

# Cold agglutinin disease in sepsis: A rare entity

## Abstract

Cold agglutinin disease (CAGD) is a type of autoimmune hemolytic anemia which generally occurs in adults and is characterized by the presence of IgM antibodies directed against polysaccharide antigens on red blood cell surface. A 16-year-old male, having clinical picture of sepsis and anemia, presented to the Emergency Department of our Institute in an Hemodynamically unstable condition. Investigation profile revealed hemolysis due to CAGD, which responded to corticosteroids, antibiotics and supportive treatment. This case highlights the importance of recognizing this entity in such type of cases presenting with sepsis and anemia.

### Key words:

*Autoimmune hemolytic anemia, cold agglutinin, hemolysis, sepsis*

## Introduction

Autoimmune acquired hemolytic anemia is one of the type of hemolytic anemia that results from the development of antibodies directed against antigens on the surface of patients own red blood cells (RBCs), that act as auto antibodies. It is generally classified either according to temperature at which the antibodies react with the RBCs into warm antibody and cold antibody types or according to etiology, which can be idiopathic or secondary.<sup>[1]</sup> Cold agglutinin disease (CAGD) occurs in adults of both sexes older than 50 years of age and is rare in children. CAGD is rare, accounting for 15% of autoimmune hemolytic anemia with an incidence of 1 case/million people per year.<sup>[2]</sup> CAGD is typically characterized by the presence of IgM antibodies (rarely IgA or IgG) directed against polysaccharide antigens on the red blood cell surface.

The most common cold agglutinins are designated as anti-I. At birth, infant's RBCs express i-antigen, which is converted to I antigen.<sup>[3]</sup> This pathologic entity is diagnosed by the presence of severe anemia (normocytic normochromic), reticulocytosis, indirect hyperbilirubinemia, raised lactate dehydrogenase level and positive direct coombs test. This condition has most commonly been reported following viral infections, *Mycoplasma pneumoniae*, and infectious mononucleosis.<sup>[4]</sup> They may also occur in normal adults mostly in the seventh decade of life,<sup>[5]</sup> in association with lymphoproliferative disorders,<sup>[6]</sup> CLL, Kaposi sarcoma, Waldenstrom's macro globulinemia and various other infections such as hepatitis A,

malaria, human immunodeficiency virus,<sup>[7]</sup> CMV, Rubella, infective endocarditis and influenza. We describe a rare case of an adolescent who presented with features of sepsis and anemia to our Emergency Department.

## Case Report

A 16-year-old male patient was admitted to our Emergency Medicine Department with complaints of continuous high grade fever associated with chills and rigors for 8 days, yellowish discoloration of urine and eyes for 2 days, vomiting for 1 day along with generalized weakness. There was no history of loose stools, dysuria, cough, rash, arthritis or bleeding from any site. He had similar complaints 1-year back when he was admitted in a private hospital and was transfused one unit of AB<sup>+</sup> blood and discharged. Family history was unremarkable for such disease.

Clinical examination on admission revealed altered sensorium with severe pallor, icterus, tachycardia (102/min), tachypnea (24/min), blood pressure of 90/60 mmHg, with no evidence of hepato-splenomegaly or lymphadenopathy. Cardiovascular, respiratory, and central nervous system examination was unremarkable.

Peripheral blood film revealed anisopoikilocytosis with presence of microcytes, macrocytes and macro-ovalocytes with severe hypochromia, leukocytosis with the shift to the

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left, nucleated RBC's 31/100 white blood cells while platelet count was normal. Coomb's test showed positive DCT and weakly positive ICT [Tables 1 and 2]. Blood grouping was performed, but due to the presence of auto-agglutination in the sample at room temperature (~7–8°C), it was difficult to perform cell and serum grouping. The fresh blood sample in citrate vial was taken and incubated at 37°C for 30 min. Then, cell washing was done 8–10 times with warm normal saline at 37°C. 5% cell suspension of washed sample was prepared. Cross-match was done with AB<sup>+</sup> packed red blood cells (PRBCs) unit with tube method, and gel method and it was found to be compatible with patient's serum. Then, the PRBCs unit was washed three times with warm normal saline

and subsequently issued to the patient. The PRBCs unit was transfused when the temperature of the unit reached to about 37°C, that is, body temperature, so as to avoid any hemolytic reaction. Overall, three units of washed PRBCs of AB<sup>+</sup> blood group were transfused: 1 unit/day on alternate days.

The chest X-ray and abdominal ultrasonography were unremarkable. In addition to blood component transfusions, he was administered corticosteroids, antibiotics and other supportive treatment and was discharged in a satisfactory condition.

