Blood Reviews (2008) 22, 1–15

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REVIEW

Cold antibody autoimmune hemolytic anemias

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KEYWORDS
Autoimmune hemolytic anemia;
Cold agglutinin syndrome;
Paroxysmal cold hemoglobinuria

Summary The cold antibody autoimmune hemolytic anemias (AIHAs) are primarily comprised of cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH) but, in addition, there are unusual instances in which patients satisfy the serologic criteria of both warm antibody AIHA and CAS (''mixed AIHA''). CAS characteristically occurs in middle-aged or elderly persons, often with signs and symptoms exacerbated by cold. The responsible antibody is of the IgM immunoglobulin class, is maximally reactive in the cold but with reactivity up to at least 30 °C. Therapy is often ineffective, but newer agents such as rituximab have been beneficial in some patients. PCH occurs primarily in children, often after an upper respiratory infection. The causative antibody is of the IgG immunoglobulin class and is a biphasic hemolysin that is demonstrated by incubation in the cold followed by incubation at 37 °C in the presence of complement. Acute attacks are frequently severe but the illness characteristically resolves spontaneously within a few days to several weeks after onset and rarely recurs. Treatment consists of supportive care, with transfusions frequently being needed.

Introduction

The immune hemolytic anemias are classified as indicated in Table 1.[1] This classification divides these disorders into distinctive categories which have differing clinical manifestations, prognosis and therapy, as indicated in Table 2. The cold antibody autoimmune hemolytic anemias (AIHAs) are primarily comprised of cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH) but, in addition, there are unusual instances in which patients satisfy the serologic criteria of both warm antibody AIHA and CAS. Such cases are designated as combined cold and warm AIHA or ''mixed AIHA.''

These disorders are diagnosed on the basis of characteristic serologic reactions. The majority of cases of AIHA are mediated by warm-reactive autoantibodies, i.e., antibodies displaying optimal reactivity with human RBC at 37 °C and which are usually of the IgG immunoglobulin class. In contrast, CAS is generally caused by IgM autoantibodies which exhibit maximal reactivity at 4 °C.

The causative in PCH antibody is an IgG immunoglobulin with specificity that differs from that found in CAS. The antibody is best detected *in vitro* by its ability to cause hemolysis of normal RBC in a two-step procedure, which requires incubation in the

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0268-960X/$ - see front matter
doi:10.1016/j.blre.2007.08.002

Table 1 Classification of immune hemolytic anemias.

Autoimmune hemolytic anemias (AIHA)
Warm antibody AIHA
Idiopathic
Secondary (e.g., chronic lymphocytic leukemia, lymphomas, systemic lupus erythematosus)
Cold agglutinin syndrome
Idiopathic
Secondary
Non-malignant disorders (e.g., mycoplasma pneumoniae infection, infectious mononucleosis, other virus infections)
Malignant disorders (e.g., lymphoproliferative disorders)
Paroxysmal cold hemoglobinuria
Idiopathic
Secondary
Viral syndromes
Syphilis
Combined cold and warm AIHA (''mixed AIHA'')
Drug-induced immune hemolytic anemia
Drug-related antibody identifiable
Drug-induced AIHA
Alloantibody-induced immune hemolytic anemia
Hemolytic transfusion reactions
Hemolytic disease of the fetus and newborn

Table 2 Some characteristic features of autoimmune and drug induced immune hemolytic anemias.

Warm antibody AIHA
Clinical manifestations: Variable, usually symptoms of anemia, occasionally Acute hemolytic syndrome
Prognosis: Fair, with significant mortality
Most effective therapies: Steroids, splenectorny, immunosuppressive drugs
Cold agglutinin syndrome
Clinical manifestations: Moderate chronic hemolytic anemia in middle-aged or elderly person, often with signs and symptoms exacerbated by cold
Prognosis: Good, usually a chronic and quite stable anemia
Most effective therapies: Avoidance of cold exposure, immunosuppressive drugs
Paroxysmal cold hemoglobinuria
Clinical manifestations: Acute hemolytic anemia, often with hemoglobinuria, particularly in a child with history of recent viral or viral-like illness
Prognosis: Excellent after initial stormy course
Therapy: Not well defined; steroids empirically and transfusions if required
Drug-induced immune hemolytic anemia
Clinical manifestations: Variable, most commonly subacute in onset, but occasionally acute hemolytic syndrome
Prognosis: Excellent
Therapy: Stop drug; occasionally a short course of steroids empirically

cold followed by incubation at 37 °C in the presence of complement.

AIHA is designated as ''idiopathic'' if it is unassociated with any demonstrable underlying disease. In contrast, AIHA is categorized as ''secondary'' if it is associated with an additional disorder and there is reason to suspect that the association is not merely fortuitous.

The ingestion of some drugs causes hemolytic anemia in which the causative antibody can be shown to have specificity for the drug or its metabolites. Although the antibody reacts with the patient's own RBCs, these disorders are not autoimmune disorders because the antibody does not have specificity for autoantigens. In other quite remarkable cases, ingestion of a drug causes the development of red cell autoantibodies, i.e., the antibody in the patient's serum and in an eluate from the patient's red cells reacts with red cells similarly to autoantibodies in idiopathic AIHAs, and no relationship between the drug and the antibody can be demonstrated *in vitro*. Such cases are appropriately