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Pancytopenia: A New Manifestation of *Mycoplasma pneumoniae*

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INTRODUCTION

Mycoplasma pneumoniae initially was identified in 1944 as the pleuro-pulmonary like organism found in the sputum of patients with primary atypical pneumonia.[1,2] It is a common pathogen responsible for upper and lower respiratory infections in young adults and school-aged children.[1,3-5] It usually has a self-limited course characterized by cough, headache, and fatigue.[6] Respiratory infections including bronchitis, bronchiolitis, community-acquired pneumonia, and tracheobronchiolitis are common presentations.[1,6,7]

Extrapulmonary manifestations have been described in 25% of *Mycoplasma pneumoniae* cases and they usually manifest in the presence or absence of lung infection.[2] The presence of multiple extrapulmonary manifestations is considered a poor prognostic factor. These manifestations include neurological, hematological, cardiac, gastrointestinal, or dermatologic findings.[1-3,5-9] Hematological manifestations include hemolytic anemia, thrombocytopenic purpura, and disseminated intravascular coagulation.[2] When accompanied by respiratory disease, extrapulmonary manifestations tend to occur three or more days after the onset of respiratory disease and may last up to three weeks after resolution of the respiratory illness.[1,2]

We describe the first known adult case of *Mycoplasma pneumoniae* presenting with pancytopenia.

CASE REPORT

A previously healthy 23-year-old Asian female presented during mid-winter with a ten-day history of diarrhea and fever. She denied any other symptoms except for occasional cough of clear sputum. Her blood pressure on admission was 90/54 mmHg and her temperature was 101.2°F. Her physical exam was unremarkable. The white blood cell count was 1.1 K/uL with an absolute neutrophil count of 940 K/uL and absolute lymphocyte count of 70 K/uL. Hemoglobin was 12 g/dl with mean corpuscular volume of 81.6 fL and platelet count 100 K/uL. Aspartate transaminase and alanine transaminase were elevated at 74 and 116 U/L, respectively. Erythrocyte sedimentation rate (ESR) was 23 mm/hr and C-reactive protein (CRP) was less than 0.5 mg/dL. A chest x-ray revealed bilateral infiltrates, greater on the right side. Cultures of blood and sputum also were negative.

Respiratory virus panel PCR for influenza A subtype H1 and H3, influenza B, RSV subtype A and B, adenovirus, rhinovirus, parainfluenza virus 1, 2, and 3, and human metapneumovirus were negative. Urine *streptococcus pneumoniae* and *legionella pneumophilia* group 1A and *Histoplasma* urine antigen were negative. Stool culture and studies for ova and parasites, occult blood, *clostridium difficile* toxin B PCR, *giardia* antigen, shiga toxin 1 and 2 also were negative. Direct Coombs test was positive with a low haptoglobin at 3 mg/dL (normal: 36 - 195), elevated lactate dehydrogenase at 680 U/L (normal: 98 - 192), elevated schistocyte count, and normal reticulocyte count indicative of autoimmune hemolytic anemia. Vitamin B12, iron panel, thyroid-stimulating hormone, and folate levels were insignificant. Ferritin level was elevated at 1528 ng/ml (normal: 11 - 307). Glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase level, and hemoglobin electrophoresis were normal. Disseminated intravascular coagulation (DIC) panel was negative.

Bone marrow aspirate revealed complete and nondysplastic erythroid and myeloid maturation; megakaryocytes were absent. Flow cytometry showed no increase in blasts and no immunophenotypic evidence of lymphoma. Leukemia flow panel was negative. Bone marrow karyotype had no clonal abnormality noted.

Mycoplasma pneumonia IgG and IgM levels were positive at 40,218 mg/dL and 1.23 mg/dL, respectively (reference range 0.00 to 1.09). *Chlamydia*, parvovirus B19, and hepatitis serology were negative. Polymerase chain reaction (PCR) was negative for other causes of autoimmune hemolytic anemia, such as cytomegalovirus, Epstein-Barr virus, in addition to HIV 1 and 2 antibodies.

Cerebrospinal fluid studies, including cell count, bacterial, acid-fast bacillus, viral and fungal culture, immunofixation, enterovirus, and herpes simplex virus PCR were negative. West Nile IgG and IgM antibodies, Venereal Disease Research Laboratory test, and cryptococcal antigen also were negative. C3 and C4 complement in blood were low. No blood parasites noted.

The patient was treated with 500 mg azithromycin for one day followed by 250 mg for four days. She showed improvement with resolution of symptoms, infiltrates, and neutropenia. A repeat complete blood count five days after completion of therapy revealed a white blood count of 5.7 K/uL, hemoglobin of 8.6 g/dl, and a platelet count of 192 K/uL.

