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# *Mycoplasma pneumoniae* infection presenting as neutropenia, thrombocytopenia, and acute hepatitis in a child

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Extrapulmonary manifestations of *Mycoplasma pneumoniae* pneumonia are uncommon and include hematologic, gastrointestinal, musculoskeletal, dermatologic, and neurologic complications. We report a case of serologically-confirmed *M. pneumoniae* infection complicated by severe neutropenia, thrombocytopenia, and hepatitis. The presence of antiplatelet and antineutrophil antibodies suggested that these autoantibodies caused the cytopenias. The disease had an acute course and the patient recovered after steroid treatment. This case indicates that neutropenia, thrombocytopenia and hepatitis are possible clinical manifestations of *M. pneumoniae* infection.

**Key words:** Acute, hepatitis, *Mycoplasma pneumoniae*, neutropenia, thrombocytopenia

*Mycoplasma pneumoniae* infection of the upper respiratory tract is common in older children and young adults. The majority of *M. pneumoniae* infections are mild and may pass unnoticed. Although uncommon, a wide variety of complications may occur in patients with *M. pneumoniae* infection. Hemolytic anemia is the most common hematologic complication, and thrombocytopenia has also been reported [1,2]. The simultaneous development of acute hepatitis, neutropenia and thrombocytopenia due to *M. pneumoniae* infection is rare.

## Case Report

A well-nourished 4-year-old girl with an unremarkable medical history was admitted to a local hospital with the chief complaints of upper respiratory tract symptoms such as cough, runny nose and intermittent fever for 4 days. Icteric skin and sclerae developed just before admission. She had no recent history of insect bite. Complete cell counts were leukocyte count 8700/mm$^3$ (normal range, 5500 to 15500/mm$^3$) [42% neutrophils], hemoglobin 11.9 g/dL (normal range, 11.5 to 15.5 g/dL), and thrombocytopenia with platelet count of 27,000/mm$^3$ (normal range, 150,000 to 400,000/mm$^3$). Blood biochemistry revealed abnormal liver enzyme levels [aspartate aminotransferase (AST) 783 U/L (normal range, 15 to 55 U/L), alanine aminotransferase (ALT) 1123 U/L (normal range, 5 to 45 U/L), total bilirubin 10.7 mg/dL (normal range, 0.2 to 1.0 mg/dL) and direct bilirubin 8.7 mg/dL (normal range, 0 to 0.2 mg/dL)]. Anti-HAV IgM (hepatitis A virus immunoglobulin M), anti-HBc (hepatitis B core antigen) antibody and HBsAg (hepatitis B surface antigen) by enzyme immunoassay (EIA) were all negative. Acute non-A non-B hepatitis was impressed and she was discharged after liver function returned to normal without special treatment 1 week later.

At follow-up exam 2 weeks after discharge, numerous bruises were noted over the face and extremities, and she was transferred to our hospital. At admission, physical examination was unremarkable except for signs of petechiae and mild splenomegaly. Laboratory investigations revealed the following values: leukocytes 1880/mm$^3$ with absolute neutrophil count of 451/mm$^3$; hemoglobin 11.9 g/dL; and platelet count of 0/mm$^3$. Further laboratory results were as follows: AST 1131 U/L, ALT 998 U/L, total bilirubin 9.4 mg/dL, direct bilirubin 6.3 mg/dL, lactate dehydrogenase 1488 U/L (normal range, 150 to 500 U/L), and gamma-glutamyl transpeptidase (GGT) 172 U/L (normal range, 5 to 32 U/L). Clotting tests including prothrombin time and activated partial thromboplastin time were within normal ranges. Cultures of blood collected on admission did not grow a pathogen. Serum immunoglobulin and complement levels were normal. Direct Coombs' test

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with erythrocyte bound C3d was strongly positive although there was no significant drop of hemoglobin. Antiplatelet (solid phase red blood cell adherence assay) and antineutrophil antibodies (granulocyte immunofluoresence test) were also found during the hemolytic process. Serologic investigations were negative for hepatitis A, B, C, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus. IgM antibody against *M. pneumoniae* was found by EIA (Savyon® Diagnostics Ltd. SeroMP™ IgM kit, Ashdod, Israel). Chest roentgenogram revealed no abnormalities. The marrow aspirate revealed normal cellularity with hyperplasia of megakaryocytes and lymphocytes. No hemophagocytosis was found.

The patient received 1 unit of platelet concentrate on the first, second, and third day of hospitalization (day 1, 2, 3). A dose of intravenous immunoglobulin (IVIG) (2 g/kg) did not modify the blood cell count (day 5) and oral steroids 2 mg/kg per day were then administered for 2 weeks. Additional antibiotic therapy was not given because the patient's liver function and cytopenias had been improving spontaneously.

