Autoimmune Hemolytic Anemia

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KEYWORDS

• Anemia • Hemolysis • Autoantibodies

KEY POINTS

- Autoimmune hemolytic anemia results from antibody-mediated destruction of red blood cells.
- It can be a primary disorder or associated with other immune and nonimmune disorders.
- In most cases, immune modulation is required for treatment.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is an acquired heterogeneous autoimmune disorder characterized by the development of antibodies directed against antigens on autologous erythrocytes. It is a relatively rare disorder, with an estimated incidence of 1 to 3 cases in 100,000 persons per year.[1] Depending upon the type and concentration of the autoantibody, erythrocyte destruction can occur by extravascular red blood cell phagocytosis in the spleen, liver, and bone marrow, or by intravascular complement-mediated lysis of the erythrocyte.

The heterogeneity of the disorder is exemplified by the different types of autoantibodies associated with hemolysis and the differing clinical presentations. There are generally 4 serologic forms of the disease.[2–8] Most common are hemolytic anemias mediated by immunoglobulin G (IgG, termed warm) autoantibodies that bind to red cells at 37°C. The red cell destruction occurs extravascularly by erythrocyte phagocytosis mediated by antibody binding to tissue macrophage Fc receptors.[2–4] Warm antibody hemolytic anemia accounts for 65% to 70% of autoimmune hemolytic anemias. Depending on the IgG antibody subtype (IgG1, IgG3) and concentration, the antibodies may also fix complement to the red blood cell, resulting in both intravascular hemolysis and additional extravascular phagocytosis medicated by complement C3b receptors.

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Cold agglutinin hemolysis is associated with the development of IgM autoantibodies that can agglutinate red cell at cold temperatures.[2,3,5] In patients with cold agglutinin antibodies of higher thermal binding; the IgM autoantibodies rapidly fix complement-inducing intravascular lysis of red blood cell. Approximately 20% to 25% of AIHAs result from cold agglutinin antibodies. He IgM antibodies can be either polyclonal or monoclonal as observed in some patients with plasmacytoid lymphocytic lymphomas such as Waldenstrom macroglobulinemia. An additional 8% of patients with AIHA have both warm IgG and cold IgM antibodies and are termed mixed autoantibody hemolytic anemias.[6]

A rare form of cold-induced intravascular hemolysis results from the formation of IgG autoantibodies that bind to erythrocytes in the cold, but activate complement lysis when the cells are warmed to 37°C.[2,7] These IgG autoantibodies, termed Donath-Landsteiner antibodies, were historically described in paroxysmal cold hemoglobinuria (PCH) in patients with secondary syphilis. It is now most frequently described in children and adults following viral infections. Cases of PCH may account for 1% to 3% of acquired AIHAs.

The fourth serologic form of the disorder is the warm AIHA-direct antiglobulin (Coombs)-negative patient.[8] These patients most often have either a low affinity or low concentration (<200 immunoglobulin G (IgG)/erythrocyte) autoantibody that requires specialized laboratory studies to detect, but is still capable of mediating hemolysis. Smaller subsets of these patients have an IgA- or monomeric IgM-mediated hemolysis. In addition, AIHA can develop following the administration of certain drugs.[9–11] A listing of the more commonly reported drugs associated with AIHA is given in **Table 1**.

Autoimmune hemolytic anemia can occur as a primary (idiopathic) disorder or occur in association with other immune or nonimmune disorders (secondary AIHA). Secondary forms of AIHA may account for 40% to 50% of all patients with AIHA (**Box 1**).[12,13] The presence of another medical disorder can complicate the management of patients with AIHA. Therapy is often tailored with consideration of its effect on the associated illness. Also, the diagnosis of AIHA may precede the recognition of another underlying disorder consistent with secondary AIHA. A list of the common disorders associated with secondary AIHA is given in **Table 2**.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with AIHA can have a highly variable clinical presentation.[14] Patients may describe symptoms related to their anemia such as fatigue, weakness, dyspnea

Table 1
Serologic types of autoimmune hemolytic anemia

Form	Incidence	Antibody	Treatment
Warm antibody	65%–70%	IgG	Steroids, rituximab, splenectomy, azathioprine, cyclophosphamide
Cold antibody	20%–25%	IgM	Rituximab, cyclophosphamide, cold avoidance
Paroxysmal cold hemoglobinuria	1%–3%	IgG	Steroids, rituximab, cold avoidance
Coombs negative	~5%	Low titer IgG, monomeric IgM, IgA	Steroids, rituximab, cyclophosphamide, splenectomy, azathioprine