

Mycoplasma pneumoniae Associated with Severe Autoimmune Hemolytic Anemia: Case Report and Literature Review

Fahmi Yousef Khan and Mohamed A.yassin

Department of Medicine of Hamad General Hospital; Doha-Qatar

We report a case of severe hemolytic anemia following *Mycoplasma pneumoniae* infection in a 29-year-old male patient who was treated with azithromycin. Direct Coombs' test was strongly positive and the cold agglutinin titer was high, with anti-I specificity. Antimycoplasma antibody titer by complement fixation was high 1:10,240. The patient was discharged after 12 days of hospitalization in good health. He remains clinically well with no recurrence of jaundice.

Key-Words: *Mycoplasma pneumoniae*, hemolytic anemia, leucocytosis, cold agglutinins.

Mycoplasma pneumoniae infections are often asymptomatic but can involve multiple organ systems. Respiratory tract involvement is generally benign, though 3 to 10% of patients develop clinical pneumonia [1,2]. Twenty-five percent of the patients develop extra-pulmonary complications, involving the central nervous system as well as the cardiovascular, gastrointestinal, and hematological systems; these extrapulmonary complications may present before, during, after, or in the absence of pulmonary signs, with autoimmune reactions thought to play a role in their pathogenesis [3]. Formation of cold agglutinins is frequently observed during *Mycoplasma pneumoniae* infections. Cold agglutinins were presumed to cause antibody mediated hemolysis in 10% of the patients [4]. Nevertheless, severe hemolysis is exceptional [5,6]. We report a case of severe autoimmune hemolytic anemia secondary to *Mycoplasma pneumoniae* infection in a 29-year-old man. The importance of reporting this case is to highlight the spectrum of multiple organ involvement in *Mycoplasma pneumoniae* infections that can be missed by busy doctors or interns.

Case Report

A 29-year-old male patient was admitted to the hospital with an eight-day history of fever and productive cough, followed by jaundice and passing dark urine for three days. The patient was previously healthy and was not using any drugs. There was no family history of hemolytic attacks. Upon physical examination, the patient appeared ill, febrile, dyspneic with yellowish discoloration of the sclera. Blood pressure was 110/60 mmHg, pulse rate was 110/minute and temperature 39.8°C. Chest examination showed bilateral basal crepitations. The rest of the examination was unremarkable.

Initial investigations showed a hemoglobin level of 6.3 g/dL, mean cell volume (MCV) 94 fL (normal MCV can be

explained by early occurrence of hemolysis), total leukocyte count 43,100/mm³, with 74.6% neutrophils, 15% lymphocytes, 9% monocytes, platelets 738,000/mm³, and erythrocyte sedimentation rate (ESR) 75 mm/hour. A peripheral blood film showed marked leucocytosis and agglutination (Figures 1 and 2). Chest X-ray showed bilateral basal opacities. Reticulocyte count was 3.4%. Lactate dehydrogenase (LDH) was 2,758 U/liter (normal 240-480). Haptoglobin was < 5.8 mg/dL (normal 27-139). Total bilirubin was 64 µmol/L (normal 3.5-24), of which 20.2 µmol/L was direct (normal 0-7). Other blood chemistry, liver profile, and coagulations studies were within normal limits. Malaria parasite smear was negative, urine dipstick and microscopy were normal. A tuberculin skin test was negative. Blood culture, urine analysis, urine culture, and *Brucella* serology were negative. Hepatitis A IgM antibodies, hepatitis C antibody, hepatitis B markers and antibodies to human immunodeficiency virus were likewise negative. The patient was transfused two units of packed red cells, after which his hemoglobin increased to 8.5 gm/dL. Based on this information, the following diagnoses were considered: acute intravascular hemolysis complications from an *M. pneumoniae* infection, hemolytic uremic syndrome and leukemia. The patient was treated for community-acquired pneumonia, and was started on 2 g ceftriaxon once daily intravenously, plus azithromycin 500 mg once daily orally. Hemolytic anemia work up was initiated. G6PD deficiency was not found. Serum vitamin B12, red blood cell folate and hemoglobin electrophoresis all gave results within normal limits. Direct Coombs' test was strongly positive and cold agglutinin titer was high, with anti-I specificity. A bone marrow biopsy was performed in order to rule out the possibility of an underlying leukemia. It revealed increased erythropoiesis, but no changes indicative of a hematological malignancy.

