





Cryoagglutinin autoimmune hemolytic anemia secondary to *Mycoplasma pneumoniae* infection in patient with pernicious anemia: A case report

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ABSTRACT

This report describes the rare case of a patient with autoimmune hemolytic anemia due to cryoagglutinins secondary to *Mycoplasma pneumoniae* infection, coexisting with pernicious anemia. A 56-year-old man presented with a ten-day history of cough and mucocutaneous pallor. Laboratory studies revealed megaloblastic anemia with low vitamin B12 levels, positive antibodies against intrinsic factor and parietal cells, as well as hemolysis parameters and a positive direct Coombs test for complement (C3d) with cryoagglutinins active at low temperatures. *M. pneumoniae* infection was confirmed by indirect immunofluorescence for IgM and IgG. Intramuscular B complex supplementation and doxycycline were administered for 14 days, improving hemoglobin and other hematological parameters within four weeks. This case highlights the diagnostic complexity in patients with rare hemolytic anemias in the context of atypical infections and underscores the importance of a multidisciplinary approach for their diagnosis and appropriate treatment. The coexistence of cryoagglutinin-mediated autoimmune hemolytic anemia and pernicious anemia poses diagnostic and therapeutic challenges that are relevant to clinical practice.

KEYWORDS Autoimmune hemolytic anemia, pernicious anemia, *Mycoplasma pneumoniae*, case report

INTRODUCTION

Autoimmune hemolytic anemia accounts for approximately 5% of all anemias, with an incidence ranging from 0.4 to 2 per 100 000 individuals. It is characterized by antibody-mediated destruction of red blood cells [1]. There are two main types: 'warm' AIHA (IgG antibodies) and 'cold' or cold agglutinin AIHA (IgM antibodies), the latter with the ability to activate the complement system and induce intravascular hemolysis at low temperatures [2]. Cold agglutinin autoimmune hemolytic anemia is relatively rare, accounting for only 10 to 20% of cases, and is often associated with infections by pathogens such as *Mycoplasma pneumoniae*, Epstein-Barr, and cytomegalovirus, among others [3].

Pernicious anemia, on the other hand, is a form of megaloblastic anemia caused by autoimmune gastritis, characterized by the destruction of gastric parietal cells and impaired vitamin B12 absorption due to antibodies against intrinsic factor [4]. This condition presents with severe anemia and marked hematologic changes, with the diagnosis based on the identification of specific antibodies and the endoscopic confirmation of gastritis [5].

The aim of this report is to describe a rare case of cold agglutinin autoimmune hemolytic anemia secondary to *M. pneumoniae* infection in a patient with pernicious anemia. As both conditions are unusual and pose a significant diagnostic challenge, this case provides a systematic approach to the management and diagnosis of complex anemia in patients with atypical infections.

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CASE REPORT

A 56-year-old man, originally from Buenos Aires, working as an administrative employee, sedentary, and overweight, had no relevant medical history or family history of autoimmune diseases. The patient reported attending regular medical check-ups, the last being 6 months ago, which revealed no

MAIN MESSAGES

- We present a rare case of cold agglutinin autoimmune hemolytic anemia secondary to *Mycoplasma pneumoniae*, associated with pernicious anemia, an uncommon association in the literature.
- This report emphasizes the need for a systematic and comprehensive diagnostic approach in anemias with dual or multiple etiologies, to optimize management and prevent further complications in high-risk patients.
- The presence of mixed laboratory findings (megaloblastic and hemolytic patterns) along with a positive Coombs test should raise suspicion of concurrent pathogenic mechanisms in patients with severe anemia.
- Conservative management of severe anemia may be appropriate in cases of cold agglutinin autoimmune hemolytic anemia, provided the patient maintains hemodynamic stability.

remarkable findings. He presented with a persistent, non-productive cough lasting 10 days, with no other associated symptoms. The initial physical examination revealed mucocutaneous pallor without other pathological findings. Initial laboratory tests revealed severe anemia with findings consistent with megaloblastic anemia: hemoglobin of 6.3 g/dL, mean corpuscular volume (MCV) of 126 fL, and mean corpuscular hemoglobin concentration (MCHC) of 36.4 g/dL. The chest radiograph was normal.

