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Diagnostic dilemma in pediatric hemolysis: A case of mixed autoimmune hemolytic anemia

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Abstract
Mixed autoimmune hemolytic anemia (AIHA) is an uncommon entity in childhood, characterized by overlapping clinical and laboratory features of both warm and cold AIHA. We describe the case of an eight-year-old boy who presented with profound anemia, discrepancies in blood grouping, and crossmatch incompatibility. Subsequent evaluation revealed the presence of warm- and cold-reactive autoantibodies following an upper respiratory tract infection, confirming the diagnosis of mixed AIHA. To our knowledge, this represents only the third reported pediatric case of mixed AIHA triggered by a respiratory infection. Early recognition is essential, as management parallels that of warm AIHA, with prompt initiation of corticosteroid therapy, adequate supportive measures, and careful long-term follow-up required to improve outcomes.

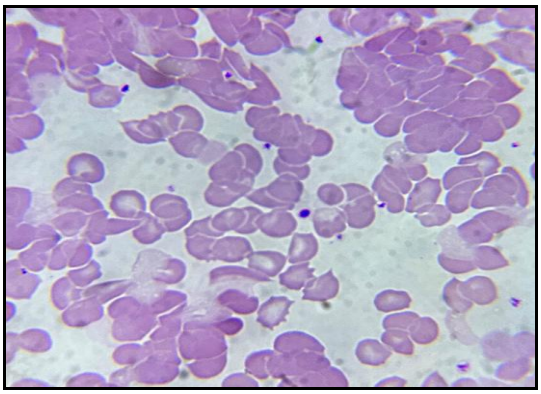
Keywords: Mixed autoimmune hemolytic anemia, pediatric, warm antibodies, cold antibodies, corticosteroid therapy, respiratory infection

Introduction
Autoimmune hemolytic anemia (AIHA) is an uncommon hematological disorder in children, with younger patients—particularly those below ten years of age—often experiencing more severe forms of the disease [1]. It is defined by shortened red blood cell survival caused by immune-mediated destruction, usually confirmed by a positive direct antiglobulin test (DAT) [2]. AIHA may occur as a primary condition or secondary to an underlying disorder, and can be further categorized as warm, cold, or mixed types, depending on the temperature at which the autoantibodies are most active. Another distinct entity, biphasic Donath–Landsteiner hemolysis, also known as paroxysmal cold hemoglobinuria (PCH), is less frequently observed in children [4].
Mixed AIHA combines the characteristics of both warm and cold subtypes [2]. Warm autoantibodies, usually of the IgG class, act independently of complement and primarily cause extravascular hemolysis, with limited intravascular involvement, mostly at the splenic level [5]. In pediatric cases, warm AIHA accounts for about 70% of diagnoses, followed by cold AIHA at roughly 25% [8]. PCH remains rare, occurring in only 4–6% of childhood cases [8].

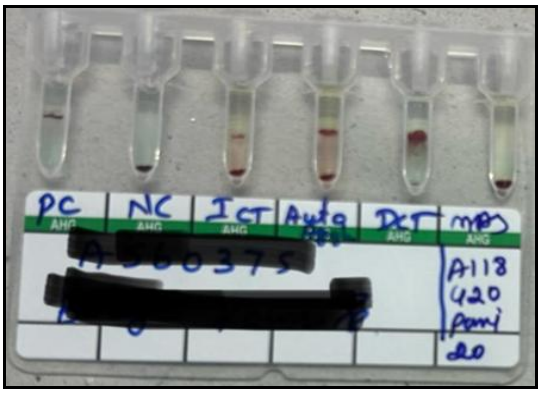
Case presentation
In this report, we present the case of an eight-year-old boy with clinical features and laboratory findings consistent with mixed AIHA.
An otherwise healthy eight-year-old boy was admitted to our pediatric ward with a five-day history of fever, cough, and cold, along with complaints of fast breathing and chest indrawing. There was no family history of hematologic disorders. On examination, he was markedly pale, but there was no lymphadenopathy, hepatosplenomegaly, bruising, or petechiae.
Chest X-ray demonstrated a left-sided pleural effusion, and contrast-enhanced CT (CECT) of the thorax suggested necrotizing pneumonia. Laboratory evaluation showed severe anemia with hemoglobin of 5.9 g/dL and hematocrit of 16.4%. Total leukocyte count was 12,300 cells/µL, platelet count was 844 × 10⁹/L, and reticulocyte count was 2.9%. Peripheral smear revealed red cell agglutination, suggestive of autoimmune hemolytic anemia. Urine hemoglobin was negative, and serum lactate dehydrogenase was elevated at 505 IU/L, while other biochemical parameters were within normal limits.

