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Fatal Mycoplasma Associated Cold Agglutinin-Mediated Acute Autoimmune Hemolytic Anemia

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Abstract

Background: Autoimmune hemolytic anemia (AIHA) is a known complication of various infections, the link between Mycoplasma infection and AIHA is relatively rare. This case emphasizes the importance of considering Mycoplasma as a potential trigger for AIHA, especially in patients presenting with progressive dyspnea, symptomatic anemia, and positive cold agglutinin test results. *Case Report*: A 72-year-old man was admitted to the hospital due to progressive dyspnea and symptomatic anemia. The patient had a history of mild anemia, indicating mild hemolysis, as evidenced by low haptoglobin and mildly elevated LDH levels on prior laboratory tests. Upon investigation, the patient's Coombs test revealed a positive result for anti-C3b/d, indicating the presence of cold agglutinin-mediated autoimmune hemolytic anemia. Additionally, Mycoplasma serology showed positive IgG results, confirming the presence of Mycoplasma infection-associated cold agglutinin syndrome (CAS). *Conclusion*: Early recognition and prompt initiation of targeted therapy are crucial to prevent disease progression and optimize patient outcomes in this rare and potentially life-threatening condition. Further research and awareness are warranted to improve the understanding and management of Mycoplasma-associated AIHA.

Keywords: Anemia, Cold Agglutinins, Dyspnea, Infections, Serology.

Introduction

Mycoplasma pneumoniae (M. pneumoniae) is a common bacterial pathogen that causes a wide range of symptoms and infections. It can cause both upper and lower respiratory tracts infections. The most common manifestation is tracheobronchitis, presenting with headache, coryza, and dry or mucopurulent productive cough [1]. This organism is also responsible for approximately 20-40% of community acquired bronchopneumonia in the general population during epidemics, up to 70% in closed populations [2]. Twenty-five percent of patients develop extra-pulmonary complications at variable durations after the onset of or even in the absence of respiratory illness [3]. These extra-pulmonary complications can involve central nervous, cardiovascular, renal, dermatological, and hematological systems [1]. The different mechanisms by which *M. pneumoniae* causes extra-pulmonary complications are cytokine mediated effects, autoimmunity or immune complexes, and vasculitis or thrombosis, as a result of cytokines and chemokines such as TNF- and IL-8 [4]. Hematological complications involve thrombocytopenia, thrombotic thrombocytopenic purpura, hemophagocytosis, and hemolytic anemia [5]. Hemolytic anemia associated with *M. pneumoniae* infection has been most commonly attributed to IgM cold agglutinins, whereby IgM autoantibodies attach to the I antigen on red blood cells causing mild hemolysis and rarely severe hemolytic anemia [6]. *M. pneumoniae* can also cause warm autoimmune hemolytic anemia, characterized by warm-reacting IgM antibodies, however it's a relatively rare complication with

an incidence ranging from 6-13%. [7]. On rare occasions, *M. pneumoniae* can be complicated by combined IgM cold agglutinins and IgG warm agglutinins hemolytic anemia [8]. Here we report a case of severe cold agglutinin mediated autoimmune hemolytic anemia induced by *M. pneumoniae* infection in a 72-year-old. We're reporting this case to emphasize the importance of early clinical recognition of the variable presentations of *M. pneumoniae* infection.

Case Report

A 72-year-old male with a medical history of atrial fibrillation, hypertension, hypothyroidism, and a previous diagnosis of bladder cancer treated with pembrolizumab, presented to the emergency department with worsening dyspnea. The patient also had a history of symptomatic bradycardia and underwent pacemaker placement, as well as surgical interventions for atrial septal defect and cleft mitral valve repair. Specifically, the mitral valve cleft was sutured, and the atrial septal defect was closed with a patch at the age of 30. However, the patient still had a residual ostium primum atrial septal defect. He was admitted to the cardiac care unit for management of acute heart failure exacerbation in the setting of congenital heart disease. He was initially treated with diuresis for management of the hypervolemia. His hospital course was complicated by worsening of dyspnea despite diuresis and hemodialysis/ultrafiltration, as well as worsening anemia. Laboratory tests were consistent with hemolysis with an indirect hyperbilirubinemia, elevated LDH level and low haptoglobin levels, as well as a positive coombs test (anti-C3b/d positive but anti-IgG negative). The patient continued to deteriorate hemodynamically with progressive cardiogenic shock in the setting of hemolysis and respiratory failure, eventually with a fatal outcome. Laboratory tests were positive for IgG mycoplasma, consistent with *M. pneumoniae* infection, and azithromycin was started, but the patient continued to deteriorate and died days later.

Throughout his hospital stay, his complete blood count showed anemia with a hemoglobin ranging between 6 to 8 (baseline hemoglobin from 6 months ago was ranging from 10 to 11.5 gm/dL). Chemistry profile was consistent with hyperbilirubinemia (total bilirubin 3.2 mg/dL with direct bilirubin 0.9 mg/dL), which was not present six months ago, elevated LDH 1,205 U/L (six months ago ranging from 300 to 400 U/L), and haptoglobin was less than 10 mg/dL. Direct Coombs anti-C3b/d was positive, but anti-IgG negative and peripheral blood smear was significant for presence of spherocytes. Furthermore, Mycoplasma IgM was negative but positive IgG. CT chest showed septal thickening.