In view of these findings, further diagnostic investigations were carried out. The reticulocyte count (adjusted for hematocrit) and the reticulocyte production index were both low (0.3%), suggesting ineffective erythropoiesis. Biochemical assessment revealed cobalamin deficiency (< 148 pg/mL) with normal folic acid levels and elevated homocysteine (16.73 μmol/L). The hemolysis tests were positive, with haptoglobin < 8 mg/dL, elevated lactate dehydrogenase (LDH) of 2444 U/L, and total bilirubin of 1.56 mg/dL (predominantly indirect). The direct Coombs test was strongly positive (4+) for complement (C3d), and the cold agglutinin test showed a titer of 1:256, with activation at 4°C and 22°C. The peripheral blood smear showed macrocytosis and hypersegmented neutrophils, findings compatible with megaloblastic anemia (Figure 1).

During hospitalization, the patient developed dizziness and tachycardia without hemodynamic decompensation and experienced a decrease in hemoglobin to 5.8 g/dL with an increase in LDH to 2770 U/L. Physical examination did not reveal lymphadenopathy, and abdominal ultrasound did not show organomegaly. Serological tests for hepatitis B and HIV were negative. Given the persistence of respiratory symptoms, a COVID-19 PCR test and a multiplex respiratory panel (adenovirus, metapneumovirus, rhinovirus, influenza A and B, parainfluenza, and respiratory syncytial virus) were negative, while indirect immunofluorescence for *Mycoplasma pneumoniae* was positive for IgM and IgG with a titer of 1:160.

To investigate the cause of megaloblastic anemia, tests for parietal cell antibody tests were ordered, which were positive at a titer of 1:80 and intrinsic factor antibodies at a value of 102 U. Upper gastrointestinal endoscopy revealed chronic gastritis with mild inflammatory activity and complete metaplasia of the gastric mucosa, without evidence of neoplasia, consistent with autoimmune gastritis.

Furthermore, a retrospective review of hematological tests performed two months earlier at another healthcare center revealed megaloblastic anemia with a hemoglobin of 9.9 g/dL, suggesting the presence of pernicious anemia before the acute hemolytic episode.

Treatment included intramuscular B-complex supplementation to optimize vitamin B12 absorption, initially at 1000 mcg daily for the first week, followed by weekly administration for the first month. For *M. pneumoniae* infection, the patient completed a 14-day course of doxycycline at 100 mg every 12 hours.

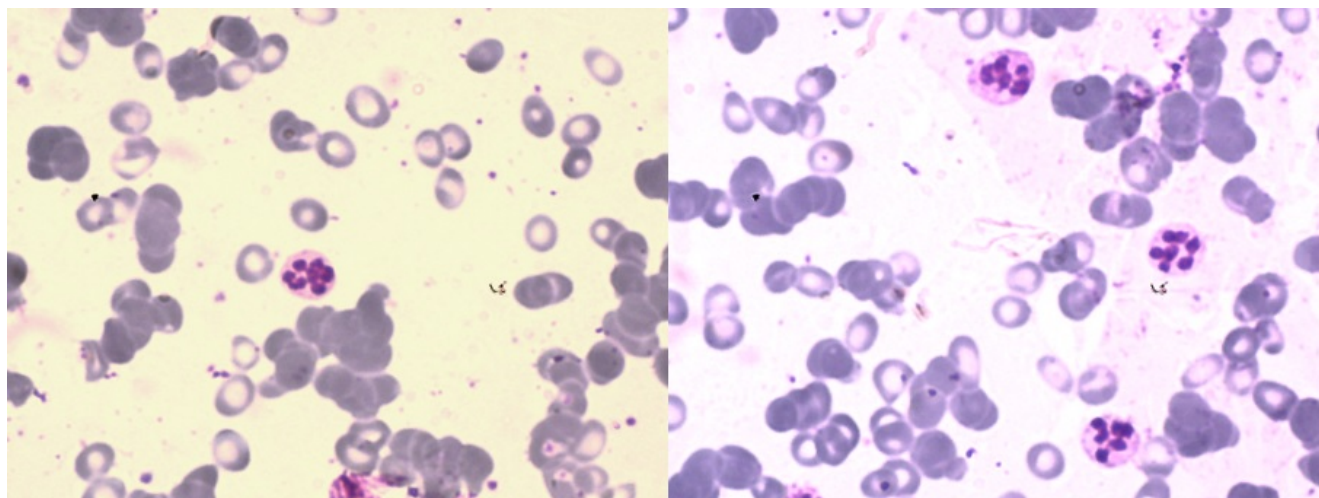
During hospitalization, the patient experienced episodes of dizziness and tachycardia, with a nadir hemoglobin of 5.8 g/dL. Despite the severity of anemia, the blood transfusion was withheld due to the maintained hemodynamic stability and concern for possible exacerbation of cryoagglutinin-mediated hemolysis. After four weeks, the patient showed a favorable clinical response with an increase in hemoglobin to 11.6 g/dL, a reticulocyte production index of 3.3%, and an improvement in hemolysis parameters (LDH of 210 U/L, haptoglobin of 84 mg/dL, and normalization of total and indirect bilirubin).