DISCUSSION

Mycoplasma pneumoniae infections traditionally involve the respiratory tract, manifesting a wide variety of symptoms ranging from productive cough to severe pneumonia. Extrapulmonary manifestations involving almost all organ systems have been reported. Narita classified the pathogenesis of extrapulmonary manifestations into three categories that are not always mutually exclusive.[10] The direct type is mediated by inflammatory cytokine released locally by bacterial cell membrane. The indirect type is based on immune modulation and cross-reaction between human cells and bacterial cell components[10] where cross-reactivity of anti-*Mycoplasma pneumoniae* antibodies causes immune-mediated damage.[3] For instance, IgM autoantibodies directed against red blood cells have been proposed as the cause of cold-agglutinin hemolytic anemia. Moreover, central nervous system complications have been thought to result from autoantibodies against glucocerebrosidase.[7] Finally, the third type is a vascular occlusion where bacterium induces vasculitis and/or thrombosis.[10] The described extrapulmonary manifestations can be classified on the basis of the proposed pathogenesis as shown in Table 1.[11,12]

Table 1. Extrapulmonary manifestations classified by proposed mechanisms.

Extrapulmonary Manifestations	Direct Type	Indirect Type	Vascular Occlusion
Cardiovascular	• Endocarditis • Pericarditis	• Kawasaki Disease • Myocarditis	• Aortic Thrombus • Cardiac Thrombus
Dermatological		• Erythema Multiforme • Stevens-Johnsons Syndrome • Urticaria	
Digestive System	• Early Onset Hepatitis	• Late Onset Hepatitis	• Pancreatitis
Hematological/ Hematopoietic		• Autoimmune Hemolytic Anemia • Hemophagocytic Syndrome • Infectious Mononucleosis • Thrombocytopenic Purpura	• Disseminated Intravascular Coagulation • Splenic Infarct
Neurological	• Aseptic Meningitis • Early Onset Encephalitis	• Acute Cerebellar Ataxia • Guillain-Barre Syndrome • Late Onset Encephalitis	• Psychological Disorders • Striatal Necrosis • Stroke • Thalamic Necrosis

This report is the first known to describe pancytopenia in an adult as an extrapulmonary manifestation of *Mycoplasma pneumoniae* infection. Some cases reported leukocytosis with white blood cell count ranging from 26,000 to 56,000/mm^3 and rarely leukopenia with white count of 3,800/mm.[3,9,13,14] Some reports suggested a transient suppression of T-lymphocytes especially CD4+ T cells, and the immune system as a whole by unknown mechanisms.[1] Hemophagocytic lymphohistiocytosis (HLH) also was reported as a manifestation of *Mycoplasma*,[15] but the clinical presentation and bone marrow evaluation in our patient did not point to HLH.

The patient was of Chinese origin. Her last visit to Asia was a few months before presentation. *Mycoplasma* extrapulmonary infections from Asia have been reported, especially the southeast region. For instance, a similar case of mycoplasma pneumonia infection presenting with neutropenia, thrombocytopenia, and acute hepatitis was reported in a Taiwanese child in 2004,[13] but no cases have been reported in adults. Proposed ethnic differences may account for the differences in distribution and manifestations between the western communities and Southeast Asia; such as the presentation of Kawasaki disease, infectious mononucleosis, and *Mycoplasma* infection.[10] There might be a link between the ethnicity of this patient and her presentation with pancytopenia in the setting of *Mycoplasma* pulmonary infection. The underlying mechanism causing extrapulmonary manifestations and, in particular, bone marrow suppression needs to be elucidated further. Genetic and/or environmental factors might play a role in the clinical features of *Mycoplasma*. A few reports of *Mycoplasma* in HIV positive patients have been mentioned, however, no definite conclusion was reached concerning whether immunosuppression alters the incidence or severity of mycoplasma infection.[2]

Our patient received a five-day course of azithromycin and recovered. Supportive treatment also might be a reasonable approach, whereby antibiotics and steroids are given on individual basis.[1] Moreover, immune-modulatory therapeutics is entertained based on the hypothesis of an immune-mediated role in the pathogenesis of this infection.[2]

CONCLUSION

Despite the increasing knowledge about extrapulmonary manifestations of *Mycoplasma*, more research is needed in the areas of pathogenesis, epidemiological differences, host factors, and management. This case raised awareness and suspicion of possible *Mycoplasma pneumonia* infection in patients with bone marrow suppression and community acquired pneumonia especially in patients of Asian descent.

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