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Case Report

Mycoplasma pneumoiae Associated with Autoimmune Hemolytic Anemia in a Pediatric Patient: A Case Report and Literature Review

Sheila Eid[1], Elsy El Hayek[2], Peter Noun[3], Marise Feghaly[4], Chafic Abboud[4], Mohamad Farhat[5], Elias Al Skaff[6] and Desirée Feghaly[7]*

[1]MD, PGY3, Pediatric Resident Physician, Faculty of Medical Sciences, Lebanese University, Lebanon

[2]MD, PGY2, Pediatric Resident Physician, Faculty of Medical Sciences, Lebanese University, Lebanon

[3]MD, Associate Professor in Pediatrics and Pediatric Heamto-Oncology, Lebanon

[4]Med 4 Student, Faculty of Medical Sciences, Lebanese University, Lebanon

[5]MD, PGY5, Pediatric Hemato-Oncology Fellow Physician, Faculty of Medical Sciences, Lebanese University, Lebanon

[6]MD, PGY1, Pediatric Resident Physician, Faculty of Medical Sciences, Lebanese University, Lebanon

[7]MD, Associate Professor in Pediatrics, Lebanon

***Corresponding Author:** Desirée Feghaly, MD, Associate Professor in Pediatrics, Lebanon.

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Abstract

Introduction: Autoimmune hemolytic anemia is a rare encountred extrapulmonary manifestation of *Mycoplasma pneumonia*. In this article we discuss a case of severe hemolysis diagnosed and treated in 72 hours.

Case Description: 3 years old girl presenting for high grade fever, anorexia paleness and non productive cough of 10 days duration.

Discussion: In literature arround 10 cases of *M. pneumonia* inducing autoimmune hemolytic anemia are reported since 2012. Only one theory explaining why it is being more discovered is that laboratory tests are improving and physicians are having a greater index of suspicion for such infections.

Conclusion: Hemolysis associated with *M. pneumoniae* must be carefully investigated and diagnosed early for a better outcome. Early diagnosis and Treatment with immunomodulators can protect the patient from short and long-term complications.

Keywords: *Mycoplasma pneumoniae; Autoimmune Hemolytic Anemia; Pediatrics*

Introduction

M. pneumonie infections cause a mild self-limiting pneumonia. But extrapulmonary symptoms, although rare, include: hemolysis, rash (maculopapular or urticaria), arthralgia, glomerulonephritis, cardiac (conduction abnormalities, congestive heart failure, myocarditis, pericarditis), gastrointestinal (hepatitis, pancreatitis), and central nervous system (encephalitis, cerebellar ataxia, peripheral neuropathy, Guillain-Barré syndrome) manifestations. 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.

In rares circumstances *Mycoplasma pneumoniae* cause severe IgM mediated autoimmune hemolytic anemias. And treatement with corticotherapy and immunomodulators such as IVIG is useful in refractory cases.

In this article we present an exceptional case of IgG mediated hemolysis in addition to common IgM agglutinins associated with *Mycoplasma pneumoniae* infection. Patient was treated with IVIG and corticotherapy with excellent outcomes.

History and Presentation

A 3 years old previously healthy girl, with no prior hospitalization, presented to the emergency department of "Sacré-Coeur Hospital" for 10 days history of high-grade fever (reaching 40C, peaking every 4 hours, responding to antipyretics); associated with anorexia and mild diffuse abdominal pain (without alleviating or exacerbating factors, not associated with nausea or vomiting). The girl received cefixime for 5 days, prescribed by another outpatient clinic, for possible UTI, without any spacing of fever or clinical improvement; then productive cough started.

Upon presentation, patient was febrile and tachycardia (HR = 140); oxygen saturation was 93% on room air. On physical exam, the girl was pale, no jaundice. She was hypoactive. Lungs auscultation showed marked decreased air entry and crackles on the right side. Left lung air entry was normal and clear. The abdomen was soft and non-distended, but hepatomegaly and mild splenomegaly were noted. Examination was otherwise normal.

Diagnostic focus and assessment

In ER, a peripheral IV line was inserted, and hydration started urgently. Blood was drawn for hematologic and biochemical tests, with blood culture; results are shown in table 1. A urine sample was taken for analysis and was normal with no RBC. A chest X-Ray was also ordered, and showed right middle and inferior lobes consolidation, with bronchograms (Figure 1).

