

Cold Agglutinin Urticaria Secondary to Mycoplasma Pneumoniae Infection in Childhood: A Case Report

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Abstract: This case report discusses a 13-year-old child presenting with bilateral middle-basal pneumonia attributed to Mycoplasma pneumoniae infection. Despite the absence of hemolysis, the patient exhibited symptoms consistent with cold agglutinin syndrome (CAS), including an erythematous-pomfoid urticaria-like rash. Laboratory analyses confirmed CAS with elevated cold agglutinin titers and a recent Mycoplasma pneumoniae infection. Treatment with clarithromycin resolved the pneumonia, and the rash spontaneously regressed. Additionally, hepatic steatosis was detected, likely associated with the patient's overweight status. This case highlights the importance of considering CAS in children with atypical symptoms following Mycoplasma pneumoniae infection.

Keywords: Cold agglutinin syndrome, Mycoplasma pneumoniae, Childhood, urticaria, Hemolytic anemia.

INTRODUCTION

Cold agglutinin syndrome (CAS) is a rare autoimmune disorder characterized by the presence of cold-reacting autoantibodies targeting red blood cells. While typically associated with hemolysis, CAS can present with varied clinical manifestations, including urticarial skin lesions. Here, we present a case of CAS secondary to Mycoplasma pneumoniae infection in a child, emphasizing the importance of recognizing atypical presentations of this syndrome. Mycoplasma Pneumoniae infection. This bacterium causes an intracellular infection and clinically atypical pneumonia. In atypical pneumonia, the patient is often in good general condition and can carry out his daily activities (walking pneumonia), presenting dry cough, low-grade fever, and signs of upper airway infection (sore throat, conjunctivitis, otitis) or symptoms like a viral infection (headache, muscle pain, skin rash) [1]. In the case described, acquired cold urticaria had to be considered. However, it was excluded based on laboratory results. Cold urticaria, the most common form of physical

urticaria, is characterized by skin hyperreactivity to cold exposure, resulting in painful, pruritic erythema that typically resolves within 24-48 hours. Unlike CAS, cold urticaria is diagnosed clinically via an ice cube test and does not involve cryoagglutinins or related hematological abnormalities. Familial (hereditary) and essential (acquired) forms exist, with the latter often linked to infections or autoimmune diseases [2].

METHODS

The patient was selected due to the rare and atypical presentation of CAS secondary to Mycoplasma pneumoniae infection without hemolysis, providing a unique opportunity to document and analyze this unusual clinical scenario. The child has been admitted to Messina Hospital, Sicily and we obtained consent from the parents.

CASE PRESENTATION

We report a case of a 13-year-old Italian child, who was admitted to our hospital with low-grade fever (37.5°C) and a two-week history of unproductive cough. Physical examination and chest X-ray revealed bilateral middle-basal pneumonia. Laboratory analyses were unremarkable, except for markedly elevated C-reactive protein (CRP) which was 15 times the norm.

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Serologies for various infectious agents, including Mycoplasma pneumoniae and Chlamydia Pneumoniae as well as Epstein-Barr virus, cytomegalovirus, Varicella zoster virus, human immunodeficiency virus (HIV1-2), Parvovirus B19, Hepatitis virus (A -B -C -E) were conducted and ruled out recent infections. Consequently, the patient was started on a course of amoxicillin-clavulanate antibiotic for 10 days. Despite becoming afebrile within a few days, he experienced increasing asthenia. Subsequent laboratory analysis revealed persistent elevation of CRP, accompanied by a decrease in hemoglobin, hematocrit and red blood cells count, while mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were increased (Hb 10g/dl, Hct 33%, GR 3650000mmc, MCV 90.3fl, MCH 37pg, MCHC 42.3%). Moreover, the patient developed erythematous-pomfoid urticaria-like skin lesions on the lower limbs, which regressed spontaneously within 48 hours.

Suspecting CAS, laboratory analysis was repeated at 37°C incubation, revealing a normal setting of hemoglobin, hematocrit, red cells, MCV, MCH and MCHC (Hb 12.2 g/dl, Hct 38%, GR 4050000mmc, MCV 84fl, MCH 25.7pg, MCHC 35%).

The diagnosis was confirmed by cold agglutinin (CA) dosage (1:1024). Repeat serologies for Chlamydia and Mycoplasma indicated recent Mycoplasma pneumoniae infection (IgG and IgM > 75 BU). Consequently, amoxicillin- clavulanate antibiotic was discontinued and clarithromycin was immediately initiated.

To exclude other CAS-associated organic conditions, the patient underwent abdominal ultrasound, revealing moderate/severe hepatic steatosis, confirmed by liver elastomeric study, likely due to being overweight (95° percentile).

Following a two-week course of oral clarithromycin, the pneumonia resolved, and laboratory analysis documented progressive normalization of CRP. Notably, no specific treatment was necessary for the urticaria-like rash.

The patient was advised to avoid cold temperatures and keep peripheral extremities warm, eg, by wearing gloves.

DISCUSSION

Autoimmune hemolytic anemia (AIHA) encompasses a spectrum of disorders characterized by

immune-mediated destruction of red blood cells. Cold Agglutinin Syndrome (CAS), a subset of AIHA, typically manifests with hemolysis in response to cold temperatures [3-5]. CAS represents about 10%-20% of all autoimmune hemolytic anemias [6] and can be classified into idiopathic and secondary forms, with secondary CAS often associated with non-malignant or malignant diseases. In this case, our patient presented with CAS secondary to a recent Mycoplasma pneumoniae infection, highlighting the post-infectious etiology of CAS, particularly in pediatric populations.

