Pediatric Oncall Journal
Volume : 22, Issue 1:53-54
DOI: https://doi.org/10.7199/ped.oncall.2025.73

PEDIATRIC ONCALL
CHILD HEALTH CARE

TEACHING FILES (GRAND ROUNDS)

COLD AGGLUTININ SYNDROME ASSOCIATED WITH A PEDIATRIC SEVERE SYSTEMIC MYCOPLASMA PNEUMONIAE INFECTION

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ARTICLE HISTORY
Received 12 November 2024
Accepted 04 December 2024

KEYWORDS
autoimmune hemolytic anemia, cold agglutinin syndrome, cold agglutinins, Mycoplasma pneunomiae.

Clinical Problem:

A healthy 14-year-old boy presented to the emergency department with a 3-day history of fever, dry cough, sore throat and dizziness. On physical examination, peripheral oxygen saturation was 84% (FiO2 0,21), he had a moderate respiratory effort and breathing sounds were decreased on the left lung's base. A complete blood count (CBC) revealed a normal hemoglobin (16,1 g/dL), lymphopenia (470/µL) and mild thrombocytopenia (118000/µL) and C-reactive protein (CRP) was 291 mg/L. Chest radiograph showed a hypotransparency in the lower 2/3 of the left hemithorax. After ultrasound confirmation of pleural effusion, thoracocentesis was performed, draining 250 ml of serohematic fluid. Bacteriological study of the pleural effusion was negative and nasopharyngeal aspirate did not reveal any respiratory viruses. The patient was admitted to the pediatric ward (PW) and started treatment with intravenous ceftriaxone and clindamycin. By day 3, due to persistent fever and increasing oxygen requirements, vancomycin was added. On the following day, due to the need for noninvasive ventilation, he was transferred to Pediatric Intensive Care Unit (PICU). Previously ordered *Mycoplasma pneumonia* (MP) PCR test result was positive, so clindamycin was replaced by azithromycin. Nevertheless, fever persisted after a 5-day course of azithromycin and it was decided to start levofloxacin because of possible macrolide resistance. By day 9 in PICU, clinical improvement was observed and he was transferred to the PW. By day 3 in this ward, the patient was afebrile and with no supplemental oxygen need. However, looking at the several CBCs that had been done since admission, a progressive decrease in hemoglobin was noted (16,1 g/dL to 8,2 g/dL) with de novo erythrocyte agglutination in peripheral blood smear (PBS). There was a reticulocyte count of 84000/uL (3,18%) and TGO and DHL were elevated for the first time since hospital admission (131 U/L and 407 U/L, respectively), with normal total bilirubin. The direct antiglobulin test (DAT) was positive (4+), monospecific for the complement component C3d and anti-I IgM autoantibody was identified. Therefore, management started with cold avoidance (room temperature and intravenous solutions at 37ºC and heated food). An improvement was observed, with hemoglobin level of 10,9 g/dL 9 days later, with reticulocytosis. TGO and LDH also returned to normal levels. Globally, he completed an antibiotic regimen of ceftriaxone (10 days), clindamycin (3 days), vancomycin (8 days), azithromycin (5 days) and levofloxacin (10 days). The patient was discharged after a 25-day hospital stay, with positive DAT. Cold avoidance measures were kept at home until negative DAT obtained, three months later. He had normal CBC three weeks after CAS diagnosis. Ten months later, chest radiograph was normal and he had occasional dry cough, with no other respiratory complaints.

Which anemia should be suspected of when approaching this Mycoplasma pneumoniae infection and how can it be treated?

Discussion:

MP is a frequent cause of respiratory infections, mainly in children and young adults and most patients develop mild and self-limited upper respiratory symptoms.[1,2,3] However, some patients may develop community-acquired pneumonia and 20-25% of infected patients can also have extrapulmonary manifestations.[2,4,5,6] These can affect the central nervous system, skin, gastrointestinal, cardiovascular and hematological systems.[3,7] Autoimmune hemolytic anemia is the most common hematologic complication and it is often asymptomatic.[5] Severe hemolysis is very rare and usually develops in patients with marked pulmonary involvement.[8,9] Autoimmune hemolytic anemia (AIHA) is an acquired autoimmune disorder characterized by the production of autoantibodies targeted against red blood cell (RBC) membrane antigens, leading to their premature destruction.[10,11,12] AIHA is rare in

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childhood, with an annual incidence of 0.8/100000 individuals under 18 years old.[13] AIHA is referred to as primary or idiopathic when there is no recognized underlying condition, with poorly understood pathogenesis.[10,12,14,15] The secondary form occurs in around two thirds of the patients with AIHA[12] and consists of a single manifestation of a systemic illness, such as autoimmune diseases, immunodeficiencies, malignancies or as in the present case, infections.[10,14] AIHA is also classified according to the autoantibodies' type and the temperatures at which they present maximal reactivity against RBCs.[10,11,14,16] It is divided into warm antibody AIHA (w-AIHA), cold agglutinin syndrome (CAS), cold agglutinin disease (CAD), paroxysmal cold hemoglobinuria and mixed AIHA.10 W-AIHA is the most frequent, described in 60 to 80% of AIHA cases.[14,16,17,18] Cold agglutinins may be found in CAD and CAS, two entities that should be distinguished. CAD refers to a chronic AIHA due to cold reactive antibodies typically seen in adults with a clonal B-cell lymphoproliferative disorder.[10,19] CAS is an AIHA that occurs mainly in children secondarily to specific infections, such as MP pneumonia and Epstein-Barr virus infection or malignancies.[19,20] In most CAS cases, IgM autoantibodies coat RBCs and activate the complement system, causing extravascular but also intravascular hemolysis.[10,18,21] These antibodies show maximal reactivity at 4ºC.[16,21] As in our patient, DAT pattern is C3 positive and IgG negative.[10,18] As expected, other laboratory signs of hemolysis were also present, such as low hemoglobin levels, reticulocytosis, increased LDH and RBC agglutination in PBS. Despite being considered an autoimmune disorder, the underlying mechanism for the MP-associated CAS remains to be fully elucidated.[6,9] Cold agglutinins cross-reactivity has been considered between ciliated cells of the bronchial epithelium and the I antigen on the erythrocyte membrane.[2,3,6] As described in the literature, the course of our CAS case was short and self-limited.[10] Only the most basic measures were needed, such as keeping the patient warm until disease resolution (while IgM antibody is still present).[14,16] When transfusion is indicated, it may be prudent to use pre-warmed RBCs in order to reduce the risk of transfusion-related hemolysis.[5,18] The underlying disease was already being properly addressed, which should always be a priority in CAS approach.[10] This case highlights the importance of investigating possible extrapulmonary manifestations during MP infection approach, including hematologic complications. Despite the marked pulmonary involvement, no severe hemolysis occurred and only supportive care was necessary.

The authors emphasize the need to always carefully value and interpret anemia in patients with underlying infections, because of its multiple possible etiologies. Although it is a rare condition, CAS demands a specific approach that should be promptly initiated.

Compliance with ethical standards
Funding : None
Conflict of Interest : None

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