CASE REPORT

JIACM 2024; 25 (1-2): 61-62

Cold Agglutinin Syndrome Secondary to Acute Hepatitis A Infection in an Adult

Prabhat Kumar, Kaushal Maheshwari***

Abstract

Cold agglutinin syndrome (CAS) is a rare condition characterised by formation of cold agglutinins which cause destruction of erythrocytes. CAS is associated with other clinical conditions like infections, malignancies, lymphomas or autoimmune disorders. We describe a young patient who presented with jaundice and anaemia for two weeks. On evaluation, he was found to be having cold agglutinin related haemolytic anaemia secondary to acute hepatitis A infection. He was treated successfully with blood transfusion and a short course of steroids. This case highlights an unwonted extrahepatic manifestation of hepatitis A infection.

Key words: Coomb's test, haemolytic anaemia, steroids.

Introduction

Autoimmune haemolytic anaemia (AIHA) is an acquired disorder characterised by production of antibodies directed against red blood cells (RBCs) surface antigen causing their destruction[1]. AIHA is further classified into two major types based on the optimal temperature at which antibodies react with erythrocyte antigen: warm AIHA (usually IgG) optimal around 37^0 C and cold agglutinin (usually IgM) optimal at 4^0 C. Cold-antibody AIHA is relatively uncommon, accounting for 15 - 30% of AIHA. Cold-antibody AIHA is termed as cold agglutinin disease (CAD) when it is primary and is called cold agglutinin syndrome (CAS) when it is secondary to other clinical diseases like infections, autoimmune disorders, lymphomas or other malignancies[2]. Infections associated with CAS include *Mycoplasma pneumoniae*, Epstein-Barr Virus, Cytomegalovirus, Human Immunodeficiency Virus, Varicella Zoster, SARS-COV-2 and influenza virus[3]. Herein, we present a rare case of CAS secondary to acute Hepatitis A Virus (HAV) infection in an adult.

Case report

A 32-year-old male presented in the month of December with complaints of yellowish discoloration of eyes, weakness and fatigue for the last two weeks. On general physical examination, he had pallor and icterus. Systemic examination revealed moderate hepato-splenomegaly. Blood investigations showed low haemoglobin of 7.2 g/dL, raised MCV - 105 fl, low RBC count - $1x10^6$, haematocrit of 11.7% and MCHC - 61 g/dL with normal total leucocyte and platelet counts. Peripheral smear showed anisocytosis, nucleated RBCs, polychromatophils and RBC agglutination (Fig. 1); RBC agglutination disappeared on pre-warming the sample to 37^0 C for 20 minutes (Fig. 2). Direct Coomb's test was positive at 4^0 C with raised cold agglutinin titres and complement levels (C3 and C4) were low. Serum Lactate DeHydrogenase (LDH) level was high 507 IU/L (Normal <250 IU/L), serum haptoglobin was undetectable and corrected reticulocyte count was high (5%). Vitamin B12 and serum folate levels were normal. Liver function test was deranged with serum total bilirubin of 3.7 mg/dL (Direct bilirubin - 1 mg/dL, Indirect bilirubin - 2.7 mg/dL), aspartate transaminase of 135 U/L and alanine transaminase of 152 U/L. Hepatitis B surface antigen, Anti Hepatitis C Virus antibody and Anti Hepatitis E Virus IgM tests were negative; however, Anti Hepatitis A Virus IgM test was positive. Serum protein electrophoresis, Human immunodeficiency virus (HIV) test and *Mycoplasma*

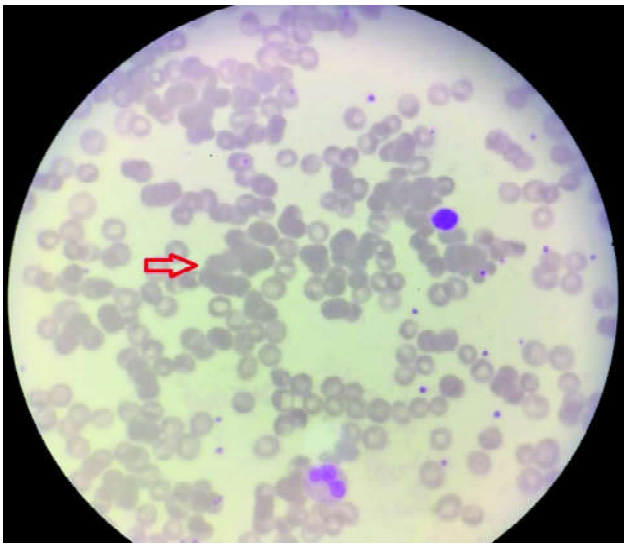

Fig. 1: *Peripheral smear showing clumping of RBCs (red arrow).*

****Senior Consultant, Department of Internal Medicine, **Senior Consultant, Department of Pathology, Kailash Hospital and Neuro Institute, Sector-71, Noida - 201 301, Uttar Pradesh.***

Corresponding Author: Dr Prabhat Kumar, Senior Consultant, Department of Internal Medicine, Kailash Hospital and Neuro Institute, Sector-71, Noida - 201 301, Uttar Pradesh. Phone: 9968123167, E-mail: drkumar.prabhat@gmail.com.

pneumoniae IgM and IgG was negative.

A diagnosis of Cold agglutination syndrome due to acute Hepatitis A Virus infection was made. He was advised to avoid cold exposure and one-unit warm packed RBCs was transfused. He was started on oral prednisolone 30 mg once a day for a week followed by gradual taper over the next two weeks. A repeat haemogram, liver function tests and LDH level done after three weeks of treatment showed normalisation of all parameters.

