ISSN: 2349-9141

Available online at http://www.ijirr.com

International Journal of Information Research and Review
Vol. 2, Issue, 08, pp. 1008-1010, August, 2015

OPEN ACCESS JOURNAL

Full Length Case Report

"COLD AGGLUTININS – A CLUE TO DIAGNOSIS?"

[1,*]Dr. Yashovardhan, A., [2]Dr. Anusha, D.R. and [3]Mr. Naveeth, S.K.

[1,3]Department of Transfusion Medicine, Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India
[2]Department of General Medicine, Narayana Medical College and Hospital, Nellore Andhra Pradesh, India

***Corresponding Author**

Received 19th July 2015; Published 31st August 2015

Abstract

Cold agglutinin disease (CAD) is a subgroup of autoimmune hemolytic anemia (AIHA). This is usually associated with cold reactive autoantibodies. Acute form of CAD is attributed to infectious or autoimmune disease and chronic form to lymphoproliferative disease. In this paper, we report a case of secondary CAD due to Mycoplasma pneumonia in a 34 year old female patient. Cold antibody test and direct coombs' test were positive. The patient was treated accordingly and get relieved from the symptoms. The specific problems that occur in the blood bank or laboratory due to cold agglutinins need to be kept in mind for the accurate diagnosis and treatment of the patient.

Keywords: Cold Agglutinins, Mycoplasma Pneumoinae, Autoagglutination.

To cite this paper: Dr. Yashovardhan, A., Dr. Anusha, D.R. and Mr. Naveeth, S.K. *2015.* "Cold agglutinins – a clue to diagnosis?", *International Journal of Information Research and Review.* Vol. 2, Issue, 08, pp. 1008-1010, August, 2015.

INTRODUCTION

Autoimmune hemolytic anemia represents a group of disorders in which presence of autoantibodies directed against self antigens leads to red blood cells (RBCs) destruction and ultimately decreased red cell survival (Sonani *et al*., 2013). AIHAs are divided into warm and cold autoantibody types based on temperatures at which antibodies are maximally react with red cells in vitro (Duffy, 2009). The entities which are included in the cold antibody group are chronic cold agglutinin disease (CAD), acute antibody mediated AIHA complicating mycoplasma pneumoniae or viral infections and paroxysmal cold hemoglobinuria (Berentsen *et al*., 2001).

Case Report

A 34 year female patient presented to out-patient of our hospital, with complaints of throat pain associated with fever, mild breathlessness and vomitings. There was no family history of similar complaints and her past and personal histories were normal. On general physical examination, the patient appeared ill and there were no significant findings on further examination. Blood pressure, pulse rate and respiratory rate were within normal limits. Temperature was slightly elevated (100.2 F). Bilateral crepitations heard on chest auscultation. Other findings on physical examination were unremarkable. Due patient condition she was transferred to inpatient department.

Her biochemical and haematological investigations were normal. X-ray chest was normal, but HRCT showed multiple small nodular lesions in both lungs, few shown tree in bud appearance likely infective. Smear for grams staining, sputum for culture and sensitivity were normal. Bronchial washings for cytology, AFB, culture and sensitivity were normal. The patient tested negative for HIV, hepatitis, malaria, typhoid, rickettsia and brucella infections. As a part of routine investigation patient sample send to Transfusion Medicine department for grouping. Forward grouping in tube showed AB positive, but weak agglutination with anti-A antisera. Macroscopically visible autoagglutiation was noted in the tube containing the anticoagulated sample (Fig 1.). Forward grouping was again performed by tube method after proper washing of cells with warm saline showed no reaction with anti-A antisera, but 4+ reaction was noted with anti-B, anti-AB, anti-D antisera and group was B positive. Revere grouping showed reaction with A cells i.e. B group was confirmed. The direct coombs' test was positive.

