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

Larissa Cristina Nascimento¹, Pollyana Cristina Bernardes Valize², Laura Silva Cardoso³, Andressa Cristine Nascimento⁴

**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.*
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. 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. Hematological complications include hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura, and hemophagocytosis and are related to cross-reaction of antibodies.

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. 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. Spherocytosis may be present as a result of cell injury.

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.

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. 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. 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 service11. Hemoglobinuria has been cited in at least 15% of the cases12; 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 TAD12, 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 agglutinins4. 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 low1-13. 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 itself14-16.

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 necrosis15,16.

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 hyperbilirubinemia17, 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 necrosis17.

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 considerations6.

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 occur4-6. The use of IVIG has been proven to be beneficial in inhibiting the process of hemolysis until spontaneous antibody clearance occurs4,9,12.

Corticosteroids, alkylating agents, azathioprine, interferon, and purine nucleoside analogs are widely used for treatment of primary cold agglutinin disease6,18. Corticosteroids, cytotoxic drugs, and plasmapheresis are of questionable value in secondary disease but may be attempted in refractory cases5.

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 cases4,11,18.

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