An acute hemolysis complicating an *M. pneumoniae* infection then seemed the most likely diagnosis, and this was later confirmed serologically. Antimycoplasma antibody titer by complement fixation was high 1:10,240. Ceftriaxon was stopped and azithromycin continued for five days. The patient responded well, fever subsided and hemoglobin reached 10.3 gm/dL, while the leukocyte count declined to normal values. The patient was discharged in good health after a 12-day hospital stay. Six months later, he remains clinically well, with no recurrence of jaundice.

Received on 31 August 2008; revised 7 January 2009.

Address for correspondence: Dr.Fahmi Yousef Khan. Attending physician, Department of Medicine. Hamad General Hospital. P.O.Box: 3050. Doha-Qatar. E-mail: fakhnqal@yahoo.co.uk. Phone: 0974 5275989. Fax: 0974 4879228.

The Brazilian Journal of Infectious Diseases 2009;13(1):77-79.
© 2009 by The Brazilian Journal of Infectious Diseases and Contexto Publishing. All rights reserved.

Figure 1. Peripheral blood smear showing red cell agglutination. (Wright stain x 1,000)

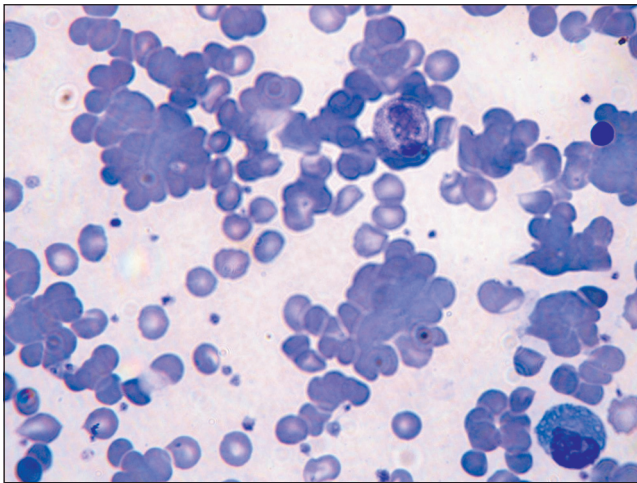
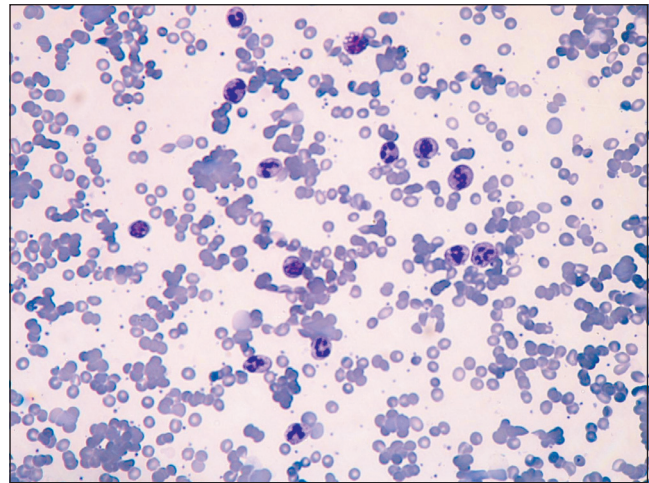


Figure 2. Peripheral blood smear showing red cell agglutination. (Wright stain x 400)



Discussion

Cold antibody hemolytic anemia (CAHA) is classified as primary (idiopathic) or secondary. In most cases, CAHA is a primary disorder that typically becomes apparent at 50 to 60 years of age. Cold antibody hemolytic anemia may also occur as a secondary disorder in association with a number of different underlying disorders, such as certain infectious diseases (e.g., mycoplasma infection and infectious mononucleosis) and lymphoproliferative diseases (e.g., non-Hodgkin's lymphoma and chronic lymphocytic leukemia) [7,8].