To solve discrepancy, autocontrols were incubated at various temperatures. Patient serum and patient cells were incubated at 4^0C, 18^0C, 22^0C at room temperature and at 37^0C in a incubator for a period of 30min. The autocontrol at 4^0C showed 4+ reaction, at 18^0C showed weaker reaction but no reaction noted in the tubes incubated at 22^0C and 37^0C. This confirms the presence of cold autoantibodies in patient.

Fig. 1. EDTA tube showing autoagglutination of blood

The titration of cold antibodies did by double dilution technique and the titer was 1 in 64 shows the benign nature of antibodies. For confirmation of antibody specificity, tested the patient serum with O positive cord and adult red cells. The patient serum showed 4+ reaction with adult and no reaction with cord red cells, when incubated the tubes at 4^0C for period of 30min. This confirms the anti-I specificity. Based on the patient clinical condition and initial lab reports we tested the patient sample for antibody against mycoplasma pneumoniae antigen, which was strongly positive. Based on the characteristics discussed in the preceding paragraphs and available literature, a diagnosis of secondary benign cold agglutinin disease due to mycoplasma pneumoniae infection was made. Patient was treated with suitable antibiotics (Macrolides – Azithromycin) after which the patient recuperated and this phenomenon didn't reappear. Fever subsided; patient improved and was discharged in good health after ten days.

DISCUSSION

The incidence of AIHA is estimated to be approximately 1:100,000 in adults. Among these, warm–reactive antibodies are responsible for 87% of the cases and cold reactive antibodies are responsible for 13% of the cases (Powers and Silberstein, 2008). Cold agglutinins (CAs) were first described by Landsteiner in 1903 (Lodi *et al*., 2010). The association of cold haemagglutination with haemolysis was described in 1937 by Rosenthal and Corten (Berentsen *et al*., 2007). In the 1950s, Schubothe coined the term CAD. Primary or idiopathic CAD is typically an affliction of older adults with a peak incidence at around 70 years of age and both sexes are affected, with a slight female predominance (Neff, 2003). Secondary CAD occurs in transient and chronic forms. Transient form occurs with mycoplasma pnumoniae or infectious mononucleiosis, primarily affecting adolescents or young adults. Chronic cold hemagglutinin disease (CCHAD) usually affects persons older than 50 years of age.

Majority have no underlying disease, remainder have lymphoproliferative disorders including CLL, hairy cell leukemia, lymphoma (Duffy, 2009). Cold reactive auto antibodies may be benign or pathologic depending primarily on the thermal reactivity of these antibodies. Benign cold autoantibodies are often seen in healthy adults, are reactive below 22^0C and have a titer of less than 64. Pathologic cold antibodies have a higher thermal amplitude and manifest either as a CCHAD or as an acute transient hemolytic anemia as seen in association with respiratory tract infections (Basu *et al*., 2009). Cold agglutinins are IgM autoantibodies, at sites of lower temperature these react with red cells and bind C1. Only single molecule of IgM is required to bind C1 and initiate the activation of classic complement pathway.C1 sequentially activates C4 and C2, which bind to the red cell and form C3 convertase enzyme complex. As the blood returns to the warmer temperature within the body, cold agglutinin dissociates from the red cell membrane, but complement activation continues (Duffy, 2009). Regulatory proteins convert the red cell bound C3 and C4 to C3d, C3dg and C4d. It is the anti-C3d component of polyspecific AHG (anti-C3d and anti-IgG) that accounts for the positive DAT and the indirect coombs' test was negative, which was seen in our case. Mycoplasma pneumonia infections are often asymptomatic; multiple organ systems can be affected. Respiratory tract involvement and extra-pulmonary complications in cold agglutinin disease manifest in 3%-10% (Clyde, 1993) and 25% patients respectively and autoimmune reactions supposedly play a role in their pathogenesis (Waites and Talkington, 2004). Antibody mediated hemolysis supposedly caused by the formation of cold agglutinins in 10% patients with Mycoplasma pneumonia infections (Salam, 2004). In mycoplasma infections the autoagglutinins is usually polyclonal IgM with anti-I specificity. Most individuals predominantly express 'I' on their mature red cells, but rarely express 'i' antigen. At birth, cord (neonatal) red cells express large amounts of 'i' antigen, 18 months after birth, the proportion of 'i' antigen decreases and expression of 'I' increases (Duffy, 2009).