## Discussion

Extrapulmonary manifestations of *M. pneumoniae* pneumonia including hematologic, gastrointestinal, musculoskeletal, dermatologic, and neurologic complications are uncommon, with cases described as single reports or small series [3,4]. Elevated liver enzyme assays are frequently observed during *M. pneumoniae* infections. Squadrini et al [5] reported that 50% of patients presenting with serologically-confirmed *M. pneumoniae* disease showed evidence of hepatic disorder. The hepatic dysfunction in these patients was transitory and recovery of normal liver function correlated directly with the resolution of the mycoplasma respiratory disease. The pathogenesis of self-limiting hepatitis may be attributed to several factors, including: a) a direct cytolytic effect mediated by the infecting mycoplasma resulting in perinecrotic edema; b) an immunological, autoimmune disorder resulting from the production of heterophil antibodies; and c) the mitogenic properties of *M. pneumoniae* acting on lymphocytes playing a role in the development of complications involving target organs [6,7].

Various mechanisms for the pathogenesis of thrombocytopenia have been described or postulated. In a previously reported fatal case, bone marrow showed decreased numbers of megakaryocytes suggesting immune-mediated suppression of thrombocytopoiesis [2]. There have been 2 previous case reports of thrombocytopenia due to thrombotic thrombocytopenic purpura (TTP) in *M. pneumoniae* infection [8,9], and 1 previous case report of antibodies bound to the surface of platelets during the course of *M. pneumoniae* infection [10]. Specific antiplatelet antibodies could be found in our patient, suggesting that antibodies had become specifically associated with the platelet surface. The megakaryocyte numbers in our patient were also increased in the bone marrow aspirate, implying increased peripheral destruction. There was no clotting derangement or red cell fragmentation to suggest disseminated intravascular coagulation or TTP. The most likely explanation for thrombocytopenia in this case is increased peripheral destruction related to this autoantibody.

Another interesting feature in this patient was the low leukocyte count. The white blood cell count is normal in 75 to 90% of cases of *M. pneumoniae* infection. In unusually severe *M. pneumoniae* pneumonia, leukocytosis of 26,000 to 56,000/$mm^3$ has been recorded [11,12]. Leukopenia (less than 3800/$mm^3$) is rare [4]. The specific antineutrophil antibodies found in our patient suggest their contribution to the spectrum of clinical manifestations.

Because *M. pneumoniae* is an intracellular pathogen, culture systems are either not available or the techniques employed are costly or time-consuming. Until molecular techniques are standardized and widely available, diagnosis will depend upon serologic confirmation [13]. Petitjean et al [14] suggested that the IgM EIA serology test is a valuable tool for the early diagnosis of *M. pneumoniae* infections in children, as long as the EIA used is specific. In adults, the difficulty in interpretation of EIAs suggests that paired sera, combined with polymerase chain reaction detection in respiratory tract specimens collected on admission, should be required to ensure accurate diagnosis [14].

IVIGs are therapeutic preparations of normal human immunoglobulin obtained from pools of blood from more than 1000 healthy donors, and exert immunomodulatory effects in autoantibody-mediated and T-cell-mediated autoimmune disorders and systemic inflammatory diseases [15]. IVIG mechanisms of action in autoimmune diseases have been extensively analyzed during the last 15 years and include the following: (i) interaction of the IgG Fc fragment with Fc receptors on leucocytes and endothelial cells; (ii) interaction of infused IgG with complement proteins; (iii) monocyte and lymphocyte modulation of synthesis and release of

cytokines and cytokine antagonists; (iv) modulation of cell proliferation and reparation; (v) neutralization of circulating autoantibodies; (vi) selection of immune repertoires; and (vii) interaction with other cell-surface molecules on T and B lymphocytes [15].

Our patient presented with severe neutropenia, thrombocytopenia, and hepatitis. The presence of antiplatelet and antineutrophil antibodies as well as positive Coombs' test suggested that these autoantibodies caused the cytopenias. Before serological confirmation of *M. pneumoniae* infection in this patient, IVIG was used due to the life-threatening, low platelet count (platelet count 0/$mm^3$). Duru et al [16] compared the prognosis in 50 children with acute immune thrombocytopenic purpura who received IVIG, high-dose methylprednisolone, or no therapy. The prognosis was significantly better in patients treated with both IVIG and high-dose methylprednisolone than in untreated patients [16]. Godeau et al also suggested that IVIG and oral prednisone seems to be more effective than high-dose methylprednisolone and oral prednisone in adults with severe autoimmune thrombocytopenic purpura [17].

Although steroid treatment has been reported to be beneficial in some patients [18,19], no controlled study has been done to determine its value. Tetracycline and erythromycin are antibiotics with specific action against *M. pneumoniae* pneumonia. However, at the time hemolysis begins the pneumonia has nearly resolved, and *M. pneumoniae* is usually absent in the sputum. Hence, antibiotic use at this stage is of doubtful value.

This case shows that, even in the absence of marked clinical evidence of pneumonia, infection by *M. pneumoniae* should be considered as a possible underlying disease in a patient presenting with severe neutropenia, thrombocytopenia as well as acute hepatitis.

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