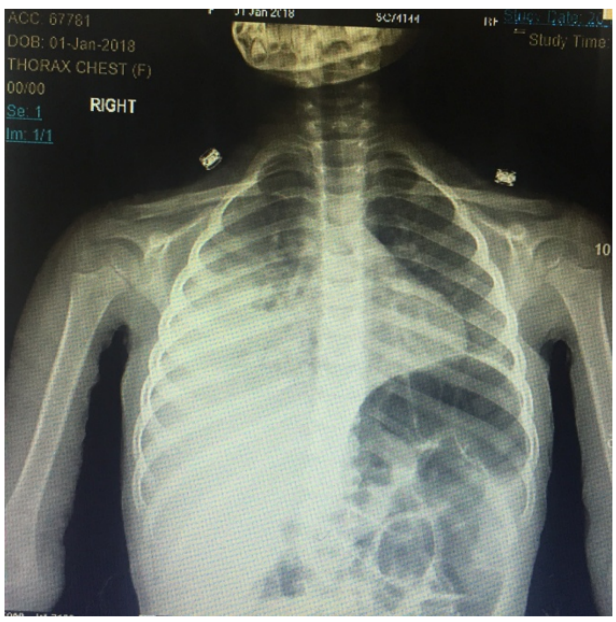

Figure 1: *Chest X-Ray upon presentation.*

Hematology		Units
WBCs	29 330 (high)	$x10^3/\mu L$
Hemoglobin	5.2 (low)	g/dL
MCV	96	fL
Platelet count	1.100.000 (high)	$x10^3/\mu L$
Neutrophils	76	%
Chemistry		
Creatinine	0.2	mg/dL
CRP	27.95 (high)	mg/dL
SGPT	10	U/L

Table 1: *Hematology and chemistry test results upon presentation.*

Therapeutic focus and assessment

The girl was started on intravenous ceftriaxone and teicoplanin for the severe pneumonia. Oxygen by nasal cannulae was applied to ameliorate the oxygen delivery to the tissues, in presence of the profound anemia. Anemia workup was taken and Packed RBCs (PRBCs) were ordered to be prepared and transfused.

During the preparation of PRBCs, the direct Coombs test was found to be positive to IgM and complement C3d, and markedly positive to IgG. Our patient was diagnosed to have autoimmune hemolytic anemia. Other anemia workup results are shown in table 2. Haptoglobin and electrophoresis were not available to be done at our institution.

Total Bilirubin	1 (normal)	mg/dL
Reticulocytes count	7 (high)	%
Peripheral smear	Anisocytosis, anisochromia, macrocytosis	
LDH	367 (normal)	U/L
Ferritin	2211 (High)	ng/mL
Iron	26 (normal)	µg/dL
Vitamin B12	2196 (high)	pmol/L
Folate	26.8 (normal)	nmol/L

Table 2: *Anemia workup done at day 1 of hospitalization.*

In the context of Positive direct Coombs test associated with pneumonia, cold agglutinins test and *Mycoplasma* serology (IgM) were done, and came back positive. So the diagnosis of right lobe pneumonia due to atypical bacteria (*Mycoplasma pneumoniae*), complicated by severe autoimmune hemolytic anemia, was done.

Clarithromycin was added to previous antibiotics regimen (dose: 15 mg/kg/day). One pack of blood was prepared to be transfused in case of a life-threatening issue.

Concerning the severe autoimmune hemolytic therapy, methylprednisolone was started at high dose (4 mg/kg/day) at day 2 of hospitalization. The hemoglobin continued to drop progressively and reached 4.5 at day 3 (Table 3).

IVIG were available on day 3 of hospitalization, and were given on 2 consecutive days for a total dose of 2 g/kg.

Follow up labs showed a progressive increase in hemoglobin post IVIG and steroids treatment (Table 3).

Simultaneously, WBCs and platelet count decreased progressively, while the infection was being treated by antibiotics.

Parameter	Day 1	Day 3 (*)	Day 4 (*)	Day 10
Hemoglobin	5.2	4.5	4.2	6.8
WBCs	29 330	20 500	18 420	13 790
Platelet count	1.098.00	1.176.00	1.060.000	438.000

Table 3: *Progression of hemoglobin level, WBCs number and platelet count over the hospitalization. (*) IVIg infusion.*

Discussion

Mycoplasma peumoniae is a short rod DNA bacterium, lacking a cell wall, and considered the smallest self-replicating prokaryote [1]. It is a fastidious bacterium requiring a special media for culture [2], and necessitates a long period of time in order to replicate. *M. peumoniae* is currently considered a frequent cause of community-acquired pneumonia; its incidence increases progressively with age. Transmission occurs from person to person by respiratory droplets. Incubation period ranges from 2 to 4 weeks [3].

The bacterium attaches to epithelial membranes, especially the respiratory tract epithelium, via adherence proteins, and an injury of the epithelial cells ensues. Activation of B lymphocytes and CD4+ T cells is the hallmark of the infection, and an inflammatory reaction is produced by the activation of inflammatory cytokines [4]. The antibodies produced against *M. pneumoniae* will crossreact with human red blood cells and brain cells; thus, acting as autoantibodies, and causing an autoimmune hemolytic anemia.

M. pneumonie can cause either an asymptomatic infection, or a gradual disease with symptoms such as headache, malaise, low-grade fever, and irritative cough. Other respiratory symptoms can also be found, such as rhinorrhea, pharyngitis, otalgia [5]. In general, it is a mild self-limiting pneumonia. Extrapulmonary symptoms, although rare, include: hemolysis, rash (maculopapular or urticaria), arthralgia, glomerulonephritis, cardiac (conduction abnormalities, congestive heart failure, myocarditis, pericarditis), gastrointestinal (hepatitis, pancreatitis), and central nervous system (encephalitis, cerebellar ataxia, peripheral neuropathy, Guillain-Barré syndrome) manifestations.

