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CASE REPORT

Autoimmune hemolytic anemia and acute kidney injury associated with *Mycoplasma pneumoniae* infection

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Abstract

Mycoplasma pneumoniae is a common respiratory pathogen responsible for a variety of infectious manifestations ranging from an infection of the upper airways to severe atypical pneumonia and extrapulmonary manifestations in association or in the absence of respiratory symptoms, such as autoimmune hemolytic anemia and acute kidney injury. Cryoagglutinins formation is often observed during these infections featuring cold agglutinin disease. There are some reports of severe cold agglutinin disease associated with infection by *Mycoplasma pneumoniae.* We report the case of a child with severe case of autoimmune hemolytic anemia and acute kidney injury associated with *Mycoplasma pneumoniae infection.*

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INTRODUCTION

Mycoplasma pneumoniae is a common respiratory pathogen responsible for a variety of infectious manifestations, ranging from upper airway infection to severe atypical pneumonia. Children under the age of 5 usually present with upper airway symptoms; progression to pneumonia is relatively uncommon[1].

Extrapulmonary presentations associated with infection by *M. pneumoniae* include hematological, dermatological, neurological, musculoskeletal, renal, cardiac, and gastrointestinal manifestations. These manifestations are infrequent and may be present before, during, after, or in the absence of respiratory symptoms[2]. Hematological complications include hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura, and hemophagocytosis and are related to cross-reaction of antibodies[1,3].

Formation of cold agglutinins is frequently observed during these infections, and can emerge 1 week after the start of symptoms, reducing to undetectable levels in around 2 - 6 weeks. In a presumed 10% of cases, antibody-mediated hemolysis occurs; severe hemolysis is rare[4]. We describe here a case of severe autoimmune hemolytic anemia and acute kidney injury associated with *M. pneumoniae* infection.

CASE REPORT

A 3-year-old white male patient was admitted in July 2015 due to abdominal pain, dark urine, oligoanuria, vomiting, and pallor for 2 days. On admission, he was conscious, oriented, pale, anicteric, and had generalized edema (weight gain of 5 kg). He had a history of dry cough and rhinorrhea, self-limited, in the previous week. There was no personal or family history of kidney or hematological disorders.

Physical examination revealed no organomegaly or other abnormal findings. Complementary tests showed hemoglobin, 4.6 g/dL; mean corpuscular volume (MCV), 80 fL; total leukocyte count, 7.0 × 10^9/L (62% neutrophils); platelet count, 96 × 10^9/L; and reticulocytes, 0.6%. Total bilirubin was 1.57 mg/dL, whose indirect fraction was 1.08 mg/dL; lactate dehydrogenase, 1,709 IU/L; serum creatinine, 2.8 mg/dL; and urea, 178 mg/dL.

Urinalysis showed hemoglobinuria (+++), bilirubinuria (+), and proteinuria (+++); protein in 24-h urine was 72 mg/kg/24 h. Peripheral blood smear showed anisocytosis and spherocytes, with negative schistocytes test. Transfusion of red blood cells was indicated; the pre-transfusion direct antiglobulin test (Coombs - DAT) was positive (polyspecific reagent), and the cold agglutinin test was positive in low titers (1:1).

Despite the transfusion with compatible crossmatch, the patient evolved with worsening of anemia and hemoglobinuria. A dissociation of the hemoglobin/hematocrit ratio was observed in a new blood test, and agglutination of red blood cells was observed in smear test. The patient also presented with worsening of renal function, requiring renal replacement therapy with hemodialysis for 4 days. A myelogram was performed to rule out underlying onco-hematological diseases, which revealed normocellular bone marrow with erythroblastic hyperplasia; other analyses were normal.

Pulse therapy with methylprednisolone was initiated; after 3 days, it was replaced by oral prednisolone and the transfusions were suspended. Three days later, the patient presented with a new hemolytic crisis (3.6 g Hb/dL). He received intravenous immunoglobulin (IVIG) and transfusion of red blood cells in aliquots, from a compatible crossmatch, without complications. He presented with progressive improvement in anemia and thrombocytopenia.

Serology (ELISA) for *M. pneumoniae* was positive for IgM. Renal biopsy revealed lesions consistent with evolving acute tubular necrosis, absence of immune complex deposits in immunofluorescence, and normal glomeruli. The patient tolerated weaning of corticosteroid therapy, and 6 months after discharge, he is clinically well, with normal renal function and without anemia.

DISCUSSION

This study reports a pediatric case of infection by *M. pneumoniae* presenting as a severe autoimmune hemolytic anemia associated with acute kidney injury. In this case, the respiratory symptoms were restricted to dry cough and self-limited hyaline rhinorrhea. After the positive DAT, associated with the presence of cold agglutinins in plasma and signs of *in vitro* hemagglutination, infection by *M. pneumoniae* was suspected, and the diagnosis was subsequently confirmed by positive serology for IgM antibodies (ELISA).