Extrapulmonary complications may present before, during, after, or in the absence of pulmonary signs. An increase in cold agglutinin titers is frequently observed during *M. pneumoniae* infection; it has been reported that 50%-60% of these patients had cold agglutinins [9,10], which appear one week after the onset of the illness and decline toward undetectable levels after two to six weeks [5]. Cold agglutinins appear to be more specific for I antigen of the red blood cell surface and often result in mild, subclinical hemolysis and mild reticulocytosis. Severe hemolytic anemia is rare and is usually associated with marked pulmonary involvement [11]. In 90% of such patients, cold agglutinin disease is mediated by an IgM molecule [12]. Six days after pulmonary signs, our patient developed severe hemolysis, which required blood transfusion.

Although post *M. pneumoniae* infection CAHA is known to be an autoimmune disorder, its underlying cause is not fully understood. It has been suggested that antibodies are directed against the I antigen, which is present on the surface of both erythrocytes and ciliated cells of the bronchial epithelium. In the latter site, it is contained in long-chain sialooligosaccharides that serve as receptors for *M. pneumoniae*. The induction of cold agglutinins may be triggered by the formation of mycoplasma-receptor complexes, in which the lipid-rich mycoplasma surface plays the role of an adjuvant [5].

The phagocytic and other destructive cells of the immune system do not have receptors for IgM as they do for IgG and IgA. Thus, since cold agglutinins are usually IgM, destruction of RBCs is primarily complement-mediated, occurring either by direct destruction of the membrane (direct lysis) or immunoadherence mediated by target-bound components (indirect lysis) [12,13]. Both of these processes are relatively inefficient in the absence of exposure to cold.

Typical laboratory features common to all forms of extravascular hemolysis include indirect hyperbilirubinemia and increased concentration of lactate dehydrogenase, whereas the hallmarks of intravascular hemolysis include a decrease in the serum level of haptoglobin and an increase in plasma-free hemoglobin [14]. The coincidence of elevated serum levels of lactate dehydrogenase and bilirubin with low levels of haptoglobin is common in hemolytic anemia caused by cold agglutinins [5]. Our patient showed both features of extra- and intravascular hemolysis.

Clues to the diagnosis of cold agglutinin disease include acrocyanosis and Raynaud's phenomenon. Moreover, autoagglutination on the peripheral blood film, which disappears on warming the blood sample, suggests a cold antibody.

Diagnosis of CAHA is based on a positive direct Coombs test in the presence of cold agglutinins.

The organism is fastidious and difficult to grow in culture. Therefore, diagnosis of mycoplasma infection is usually confirmed with serological tests or polymerase chain reaction-gene amplification techniques. In our patient, the diagnosis of post *M. pneumoniae* pneumonia CAHA was based on the high antimycoplasma antibody titer (1:10,240) and a positive direct Coomb's test in the presence of cold agglutinins.

Post *M. pneumoniae* pneumonia CAHA is usually self-limiting and most patients recover with supportive care [14,15]. Antibiotics are likely to be of limited value in mycoplasma-associated hemolytic anemia [5]; however, treatment of the

underlying mycoplasma infection has been associated with more rapid resolution of the hemolytic process [14]. Furthermore, in the setting of an autoimmune hemolytic anemia, packed red blood cell transfusions can potentiate hemolysis, and their use should be limited [13]. Although the evidence is weak, the risk of transfusion-related hemolysis could be reduced by using an in-line blood warmer at 37°C and keeping the patient warm [14,15]. Our patient was treated with azithromycin and was transfused two units of packed red cells.