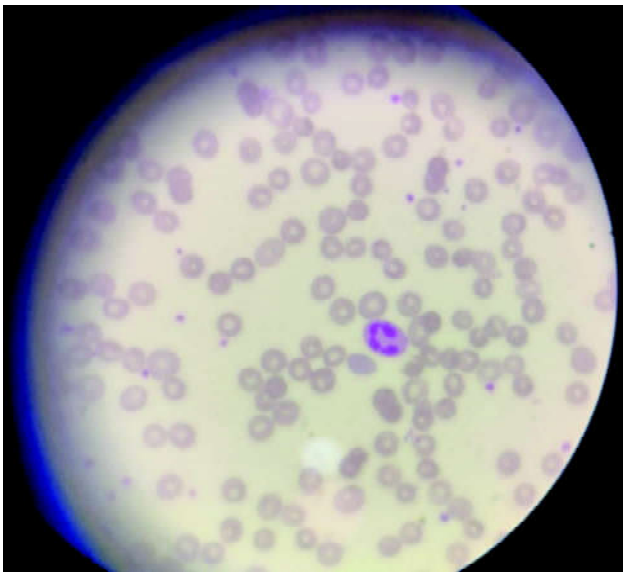

Fig. 2: *Complete resolution of clumping on prewarming the sample at 37°C.*

Discussion

Cold agglutinin syndrome (CAS) occurs secondary to autoimmune disorders, lymphomas, solid malignancies and various bacterial and viral infections. Post-infectious cold agglutinins are seen with *Mycoplasma pneumoniae*, Hepatitis B and C, Human Immunodeficiency Virus, Influenza Virus, Varicella, Epstein-Barr Virus and SARS-COV-2. HAV infection is the most common cause of acute hepatitis in developing countries with low socio-economic condition and poor sanitation. Extra-hepatic manifestations like nephritis, pancreatitis, pericarditis, pneumonitis, and haemolysis occur rarely. Acute HAV infection associated warm type AIHA has been reported earlier, but CAS is very rare with just one prior reported case in a child[4-5]. To the best of our knowledge, this is the first reported case of hepatitis A virus associated CAS in an adult.

CAS is characterised by formation of cold agglutinins (IgM antibodies) against I antigen on the surface of erythrocytes, which readily bind to RBCs as blood passes through the cooler peripheral circulation. Once bound, IgM cold agglutinins activate the complement cascade resulting in binding of C3b to the cell surface. Upon reaching the central circulation at 37^0 C, cold agglutinins detach from the erythrocyte, whereas C3b remains bound. This C3b-coated cells are further sequestered by the macrophages of the reticuloendothelial system resulting in extravascular haemolysis. Also, activation of C5 complement leads to formation of membrane attack complex and intravascular haemolysis in severe cases[6]. The clinical features include symptoms of primary disease along with non-specific symptoms like fatigue, malaise and weakness. Diagnosis is made by presence of haemolytic anaemia with positive direct antiglobulin test (DAT) and high titres of cold agglutinins in the blood.

Management of CAS includes non-pharmacological measures like avoiding cold exposure, warm clothing, and blood transfusion with in-line blood warmer in severe cases. No definite therapy has been established except treatment of the underlying disease[7]. CAS secondary to infection is generally self-limiting; however, corticosteroids have been used in CAS secondary to *Mycoplasma* and various other viral infections with varying success[8-10]. Definite evidence regarding benefit of steroids is lacking due to the rarity of this condition. We gave a short course of moderate dose prednisolone as the patient had severe symptomatic anaemia and a favourable outcome was observed. Thus, clinicians should be aware of this rare association, and Hepatitis A Virus screening should be done in suspected CAS cases.

References

1. Jäger U, Barcellini W, Broome CM *et al*. Diagnosis and treatment of autoimmune haemolytic anaemia in adults: Recommendations from the First International Consensus Meeting. *Blood Rev* 2020; 41: 100648.
2. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune haemolytic anaemia. *Blood Rev* 2012; 26: 107-15.
3. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood* 2013; 122: 1114-21.
4. Tibble JA, Ireland A, Duncan JR. Acute auto immune haemolytic anaemia secondary to hepatitis A infection. *Clin Lab Haematol* 1997; 19: 73-5.
5. Polat A, Inan M. Cold agglutinin disease after hepatitis A infection in a child. *J Pediatr Hematol Oncol* 2003; 25: 835.
6. Berentsen S. New Insights in the Pathogenesis and Therapy of Cold Agglutinin-Mediated Autoimmune Haemolytic Anaemia. *Front Immunol* 2020; 11: 590.
7. Berentsen S. Cold agglutinin disease. *Hematology Am Soc Hematol Educ Program* 2016; 2016: 226-31.
8. Chu CS, Braun SR, Yarbro JW, Hayden MR. Corticosteroid treatment of haemolytic anaemia associated with Mycoplasma pneumoniae pneumonia. *South Med J* 1990; 83: 1106-8.9.
9. Maekawa T. Corticosteroid therapy for haemolytic anaemia and respiratory failure due to Mycoplasma pneumoniae pneumonia. *Intern Med* 2002; 41: 229-32.
10. Walia H, Jain R, Bansal RK, Gupta GN. Cold agglutinin disease with erythrophagocytosis by neutrophils occurring during recovery phase of chickenpox. *J Lab Physicians* 2013; 5: 146-7.