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Case Report

Cold agglutinin mediated autoimmune hemolytic anemia due to acute cytomegalovirus infection in an immunocompetent adult

Ajay Asranna [a], *Ajit Kumar* [a,*], *Pranita* [b], *Atul Goel* [b]

[a] *Post Graduate Institute of Medical Education and Research, Dr. Ram Manohar Lohia Hospital, New Delhi, India*
[b] *Lady Hardinge Medical College, Faculty of Medical Sciences, University of Delphi, India*

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ABSTRACT

Introduction: A case of cold agglutinin syndrome due to cytomegalovirus infection is being reported.
Aim: To learn rare manifestation of cytomegalovirus (CMV) infection.
Case study: Though CMV infections are not very rare in immunocompetent individuals, CMV leading to hemolytic anemia is a rare phenomenon. We report a case of cold agglutinin mediated autoimmune hemolytic anemia (AIHA) in one such patient due to CMV infection. He recovered fully without receiving steroids or antiviral therapy.
Results and discussion: Cold agglutinin mediated AIHA accounts for 7%–25% of all causes of AIHA. The most common infections include Epstein–Barr virus and *Mycoplasma pneumoniae*. CMV is associated with cold agglutinin mediated hemolytic anemia predominantly in immunosuppressed individuals and children. A number of studies have indicated that CMV infection in the immunocompetent host may be more common than previously thought. It can present itself in many ways but AIHA is rare. We present this case for its rarity.
Conclusions: CMV may also cause serious manifestations in an immunocompetent patient.

1. Introduction

Cytomegalovirus (CMV) infection is associated with serious systemic manifestations in immunosuppressed individuals. It is generally accepted that CMV infection rarely causes systemic illness in an immunocompetent person. However, recent reports indicate that such manifestations may not be as rare as previously thought.[1–3]

Cold hemolytic anemia accounts for a significant percentage of autoimmune hemolytic anemias (AIHAs). It may be caused by lymphoproliferative diseases, infections or may be idiopathic. The most common infectious agents are Epstein–

* *Corresponding author at*: U/248, 1st Floor, Shakarpur, New Delhi 110092, India. Tel.: +91 7763084855.
E-mail address: toajitkr@gmail.com (A. Kumar).

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Barr virus (EBV) and *Mycoplasma pneumoniae*. CMV infections causing cold agglutinin hemolytic anemia are rare and mostly seen in children, in immunocompromised states such as HIV and post-transplant patients. Hemolytic anemia due to acute CMV infection in immunocompetent persons is a rare phenomenon.

2. Aim

We report a case of acute CMV infection leading to cold agglutinin mediated AIHA in a 55-year-old man with no obvious evidence of immunosuppression.

3. Case study

A 55-year-old man presented to us in February 2012 with complaints of asthenia and jaundice of about 15 days duration. He denied any history of fever, sore throat, rash or any other symptoms suggesting a prodromal illness. He had a history of smoking 5–10 cigarettes per day and regularly consumed alcohol for the past 25 years. No other significant past medical illness was present. There was no history of drug intake and he had received no medications previously. On examination he was noted to have a temperature of 38.3°C, jaundice and pedal edema. Systemic examination including the abdominal, respiratory, cardiovascular and the central nervous system was normal.

A complete blood count revealed severe anemia (4.4 g/dL) and thrombocytopenia ($20 \times 10^3/\mu L$). The complete report is mentioned in Table 1. The corrected reticulocyte count was 7.3%. The peripheral smear showed moderate anisopoikilocytosis with many normocytic, normochromic cells, macro-ovalocytes and occasional spherocytes. Red cell agglutinates and clumps of variable size were seen. No malarial parasites were seen. Liver function test revealed primarily indirect hyperbilirubinemia (total bilirubin – 5.6 mg/dL, indirect bilirubin – 4 mg/dL). AST, ALT and ALP levels were normal. Serum LDH was 5591 IU/L. Serum electrolytes, iron profile, lipid profile, serum B12 and folate levels were normal. Serum samples for HIV, Hepatitis A, B, C and E, malaria antigen tests and anti-nuclear antibody were negative. A diagnosis of hemolytic anemia was considered and cause of hemolysis investigated. Repeated blood samples in EDTA vials were found to have agglutination in the hematology lab. Hence samples were collected in pre-warmed syringes. Cold agglutinin titers and monospecific Coomb's test were also done. Cold antibodies were identified which were IgM in nature with anti I specificity at a titer of 1:256. Thermal amplitude was between 4°C and 22°C. Direct Coomb's test was positive with C3d component. The patient was diagnosed with cold agglutinin mediated AIHA. Bone marrow aspiration was done to exclude lympho-proliferative causes and was found to be normal. Heterophile antibody tests were negative. Serology for mycoplasma, EBV, rubella and HSV were negative. Serology for CMV was positive for IgM and negative for IgG indicating evidence for current exposure to CMV. Ultrasonography of the abdomen revealed a fatty liver and mild ascites.