The use of intravenous immunoglobulin for post mycoplasma pneumoniae infection CAHA reportedly has been successful in inhibiting hemolysis until spontaneous clearance of the IgM antibodies occurs [16,17]. Corticosteroids, alkylating agents, azathioprine, interferon, and purine nucleoside analogues are widely used to treat primary CAHA [14]. However, corticosteroids, plasmapheresis and cytotoxic drugs are of doubtful value in secondary CAHA, but may be tried in refractory cases.

In conclusion, a wide variety of complications may occur in patients with *M. pneumoniae* infection, CAHA is one of these complications that should be considered in any patient presenting with pneumonia and hemolysis; treatment of this condition needs supportive care and antibiotics. Corticosteroids, plasmapheresis and cytotoxic drugs are of doubtful value, but may be tried in refractory cases.

References

- Clyde W.A. Jr. Clinical overview of typical *Mycoplasma pneumoniae* infections. *Clin Infect Dis* **1993**;17 Suppl 1:S32-6.
- Foy H.M. Infections caused by *Mycoplasma pneumoniae* and possible carrier state in different populations of patients. *Clin Infect Dis* **1993**;17 Suppl 1:S37-S46.
- Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. *Clin Microbiol Rev* **2004**;17(4):697-728.
- Salama A. Acquired immune hemolytic anemias. *Ther Umsch.* **2004**;61(2):178-86.
- Daxbock F., Zedtwitz-Hiebenstein K., Burgmann H., et al. Severe haemolytic anaemia and excessive leukocytosis masking *Mycoplasma pneumoniae*. *Ann Hematol* **2001**;80(3):180-2.
- Feizi T., Loveless R.W. Carbohydrate recognition by *Mycoplasma pneumoniae* and pathologic consequences. *Am J Respir Crit Care Med* **1996**;154(4 Pt 2):S133-6.
- Gehrs B.C., Friedberg R.C. Autoimmune hemolytic anemia. *Am J Hematol* **2002**;69(4):258-71.
- Sokol R.J., Hewitt S., Stamps B.K. Autoimmune hemolysis: An 18-year study of 865 cases referred to a regional transfusion centre. *Br Med J* **1981**;282(6281):2023-7.
- Ali N.J., Sillis M., Andrews B.E., et al. The clinical spectrum and diagnosis of *Mycoplasma pneumoniae* infection. *Q J Med* **1986**;58(227):241-51.
- Hosker H.S., Tam J.S., Chan C.H., et al. *Mycoplasma pneumoniae* infection in Hong Kong –clinical and epidemiological features during an epidemic. *Respiration* **1993**;60(4):237-40.
- Cherry J.D., Ching N. *Mycoplasma* and ureaplasma infections. In: Feigin RD, Cherry JD, eds. *Textbook of Paediatric Infectious Diseases*, Vol. 2, 3rd edn. Philadelphia, PA: Saunders, **2004**; 2516-31.
- Evans R.S., Turner E., Bingham M., et al. Chronic hemolytic anemia due to cold agglutinins. II. The role of C' in red cell destruction. *J Clin Invest* **1968**;47(4):691-701.
- Logue G.L., Rosse W.F., Gockerman J.P. Measurement of the third component of complement bound to red blood cells in patients with the cold agglutinin syndrome. *J Clin Invest* **1973**; 52(2):493-501.
- Gertz M.A. Cold hemolytic syndrome. *Hematology Am Soc Hematol Educ Program* **2006**:19-23.
- Gehrs B.C., Friedberg R.C. Autoimmune hemolytic anemia. *Am J Hematol* **2002**;69(4):258-71.
- Hoppe B., Gaedicke G., Kiesewetter H., Salama A.R. Response to intravenous immunoglobulin G in an infant with immunoglobulin A-associated autoimmune haemolytic anaemia. *Vox Sang* **2004**;86(2):151-3.
- Wang J.L., Ho M.Y., Shen E.Y. *Mycoplasma pneumoniae* infection associated with hemolytic anemia: report of one case. *Acta Paediatr Taiwan* **2004**;45(5):293-5.