Concerning the diagnosis of *M. pneumoniae* infection, there are no specific clinical findings in order to differentiate it from other atypical pneumonia; although we note a more gradual onset of symptoms with a normal WBC count. Leukocytosis is reported in about one third of patients with a lower respiratory tract infection [6]. Erythrocyte sedimentation rate may be elevated [7]. If hemolysis is present, Coombs test will be positive, and reticulocyte count will be elevated. In general, a microbial diagnosis is not performed for patients presenting to outpatients clinics for community-acquired pneumonia. The bacterium lacks a cell wall; therefore, Gram staining and cultures are not useful for making the diagnosis [8]. Polymerase Chain Reaction (PCR) is the diagnostic test of choice, when available. Cold agglutinins test can also support the clinical diagnosis of *M. pneumoniae*; cold agglutinins are IgM antibodies produced 1 - 2 weeks after the primary infection, and present in about the half of cases [9]. Two theories are proposed: the first one is that they result - during the acute infection - from cross-reactive autoantibodies against the I antigen of erythrocytes; whereas the second one is that they result directly from an antigenic alteration of the erythrocytes [10]. It is impotant to notice that cold agglutinins are not specific for *M. pneumoniae*, they can be found in viral pneumonia or infectious mononucleosis due to EBV or CMV. Serologic tests (complement fixation, enzyme-linked immunoassay, immunochromatography, hemagglutination), showing either a four-fold increase in paired sera titers or a single titer of more than 1:32, are diagnostic of the infection [5].

The inflammatory response caused by *M. pneumoniae* may be manifested radiographically as diffuse and reticular infiltrates of bronchopneumonia, usually unilateral, in either perihilar regions or lower lobes; hilar adenopathy is often present. Bilateral involvement may be present in 20% of cases [11]. A lobar consolidation has been described in the litterature-as it was the case of our patient and the size of consolidation may exceed what would be expected (regarding the severity of symptoms) [12].

The treatment of *M. pneumoniae* is more effective when started within 3 - 4 days of symptoms onset. It includes macrolides, doxycycline, or fluoroquinolones [5]. The most frequently used one is azithromycin for 5 days. A 7- to 14-days course is recommended for doxycline or fluoroquinolones use. Macrolide resistance is being reported increasingly; therefore, if a patient fails to respond within the first 48h of macrolide therapy, it is important to shift toward the other antibiotics (doxycline or fluoroquinolones).

Currently, no vaccines are available for the prevention of *M. pneumoniae*. Still no recommendations are established for the prophylaxis against the infection, except for those at high risk for severe infections (sickle cell disease and immunodeficiency). The infected hospitalized patients should be placed on droplet precautions, until resolution of symptoms.

Mycoplasma pneumoniae infection associated with cold antibody hemolytic anemia is known to be an autoimmune disorder. In the case reported, IgG antibodies are moderatly positive in addition to IgM wich is exceptionnel with *Mycoplasma pneumoniae* infection; the underlying cause suggested is that antibodies are directed against the antigen of surfaces of RBC's and ciliated cells of bronchial epithelium. Also to be noted that both the age of presentation and the radiologic findings in this case are not the typical ones seen in most of the reported cases of *Mycoplasma pneumoniae*: the age is not in the school-age range, and the chest radiograph showed a unilateral infection upon presentation, not the typical bilateral presentation that is usually seen.

For treatment, first-line therapy starts with glucocorticoids: 2 to 6 mg/kg/day of methylprednisolone. The steroid response rate is usually high (up to 80%) within 24 to 72h after initiation. And it should be tapered slowly because abrupt discontinuation have been associated with disease relapse.

When the response to steroids in the acute setting is poor, as our case, or if clinically unstable within 24 - 48 hrs after steroid initiation, we proceed to the additional first-line treatment of ivIg (1 g/kg/day × 2 days).

In refractory cases, when hemoglobin has not been stabilized within 3 - 4 weeks post initiation of treatment, or when there is difficulty in weaning the child off steroids, second-line options include rituximab (anti-CD20 antibody), other immunosuppressive agents and finally splenectomy as last resort.

The case reported in this paper lightens the importance of early detection of dual antibodies IgM and IgG for early management by immunosuppresors and immunomodulators in severe hemolysis and critical patients.

Conclusion

Autoimmune hemolytic anemia associated with *Mycoplasma pneumoniae* infection is rarely described entity in literature, but it may be more frequently encountered than reported. Clinicians must have a high index of suspicion for autoimmune hemolytic anemia specially when both agglutinins IgG and IgM came positive. Early diagnosis and treatment will help to avoid severity of cases and will improve the outcomes.

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