Table 1 – Investigations of the patient.

Test	Result
Hemoglobin	4.4 g/dL
Total leukocyte count	$11 \times 10^3/\mu L$
Polymorphs	58
Lymphocytes	40
Eosinophils	2
Monocytes	0
Platelets	$20 \times 10^3/\mu L$
MCV	107.8 fL
MCH	99.8 pg
MCHC	92.5 g/dL
Reticulocyte count (C)	7.3%
Total bilirubin	5.6 mg/dL
Direct bilirubin	1.6 mg/dL
Indirect bilirubin	4 mg/dL
SGOT	26 U/L
SGPT	33 U/L
ALP	135 U/L
GGT	8 U/L
Sodium	140 meq/L
Potassium	4.8 meq/L
LDH	5591 U/L
Urine microscopy	Normal
Coomb's test – direct	Positive (C3d)
Coomb's test – indirect	Negative
Malaria antigen	Negative
HIV	Negative
Cold antibody titer	Anti I (IgM), 1:256
Anti HAV antibody	Negative
Hbs antigen	Negative
Anti HCV antibody	Negative
Anti HEV antibody	Negative
ANA	Negative
Heterophile antibody	Negative
CMV serology – IgM	Positive
CMV serology – IgG	Negative
Rubella serology	Negative

The patient was given packed cell transfusions. He was then closely monitored clinically and hematologically. No glucocorticoids were given. There was a gradual improvement in the hematological parameters over the next 2 weeks. He was discharged on folic acid and advised to avoid cold exposure. On follow up, he is asymptomatic; his hemoglobin and platelet counts are currently normal with no evidence of agglutination or hemolysis.

4. Results and discussion

Cold agglutinin mediated AIHA accounts for 7%–25% of all causes of AIHA. It usually results due to the production of IgM antibodies against the I/i antigens on the RBC. Lymphoproliferative diseases lead to a monoclonal expansion of cold antibodies while infectious causes result in a polyclonal expansion. The most common infections include Epstein–Barr virus and *Mycoplasma pneumoniae*. CMV is associated with cold agglutinin mediated hemolytic anemia predominantly in immunosuppressed individuals and children. CMV leading to hemolytic anemia in immunocompetent individuals is a rare phenomenon. According to a review of literature done by

Taglietti et al.[4] only 12 such cases have been published between 1980 and 2008. Among the 12 cases reported in the literature, the Coomb's test was positive in 4, negative in 3, and was not specified for the remaining 5 patients. Therefore hemolysis in CMV may have other mechanisms apart from immune-mediated destruction of RBCs.

The cold antibody titers in patients with hemolytic anemia are usually very high at about 1:1000 or higher. High titers of cold agglutinins with high thermal amplitudes approaching body temperature are associated with greater chances of hemolysis. Further, a low titer of cold antibody may be seen after CMV infections, which usually does not result in hemolysis. In our patient, agglutination and hemolysis were observed despite a moderately high titer and relatively low thermal amplitude. The cause of this is unclear. Cold exposure may play a role in the degree of agglutination. The patient's illness in fact coincided with the coldest days of the winter with minimum temperatures being as low as 4°C. Thrombocytopenia in our patient could be attributed to CMV infection.[5]

A number of studies have indicated that CMV infection in the immunocompetent host may be more common than previously thought.[1–3] Rafailidis et al.[1] described 214 immunocompetent patients with severe CMV infections. Among them 25 were found to have hematological disorders including symptomatic thrombocytopenia, hemolytic anemia, disseminated intravascular coagulation, myelodysplastic changes, pancytopenia, and splenic rupture.

Finally, the treatment of CMV induced hemolytic anemia is not entirely clear. While some experts opine that glucocorticoids are justified in severe anemia, others favor a ''wait and watch'' policy. Gavazzi et al.[6] and Van Spronsen et al.[7] used i.v. gancyclovir to treat hemolytic anemia. The prognosis was found to be favorable in all cases, including those patients who did not receive steroids and/or antiviral therapy. This was the case with our patient too, who recovered fully without receiving steroids or antiviral therapy. Thus, it may well be a self-limiting illness where the only treatment needed might be blood transfusions to tide over the hemolytic crisis.

5. Conclusions

CMV infections may cause serious illness in the immunocompetent person too. Patients with cold hemolytic anemia should be investigated for CMV. Cold hemolytic anemia due to CMV is mostly a self-limiting disease, where full recovery is possible despite patients not receiving steroids/antivirals.

Conflict of interest

None declared.

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