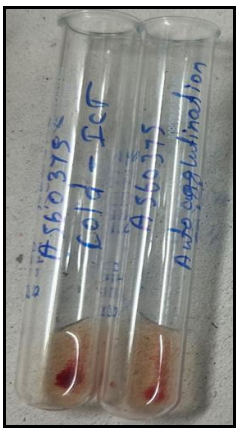
Direct antiglobulin testing (DAT) was positive with polyspecific and monospecific reagents, showing reactivity with anti-IgG and anti-C3d (3+ and 4+, respectively). Indirect antiglobulin testing (IAT) showed 3+ positivity. Mycoplasma pneumoniae serology revealed positive IgM antibody (57.70 NTU) and negative IgG antibody (3.15 NTU). Based on these findings, a diagnosis of mixed autoimmune hemolytic anemia (AIHA) was established.

Given the severity of anemia, the patient was transfused with one unit of O-negative compatible packed red blood cells. The transfusion was uneventful and resulted in a rise in hemoglobin to 7 g/Dl



Oil immersion of PS showing agglutination of RBC's.





Discussion

This case describes a child with mixed AIHA and synpneumonic effusion, confirmed through DAT, IAT, and peripheral smear evaluation. The patient exhibited severe anemia along with blood group typing discrepancies and crossmatch incompatibility, which are typical diagnostic challenges in such cases. Supportive transfusion with a compatible packed red blood cell unit was successful and uneventful.

AIHA results from antibody-mediated red blood cell destruction through activation of the mononuclear phagocyte system or complement, and is identified by a positive DAT along with evidence of hemolysis, after excluding other causes [3]. Although rare in pediatrics, its estimated incidence is 0.4–0.8 cases per 100,000 children annually [1, 10]. Infections—viral or bacterial—are frequent triggers, and AIHA may occasionally present alongside autoimmune disorders such as systemic lupus erythematosus. In 23–37% of children, concurrent thrombocytopenia is seen, termed Evans syndrome, some of which are associated with autoimmune lymphoproliferative syndrome due to Fas gene mutations [10, 12].

Diagnosis can be complicated, as DAT is negative in up to 11% of children with warm AIHA, and the intensity of DAT positivity does not reliably indicate the severity of hemolysis [3]. Classification therefore relies on both DAT specificity and thermal reactivity of the autoantibodies: warm AIHA (IgG only, IgG+C3, or C3 alone), cold AIHA (C3 with high-titer, broad thermal amplitude cold agglutinins), mixed AIHA (IgG+C3 with high–thermal amplitude cold agglutinins), and PCH (C3 positivity with a diagnostic Donath–Landsteiner test) [4].

First-line therapy in pediatric AIHA remains corticosteroids, with most children responding initially, though relapse rates in those under ten years reach approximately 23.5% following tapering [1]. Second-line options such as intravenous immunoglobulin or other immunosuppressants are reserved for resistant or relapsing disease. Transfusions are frequently required in severe warm and mixed AIHA [6].

Reports of mixed AIHA in children are exceptionally scarce, with fewer than 5% of pediatric AIHA cases estimated to fall into this category [1, 9]. To date, only two cases of primary mixed AIHA have been described in children younger than ten years. The present case therefore adds to the limited literature, highlighting the need for greater clinical awareness and more robust data to guide diagnostic and treatment strategies.

Conclusion

Mixed AIHA in children is a rare and likely underrecognized condition. Currently, there is limited information regarding its clinical course or the frequency of exacerbations in the pediatric population. Robust evidence is needed to establish standardized diagnostic and treatment protocols for AIHA, particularly the mixed subtype in children. This case is presented to highlight the importance of recognizing mixed AIHA and addressing its clinical management.

Conflict of Interest

Not available

Financial Support

Not available

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