While idiopathic and secondary malignant disorders of CAS typically affect elderly individuals, post-infectious CAS can occur in younger patients, adolescents and children following infections like chickenpox and Mycoplasma pneumoniae [7]. Less commonly, viruses, such as cytomegalo, influenza, varicella, and also different pathogens like Legionella, Citrobacter, and some strains of Listeria monocytogenes [8].

Unlike paroxysmal cold hemoglobinuria (PCH) which is caused by IgG autoantibodies and exhibits maximal reactivity at warmer temperatures, CAS is primarily caused by IgM autoantibodies that exhibit their maximum reactivity at 4°C. Clinically significant cold agglutinins occur at titers of 1:1000 with a thermal activity range extending toward warmer temperatures.

When blood temperature drops below the thermal maximum of the antibody, IgM binds to erythrocytes and causes agglutination and complement activation responsible for hemolysis. The clumped erythrocytes may occlude peripheral microvasculature, which may lead to ischemic gangrenes in severe cases.

The typical clinical manifestations of CAS consist of hemoglobinuria, acrocyanosis, Raynaud's phenomenon, cutaneous necrosis, and occasionally gangrene. The symptoms appear or worsen typically at cold temperature.

Various pathogens, can induce CA, however, symptomatic CAS mostly co-occurs with acute hemolysis in Mycoplasma pneumoniae infections during the recovery phase from pneumonia, coinciding with peak titers of cold agglutinins. The antibody occurs 2 weeks after the onset of the primary infection, reaches peak titer quickly, and may persist for 3-4 months. Hemolysis is self-limited, lasting for 1 to 3 weeks.

Interestingly, our patient, manifested CAS without hemolysis but presented with painful urticarial-like skin

lesions, due to erythrocyte sludging in the microvasculature [9]. The absence of hemolysis but the presence of cutaneous manifestations underscores the diverse clinical spectrum of CAS.

Other findings in CAS are variable and depend on underlying diseases and several pathophysiologic factors [7]. IgM weakly binds to the polysaccharide antigen at ambient temperature, but the higher the thermal amplitude of the antibodies, the greater the possibility of reaching the critical temperature at the periphery is. Although the thermal range is the most important factor, the clinical manifestation of cold agglutinins in these infections is invariably associated with elevated titers ranging between 512 and 32 000 [8]. Another factor is the capability of the IgM to fix complement. Since phagocytic cells do not have IgM receptors, red blood cell destruction is complement-mediated. Some cold agglutinins do not fix complement and patients with such antibodies may have severe agglutination symptoms (acrocyanosis) without hemolysis [10].

Our literature review, conducted via PubMed for the terms 'CAS - Mycoplasma infection - children,' identified 16 relevant articles. Notably, three case reports describe similar presentations of CAS secondary to *Mycoplasma pneumoniae*, two involving autoimmune hemolytic anemia (AIHA) and one with severe acrocyanosis but without AIHA (Atkinson *et al.*, 2016; Narita, 2010; Yoshinari *et al.*, 2015). Our case further corroborates these findings by presenting a unique manifestation without hemolysis.

This case underscores the critical need to consider CAS in pediatric patients presenting with atypical symptoms post-*Mycoplasma pneumoniae* infection. Given the global prevalence of *Mycoplasma pneumoniae* infections and the potential for serious complications like CAS, this report highlights an important diagnostic consideration for pediatric clinicians.

CONCLUSION

This case highlights the diagnostic and therapeutic challenges associated with CAS secondary to *Mycoplasma pneumoniae* infection in childhood. Our findings confirm the variability in clinical manifestations of CAS secondary to *Mycoplasma pneumoniae*, as documented in previous reports. While hemolysis is a common feature, our case aligns with reports of CAS presenting without hemolysis but with significant skin manifestations, suggesting a broader spectrum of

clinical presentations. Our case contributes to the sparse literature on CAS secondary to *Mycoplasma pneumoniae* without accompanying hemolysis, which is rarely documented. This highlights the need for heightened clinical vigilance for CAS in pediatric patients with atypical presentations. Additionally, our case underscores the importance of comprehensive diagnostic evaluations, including cryoagglutinin testing at 37°C, to avoid misdiagnosis. Clinicians should maintain a high index of suspicion for CAS in children presenting with atypical symptoms following respiratory tract infections, facilitating timely diagnosis and intervention. Further research is warranted to elucidate the pathophysiological mechanisms underlying atypical presentations of CAS and optimize treatment strategies in pediatric populations.

LEARNING POINTS

- Suspect CAS if in presence of Raynaud's-like symptoms or anemia with low red blood cell counts but incredibly high MCHC
- CAS caused by *Mycoplasma pneumoniae* infection can develop in children without hemolysis

ANTI-PLAGIARISM DECLARATION

The authors have read and understood the rules on plagiarism. We hereby declare that this piece of written work is the result of our own independent scholarly work and that in all cases material from the work of others is acknowledged, and quotations and paraphrases are clearly indicated.

No material other than that listed has been used. This written work has not previously yet been published.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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