Throughout the diagnostic and therapeutic process, the patient appreciated the detailed approach and close follow-up and felt supported and well informed about each step of his treatment and recovery. Additionally, he perceived a favorable resolution of his symptoms with the treatment administered.

DISCUSSION

We report the case of a 56-year-old man with cold agglutinin AIHA secondary to infection by *M. pneumoniae* associated with pernicious anemia. The patient presented nonspecific symptoms of persistent cough and pallor, and laboratory investigations revealed megaloblastic anemia, active hemolysis, and a positive direct Coombs test for complement. After confirmation of *M. pneumoniae* infection and vitamin B12 deficiency, a diagnosis of coexisting pernicious anemia was made. Treatment with doxycycline and B-complex supplementation resulted in significant clinical and hematological improvement in four weeks. This case highlights the importance of differential diagnosis, as these conditions can share overlapping hematological characteristics such as indirect hyperbilirubinemia, low haptoglobin, and elevated LDH.

Figure 1. Peripheral blood smear showing hypersegmented neutrophils, macrocytic erythrocytes, and agglutination.



Source: Peripheral blood smear performed by the Hematology Department of the Hospital Universitario Austral, Buenos Aires, Argentina.

Pernicious anemia, responsible for vitamin B12 deficiency in this patient, was confirmed by the presence of intrinsic factor and parietal cell antibodies, as well as findings of autoimmune gastritis on upper gastrointestinal endoscopy. This diagnosis was crucial, as pernicious anemia can exacerbate hemolytic anemia by affecting effective erythropoiesis [3,5].

On the other hand, cold agglutinin autoimmune hemolytic anemia, especially when induced by *M. pneumoniae* infection, is a rare condition that poses significant diagnostic challenges, and its coexistence with pernicious anemia adds a layer of complexity, as seen in this case. Hemolysis associated with *M. pneumoniae* is mediated by cold agglutinins, IgM antibodies directed against the red cell I antigen, which also serves as a receptor in respiratory epithelial cells. This interaction between *M. pneumoniae* and the I antigen appears to trigger the production of autoantibodies that can induce intravascular hemolysis by activating complement at low temperatures [6,7]. A distinctive aspect of our case was the timing of presentation; in a similar case report, it is indicated that hemolysis typically occurred three weeks after the onset of respiratory symptoms, while in our case, the patient developed significant hemolysis during the acute phase of the infection [8]. This difference may be related to the underlying presence of pernicious anemia, which may have altered the patient's immune response.

From a pathophysiological perspective, vitamin B12 deficiency in pernicious anemia interferes with normal erythropoiesis and, in advanced cases, may result in ineffective erythropoiesis [5]. The coexistence of cold agglutinin autoimmune hemolytic anemia requires a comprehensive diagnostic approach to differentiate hemolytic anemia from megaloblastic anemia due to cobalamin deficiency [9]. In this patient, the combination of complex serological analysis and imaging studies contributed to the differential diagnosis and appropriate management of anemia.

This case highlights the importance of differential diagnosis, as these conditions can share overlapping hematological characteristics such as indirect hyperbilirubinemia, low haptoglobin, and elevated LDH. Differential diagnoses to consider include autoimmune hemolytic anemia secondary to other infections, such as Epstein-Barr virus, hemoglobinopathies such as sickle cell disease or thalassemia, and nutritional deficiencies, such as folate deficiency. Additionally, mechanical hemolytic anemias, such as microangiopathic hemolytic anemia, should be ruled out. A thorough clinical evaluation, including laboratory tests and serological analysis, is essential for accurate diagnosis and appropriate management.