The differential diagnosis includes IgG-cold autoimmune hemolytic anemia induced by *M. pneumoniae* infection, especially in the setting of dyspnea and respiratory failure despite diuresis and optimized heart failure management, as well as positive mycoplasma IgG and Coombs test suggesting autoimmune hemolytic anemia. Other diagnoses include Immune check point inhibitor induced hemolytic anemia, especially since a temporal association exists between initiating pembrolizumab and evidence of mild hemolysis in prior laboratory tests, but it does not explain the significant worsening in hemolysis. Furthermore, the Coombs test six months ago was negative, indicating a new onset autoimmune hemolytic anemia.

The patient received supportive blood transfusions and intravenous diuresis with loop diuretics. He was also started on hemodialysis and ultrafiltration as the kidney function was compromised. Azithromycin was started after laboratory tests were positive for Mycoplasma IgG. The patient was hospitalized for a one month in the hospital between the coronary care unit and general medical floor. His respiratory status and hemodynamics continued to deteriorate despite aggressive diuresis, antimicrobial therapy and corticosteroids. The ongoing hemolysis

exacerbated his underlying cardiac disease, which led to eventual cardiogenic shock and death. Hypoxic respiratory failure was presumed to be secondary to *M. pneumoniae* pneumonia, although respiratory sample PCR was not done.

Discussion

Autoimmune hemolytic anemia (AIHA) is a rare condition characterized by the destruction of red blood cells due to autoantibodies targeting the body's own erythrocytes [9]. AIHA can be triggered by various factors, including infections, medications, and systemic diseases. In this case, the patient presented with worsening dyspnea and was found to have severe AIHA in the setting of congenital heart disease and *M. pneumoniae* infection.

The patient's medical history was notable for atrial fibrillation, hypertension, hypothyroidism, and previous bladder cancer treated with pembrolizumab [10]. Pembrolizumab, an immune checkpoint inhibitor, has been associated with immune-related adverse events, including hematological abnormalities such as hemolytic anemia [11]. Although the patient had evidence of mild hemolysis in prior laboratory tests, the significant worsening of hemolysis and the negative Coombs test six months prior to presentation suggested a new onset of AIHA rather than pembrolizumab-induced hemolysis. Congenital heart disease further complicated the patient's clinical course. The surgical interventions for atrial septal defect and cleft mitral valve repair, along with the residual ostium primum atrial septal defect, contributed to the patient's underlying cardiac abnormalities. The presence of congenital heart disease likely increased the susceptibility to heart failure exacerbation and hemodynamic instability.

Laboratory findings in this case supported the diagnosis of AIHA. The patient exhibited anemia with a decline in hemoglobin levels compared to baseline, indirect hyperbilirubinemia, elevated lactate dehydrogenase (LDH) levels, and low haptoglobin levels [12]. The positive Coombs test (anti-C3b/d positive but anti-IgG negative) indicated immune-mediated destruction of red blood cells [13]. Additionally, the peripheral blood smear showed the presence of spherocytes, characteristic of hemolytic anemia [14]. *M. pneumoniae* infection played a significant role in this case. Laboratory tests confirmed the presence of Mycoplasma IgG, indicating a previous or current infection [15]. *M. pneumoniae* has been implicated in the development of AIHA, particularly through the production of cold agglutinins [16]. Cold agglutinins are autoantibodies that cause red blood cell agglutination and subsequent hemolysis at lower temperatures. The combination of *M. pneumoniae* infection and the patient's underlying autoimmune susceptibility likely contributed to the development of AIHA. Despite the initiation of appropriate treatment, including antimicrobial therapy, supportive blood transfusions, diuresis, and corticosteroids, the patient's condition continued to deteriorate. The ongoing hemolysis exacerbated his underlying cardiac disease, resulting in progressive cardiogenic shock and respiratory failure. The respiratory failure was presumed to be secondary to *M. pneumoniae* pneumonia, although respiratory sample polymerase chain reaction (PCR) was not performed.

This case highlights the diagnostic challenges associated with AIHA in the context of multiple comorbidities, including congenital heart disease and concurrent infections. The clinical presentation of dyspnea and worsening anemia, along with laboratory findings of hemolysis and positive Coombs test, raised suspicion for AIHA. Prompt recognition and appropriate management are essential, but the prognosis of AIHA in the setting of severe underlying cardiac disease and respiratory failure can be poor, as evidenced by the fatal outcome in this case.

Further research is warranted to better understand the pathophysiology of AIHA, particularly in relation to specific triggering factors such as infections. Improved diagnostic tools and therapeutic strategies are needed to optimize outcomes for patients with AIHA, especially in those with complex medical histories and concurrent conditions.

Conclusion

By reporting this case, we aim to raise awareness among clinicians regarding the potential hematological complications associated with *M. pneumoniae* infection. Timely recognition of these complications can facilitate early intervention, appropriate treatment, and improved patient outcomes.

Contributors: MAla was directly involved in the patient care of this patient; she obtained consent and collected the data used in this case reports. She also contributed in formulating the discussion and learning points in this article. MAle contributed to the literature review on this topic and writing of the background section, as well as contributing to the discussion and conclusions sections. MAla will act as a study guarantor. Both authors approved the final version of this manuscript and are responsible for all aspects of this study.
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