The reactivity of the patient's serum with autologous cells, adult group 'O' cells showed that the antibodies were most reactive at 4^0C. Reactivity was also present at 18^0C but decreased at warmer temperature and disappeared at 22^0C and 37^0C. The patient's serum doesn't show any reaction with cord group 'O' red cells at 4, 18, 22 and 37^0C (Table 1). The titer of antibodies was 64. In addition there was evidence of recently acquired mycoplasma pneumonia infection (positive IgM for M.pneumonia). The clinical (fever, breathlessness) and laboratory findings points towards diagnosis of secondary beningn cold agglutinin disease due to mycoplasma pneumonia infection.

Table 1. Reactivity of patient serum with autologous cells, adult and cord group O red cells

Test phase	Autologous cells	Group 'O' adult cells	Group 'O' cord cells
Saline 4^0C	4+	4+	0
Saline 18^0C	1-2+	1-2+	0
Saline 22^0C	0	0	0
Saline 37^0C	0	0	0

In our case the work up for cold agglutinins helped in making the diagnosis and alteration of patient treatment accordingly and finally patient recovered and discharged after 10 days of admission. Our case highlights the fact that the cold agglutinins indirectly helpful for the diagnosis of underlying pathological condition. Hence the laboratory personnel aware of this entity so that timely diagnosis can be made and further worsening of patient condition should be avoided and appropriate treatment can be given.

REFERENCES

Basu S, Saifudeen A, Kaur P. Transient cold agglutinin disease with mycoplasma infection. J Assoc Physcians India 2009; 57: 653-4.

Berentsen, S., Beiske, K. and Tjonnfjord, G.E. 2007. Primary chronic cold agglutinin disease: An update on the pathogenesis, clinical features and therapy. *Haematology*, 12: 361-70.

Berentsen, S., Beiske, K. and Tjonnford, G.E. 2001. Primary chronic cold agglutinin disease: An update on the pathogenesis, clinical features and therapy. *Haematology*, 12: 361-70.

Clyde, W.A. Jr. 1993. Clinical overview of typical Mycoplasma Pneumonia infections. *Clin. Infect. Dis*.,17: S32-6

Duffy, T.P. 2009. Autoimmune hemolytic anemia and paroxysmal nocturnal hemoglobinuria. In: Simon TL, Synder EL, Solheim BG, Stowell CP, Strauss RG, Petrides M, editors. Rossi's principles of transfusion medicine. 4th ed. AABB: Wiley-Blackwell, 321-31.

Lodi, G., Resca, D. and Reverberi, R. 2010. Fatal cold agglutinin haemolytic anaemia: a case report. *J. Med. Case Reports,* 4: 252.

Neff, T.A. 2003. Autoimmune Haemolytic Anaemias. In: Greer JP, Foerster J, Lukens JN, editors. Wintrobe's Clinical Haematology. 11th ed. Philadelphia: Lippincott Williams and Wilkins 1157-82.

Powers, A. and Silberstein, L.E. 2008. Autoimmune Haemolytic Anaemia. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Silberstein LE, McGlave P, Heslop H, editors. Hematology: Basic Principles and Practice. 5th ed. Philadelphia: Churchill Livingstone, 645-67.

Salam, A. 2004. Acquired immune hemolytic anemias. Therapeuticische Umschau 61: 178-86.

Sonani, R., Bhatnagar, N. and Maitrey, G. 2013. Autoimmune hemolytic anemia in a patient with Malaria. *Asian. J. Transfus Sci*., 7: 151-2.

Waites, K.B. and Talkington, D.F. 2004. Mycoplasma Pneumonia and its role as a human pathogen. *Clin. Microbiol Rev.,* 17: 697-728

****