The diagnosis of autoimmune hemolytic anemia is usually established based on evidence of hemolysis and positive DAT, with antibodies or complements bound to the surface of red blood cells.[4,5] Spherocytosis may be present as a result of cell injury[4].

Cold-reactive antibodies occur in approximately 25% of autoimmune hemolytic anemias, which are subdivided into primary chronic cold agglutinin disease, cold agglutinin disease secondary to infections or malignancies, and paroxysmal cold hemoglobinuria. Cold agglutinin disease is characterized by IgM autoantibodies capable of agglutinating erythrocytes at temperatures below that of the body, inducing complement activation, which leads to hemolysis[6,7].

Hemolytic anemia secondary to *M. pneumoniae* mediated by cold antibodies is described in adults, associated with aggressive therapeutic approaches. On the other hand, most previous studies indicate that anemia has a self-limiting course in children[5,8,9]. Evidence of subclinical hemolytic anemia is present in most patients with *M. pneumoniae*; nonetheless, severe hemolysis is extremely rare and is usually associated with severe pulmonary impairment[4]. The present patient did not have severe lung symptoms but developed a severe

hemolytic picture that required transfusion support. A similar case was described by Kurugol et al.[10].

Anemia can be more severe than is usually reported in textbooks and review articles. Swiecicki et al. described an incidence of 50% for need for transfusion support during the evolution of patients with cold agglutinin disease in their service[11]. Hemoglobinuria has been cited in at least 15% of the cases[11]; it is related to complement-mediated intravascular hemolysis mechanism in association with cold agglutinins.

In cold agglutinin disease, the complement is the only detected protein bound to red blood cells in most cases, as IgM antibodies dissociate from red blood cells at higher temperatures. Thus, the anti-C3d component of the polyspecific globulin (anti-IgG and anti-C3d) is responsible for the reactivity of the TAD[12], as shown in the present case.

The autoantibodies are polyclonal, usually against the erythrocyte I antigen. They appear during the course of infection and are responsible for the reaction to cold agglutinins[4]. Titers of cold agglutinins are elevated in half of adult patients infected with mycoplasma. In children, the accuracy of the test is unknown; its sensitivity and specificity are low[1,13]. In the present patient, cold agglutinins titration was low (1:1); however, the DAT was strongly positive. Moderate, transient thrombocytopenia was also observed.

Renal manifestations associated with mycoplasma infections are rare, and some cases have been reported in children. The clinical features include progressive glomerulonephritis, nephrotic syndrome, massive transient proteinuria, acute interstitial nephritis, cystitis, urethritis, isolated hematuria, chronic renal failure due to cold agglutinins, acute renal failure due to acute nephritis, and hemoglobinuria or hemolytic uremic syndrome; they may be related to an acute kidney infection or to the immune process itself[1,14].

Renal biopsy revealed lesions consistent with evolving acute tubular necrosis; absence of immune complex deposits in immunofluorescence, and normal glomeruli under common light microscope. Acute kidney injury is a well-recognized complication in other hemolytic diseases, such as paroxysmal nocturnal hemoglobinuria. In this case, the primary injury mechanism involved is a massive hemoglobinuria resulting from intravascular hemolysis, leading to acute tubular necrosis[15,16].

Hemoglobinuria is one of the main signs of excessive intravascular hemolysis. Anemia and reticulocytes are typical associated findings; biochemical changes include increased activity of lactate dehydrogenase, aspartate aminotransferase, and indirect hyperbilirubinemia[17], in addition to reduced haptoglobin. In the present case, however, it was shown that significant intravascular hemolysis can occur in patients with apparently normal laboratory findings, with the exception of anemia and elevated serum lactate dehydrogenase. The same findings were also demonstrated by Slack et al. in a case of cold paroxysmal hemoglobinuria and acute renal failure due to acute tubular necrosis[17].

There are no evidence-based therapies for secondary cold agglutinin diseases; prospective clinical trials do not exist, and current recommendations are based on case reports, clinical experiences, and theoretical considerations[6].

Most patients with mycoplasma-associated cold agglutinin disease recover with supportive care only. Transfusion of red blood cells should be limited since hemolysis will continue to occur[4,8]. The use of IVIG has been proven to be beneficial in inhibiting the process of hemolysis until spontaneous antibody *clearance* occurs[4,12].

Corticosteroids, alkylating agents, azathioprine, interferon, and purine nucleoside analogs are widely used for treatment of primary cold agglutinin disease[5,18]. Corticosteroids, cytotoxic drugs, and plasmapheresis are of questionable value in secondary disease but may be attempted in refractory cases[5].

There are limited data to suggest the benefit of antibiotic use in autoimmune hemolytic anemia associated with mycoplasma. A relevant therapeutic outcome is not expected, since the hemolytic process is related to an immune-mediated mechanism; however, the treatment of infection has been associated with a more rapid resolution of the hemolytic process in some cases[4,11,18].