## Discussion

In the present case, anemia was most probably due to CAgD secondary to some infectious cause; however blood culture was negative. Serological test for detection of *M. pneumoniae* was not done. Cold agglutinins were confirmed by auto control positive test at 4°C and direct Coombs test (positive). Blood was transfused after 2 days because of the difficulty in cross matching. Patient responded favorably to intravenous methylprednisolone and antibiotics.

Corticosteroids and intravenous immunoglobulins are the mainstay of treatment though they are less effective in cold antibody mediated hemolysis, when the disease course is usually prolonged. Anti CD 20 molecule rituximab has been used in cold and warm agglutinin disease, the main disadvantage with their use being the possibility of flare-up of any underlying infection.<sup>[8]</sup>

In 2005, a case of autoimmune hemolytic anemia was reported in a child having sickle cell disease who developed severe anemia induced by cold agglutinin hemolysis after *Mycoplasma* infection. Complete blood count (CBC) showed falsely decreased RBC count and hematocrit and falsely elevated MCV and MCHC. Peripheral blood smear showed RBC clumping at room temperature; this disappeared after warming at 37°C. Anti C3b-C3d was present on red cells, and indirect antiglobulin test revealed a circulating cold agglutinin. Furthermore, anti-*Mycoplasma pneumoniae* IgM antibody was detected in serum. Careful evaluation of CBCs and peripheral blood smears is required in cases of worsening anemia among sickle cell patients, and consideration should be given to cold hemagglutinin disease as an etiology.<sup>[9]</sup>

In 2013, another case of cold agglutinin positive autoimmune hemolytic anemia was reported, which was diagnosed to be due to *Klebsiella* infection after ruling-out other causes that have been reported earlier. The patient continued to have hemolysis even after treatment of the underlying infection, intravenous methylprednisolone pulse and intravenous immunoglobulin. He responded to plasmapheresis with resolution of hemolysis.<sup>[10]</sup>

The present case got admitted in an hemodynamically unstable condition with sepsis and although, unlike previous studies, no specific organism could be isolated but still the whole process of agglutination appears to be attributable to sepsis. An interesting feature of our case was that as the sepsis improved,

**Table 1: Initial bio-chemical profile**

Investigations	Result
Haemoglobin	2.0 g/dl
TLC	39.73/cumm
Differential leukocyte count	Myelocytes-7, metamyelocytes 12, polymorphs-58, lymphocytes-20, eosinophils-02
PLT count	13 × 10 <sup>3</sup> /uL
Reticulocyte count %	2.1
Total serum bilirubin	5.6 mg/dl
Indirect bilirubin	4.7 mg/dl
LDH	278.7 IU/L
Malaria card test	Negative
Urine examination (routine and microscopy)	Normal
PTI %	87.5
INR	1.1
HBsAganti-HCV and anti-HIV	Nonreactive

LDH: Lactate dehydrogenase, PTI: Prothrombin time index, INR: International normalized ratio, HBsAg: Hepatitis B surface antigen, HCV: Anti hepatitis C virus, HIV: Anti human immunodeficiency virus, TLC: Total leukocyte count, PLT: Platelet

**Table 2: Comparison of initial bio-chemical profile and 1-week after treatment**

Investigation	29.12.2013	06.01.2014
Hb	2.0 g/dl	10.5 g/dl
TLC	39.73 × 10 <sup>3</sup>	13.79 × 10 <sup>3</sup>
PLT	13 × 10 <sup>3</sup> /uL	70 × 10 <sup>3</sup> /uL
MCV	155 fL	102 fL
RBS	99 mg/dl	
Blood urea	37 mg/dl	19 mg/dl
Serum creatinine	0.9 mg/dl	0.4 mg/dl
Serum uric acid	11.2 mg/dl	5.8 mg/dl
Total bilirubin	5.6 mg/dl	1.6 mg/dl
Conjugated bilirubin	0.9 mg/dl	0.3 mg/dl
Unconjugated bilirubin	4.7 mg/dl	1.3 mg/dl
SGOT	44 IU/L	48 IU/L
SGPT	18 IU/L	42 IU/L
ALP	159	247
LDH		278.7 IU/L

RBS: Random blood sugar, LDH: Lactate dehydrogenase, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, ALP: Alkaline phosphatase, TLC: Total leukocyte count, PLT: Platelet, MCV: Mean corpuscular volume

the agglutination process declined and only then it was possible to specify the blood group and give a blood transfusion.

## Conclusion

The present case highlights the importance of recognizing CAgD in patients presenting in a hemodynamically unstable condition with sepsis and severe anemia.

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