Clinically, this case highlights the importance of systematic evaluation in patients with multifactorial anemia. The timely identification and appropriate treatment of both conditions, *M. pneumoniae* infection and pernicious anemia, improved hemoglobin levels and reduced hemolysis parameters in this patient. Furthermore, the doxycycline and vitamin B supplementation treatment proved effective in resolving the infection and restoring normal erythropoiesis. The decision to avoid blood transfusion despite severe anemia was based on the understanding of the pathophysiology of cold agglutinin autoimmune hemolytic anemia and the potential risk of exacerbating hemolysis.

Proper diagnosis of pernicious anemia is critical because it allows physicians to identify a potentially reversible cause of anemia and prevent long-term complications such as neurological damage. This is particularly important when pernicious anemia coexists with other conditions like cold agglutinin autoimmune hemolytic anemia, which may obscure the diagnosis and delay treatment. Early identification benefits the patient by improving clinical outcomes, reducing morbidity, and facilitating personalized management. For physicians, it streamlines the diagnostic process and ensures evidence-based care. Furthermore, distinguishing pernicious anemia from

other types of anemia, such as those caused by hemolysis or nutritional deficiencies, is essential to avoid mismanagement and unnecessary interventions.

Clinically, this case underscores the critical importance of early and accurate diagnosis of pernicious anemia, especially when coexisting with other conditions such as cold agglutinin autoimmune hemolytic anemia. Early recognition can prevent severe complications, guide appropriate management, and optimize outcomes. Understanding the clinical and care implications of pernicious anemia, along with its potential to exacerbate hemolytic anemia, highlights the need for a systematic and timely diagnostic approach.

The main strength of this report is the detailed description of a rare association between cold agglutinin autoimmune hemolytic anemia and pernicious anemia, providing evidence for the treatment of complex anemia in the context of infection. The main limitation was the lack of similar reports, which made a direct comparison difficult and limited the ability to contrast the therapeutic approach adopted in this case.

CONCLUSIONS

This case highlights the diagnostic and therapeutic challenges of cold agglutinin autoimmune hemolytic anemia secondary to *Mycoplasma pneumoniae* infection, particularly in the presence of pernicious anemia. The coexistence of these two conditions highlights the importance of a comprehensive evaluation in patients with anemia, particularly when active hemolysis is observed in addition to the hematological parameters consistent with megaloblastic anemia. The multidisciplinary approach taken in this case was instrumental in establishing an accurate diagnosis and an effective treatment plan, resulting in a favorable clinical outcome for the patient.

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Anemia hemolítica autoinmune por crioaglutininas secundaria a infección por *Mycoplasma pneumoniae* en paciente con anemia perniciosa: reporte de caso

RESUMEN

El presente reporte describe el caso infrecuente de un paciente con anemia hemolítica autoinmune por crioaglutininas secundaria a infección por *Mycoplasma pneumoniae*, coexistente con anemia perniciosa. Un hombre de 56 años se presentó con tos de diez días de evolución y palidez mucocutánea. Los estudios de laboratorio revelaron anemia megaloblástica con niveles bajos de vitamina B12, anticuerpos positivos contra factor intrínseco y células parietales, así como parámetros de hemólisis y una prueba de Coombs directa positiva por complemento (C3d) con crioaglutininas activas a bajas temperaturas. La infección por *M. pneumoniae* fue confirmada mediante inmunofluorescencia indirecta para IgM e IgG. Se administró suplementación con complejo B intramuscular y doxiciclina por 14 días, mejorando los valores de hemoglobina y del resto de los parámetros hematológicos en cuatro semanas. Este caso enfatiza la complejidad diagnóstica en pacientes con anemias hemolíticas poco comunes en el contexto de infecciones atípicas, y subraya la importancia de un enfoque multidisciplinario para su diagnóstico y tratamiento adecuado. La coexistencia de anemia hemolítica autoinmune por crioaglutininas y anemia perniciosa plantea desafíos diagnósticos y terapéuticos que son relevantes para la práctica clínica.



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