written informed consent was obtained from the patient's parents.

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