The present patient did not receive antimicrobial therapy during evolution, even after confirmation of infection by serology, since he was asymptomatic. IVIG allowed for one last transfusion without major new hemolysis, and weaning of corticosteroid therapy was slow. Six months after discharge, the child was clinically well, with normal renal function and without anemia.

This case indicates the importance of considering extrapulmonary manifestations of mycoplasma infection even in the absence of pulmonary symptoms in cases of hemolytic anemias related to cold-reactive antibodies.

REFERENCE

1. Kashyap S, Sarkar M. Mycoplasma pneumonia: Clinical features and management. Lung India. 2010;27(2):75-85. DOI: http://dx.doi.org/10.4103/0970-2113.63611
2. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. Clin Microbiol Rev. 2004;17(4):697-728. DOI:http://dx.doi.org/10.1128/CMR.17.4.697-728.2004
3. Waites KB, Balish MF, Atkinson TP. New insights into the pathogenesis and detection of Mycoplasma pneumoniae infections. Future Microbiol. 2008;3(6):635-48. DOI: http://dx.doi.org/10.2217/17460913.3.6.635
4. Daxböck F, Zedtwitz-Liebenstein K, Burgmann H, Graninger W. Severe hemolytic anemia and excessive leukocytosis masking mycoplasma pneumonia. Ann Hematol. 2001;80(3):180-2. DOI: http://dx.doi.org/10.1007/s002770000250
5. Khan FY, A yassin M. Mycoplasma pneumoniae associated with severe autoimmune hemolytic anemia: case report and literature review. Braz J Infect Dis. 2009;13(1):77-9. DOI: http://dx.doi.org/10.1590/S1413-86702009000100018

6. Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. Blood Rev. 2012;26(3):107-15. DOI:http://dx.doi.org/10.1016/j.blre.2012.01.002
7. Berentsen S, Randen U, Tjønnfjord GE. Cold agglutinin-mediated autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015;29(3):455-71. DOI: http://dx.doi.org/10.1016/j.hoc.2015.01.002
8. Kottayam R, Rozenberg G, Cohn RJ. Unusual haematologic manifestations of Mycoplasma pneumoniae infection. J Paediatr Child Health. 2007;43(1-2):80-2. PMID: 17207061 DOI: http://dx.doi.org/10.1111/j.1440-1754.2007.01007.x
9. Unadkat R, Gurav M, Parikh R. Unusual manifestations of Mycoplasma pneumoniae infection in children. Pediatric Infect Dis. 2011;3(1):61-4.
10. Kurugol Z, Onen SS, Koturoglu G. Severe Hemolytic Anemia Associated with Mild Pneumonia Caused by Mycoplasma pneumonia. Case Rep Med. 2012;2012:649850. PMID: 23049568 DOI: http://dx.doi.org/10.1155/2012/649850
11. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood. 2013;122(7):1114-21. DOI: http://dx.doi.org/10.1182/blood-2013-02-474437
12. hrestha C, Min L, Mo Z. Cold agglutinin disease associated with mycoplasma infection in an individual with type 2 diabetes: An atypical case. J Diabetes Mellitus. 2012;2(4):402-5. DOI: http://dx.doi.org/10.4236/jdm.2012.24062
13. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al.; Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53(7):e25-76. PMID: 21880587
14. Vervloet LA, Marguet C, Camargos PA. Infection by Mycoplasma pneumoniae and its importance as an etiological agent in childhood community--acquired pneumonias. Braz J Infect Dis. 2007;11(5):507-14. DOI: http://dx.doi.org/10.1590/S1413-86702007000500012
15. Wijewickrama ES, Gooneratne L, De Silva C, Lanarolle RL. Acute tubular necrosis in a patient with paroxysmal nocturnal hemoglobinuria. Saudi J Kidney Dis Transpl. 2013;24(1):105-8. DOI: http://dx.doi.org/10.4103/1319-2442.106302
16. Chow KM, Lai FM, Wang AY, Chan YL, Tang NL, Li PK. Reversible renal failure in paroxysmal nocturnal hemoglobinuria. Am J Kidney Dis. 2001;37(2):E17. PMID: 11157403 DOI: http://dx.doi.org/10.1053/ajkd.2001.21361
17. Slack SD, Laboi P, Howard MR, Waise AA. Delayed appearance of markers of intravascular haemolysis in a case of paroxysmal cold haemoglobinuria. Ann Clin Biochem. 2009;46(Pt 4):341-3. DOI: http://dx.doi.org/10.1258/acb.2009.008190
18. Gertz MA. Cold hemolytic syndrome. Hematology Am Soc Hematol Educ Program. 2006:19-23. PMID: 17124034 DOI:http://dx.doi.org/10.1182/asheducation-2006.1.19