Warm Autoimmune Hemolytic Anemia

Rakhi Naik, MD, MHS

KEYWORDS

• Autoimmune hemolytic anemia • Spherocyte • Direct antiglobulin test
• Complement

KEY POINTS

- Warm autoimmune hemolytic anemia (AIHA) is a rare disease, occurring in both idiopathic and secondary forms; common secondary etiologies include lymphoproliferative disorders, autoimmune disease, and drugs.
- Diagnosis involves the presence of markers of hemolysis and a positive direct Coombs test, which most commonly reveals red blood cell–bound immunoglobulin G antibodies with or without C3 complement.
- Erythrocyte destruction in warm AIHA is mediated by extravascular phagocytosis in the spleen and, in some cases, may involve complement-mediated mechanisms.
- Complement may exacerbate intravascular and extravascular hemolysis and is often a major contributor to severe forms of warm hemolytic crisis.
- First-line therapy includes corticosteroids followed by splenectomy or rituximab. The role of anticomplement agents in warm AIHA is unknown.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is defined as the destruction of circulating red blood cells (RBCs) in the setting of anti-RBC autoantibodies.[1] The *in vivo* and *in vitro* behavior of these autoantibodies allows for classification of AIHA into 3 forms: a warm type that causes agglutination of the blood at 37°C, a cold agglutinin that optimally reacts at 0°C to 5°C, and mixed-type disease that displays features of both.[2] Warm AIHA is often suspected in the patient who develops hemolytic anemia with characteristic morphologic findings of microspherocytes on the peripheral smear. The disease occurs in both idiopathic and secondary settings, making investigation of potential underlying etiologies essential. The diagnosis ultimately requires confirmation with identification of an anti-RBC autoantibody by direct antiglobulin tests

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Division of Hematology, Department of Medicine, The Johns Hopkins University School of Medicine, 1830 East Monument Street, Baltimore, MD 21230, USA
E-mail address: rakhi@jhmi.edu

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(DAT) and by the presence or absence of complement fractions, which also contribute to the pathogenesis of disease.[2,3] Warm AIHA is most often associated with a positive DAT for RBC-bound immunoglobulin (Ig)G and/or C3.[2,4]

History

The first cases of acquired warm hemolytic anemia were identified in the 1890s by Georges Hayem, who described a series of patients with the hallmark features of chronic jaundice, anemia, and splenomegaly.[5] He noted that the type of jaundice was marked by a lack of biliary pigment, differentiating the condition from usual hepatic etiologies. However, despite the early initial recognition of the clinical presentation, the syndrome was not widely recognized until the mid-20th century.[5] In 1940, Dameshek and Schwartz compiled previously published cases of acquired hemolytic jaundice, leading to the hypothesis that the disease was secondary to direct RBC lysis and that the severity of disease was related to the degree of hemolysis.[5,6] Around the same time, interest in RBC immunobiology began to peak, and by 1945, the antiglobulin test was developed by an astute veterinarian, Robin Coombs. This essential blood-banking test was first used to identify pathogenic RBC antibodies in cases of hemolytic disease of the newborn,[5,7] and both the direct and indirect antiglobulin tests now bear his name. The role of nonimmunoglobulin elements, such as complement, in the pathobiology of disease was not recognized until the 1950s.[5]

Epidemiology

AIHA is known to be a rare disorder, although the non–disease-specific prevalence and incidence rates have not been widely reported. The incidence seems to be low at 0.8 to 3 cases per 100,000 person-years,[4,8,9] resulting in an overall prevalence of about 17 cases per 100,000 individuals.[10] Warm-reacting autoantibodies comprise the majority of cases of AIHA.[11] Among cases of warm AIHA, primary or idiopathic disease occurs in about 50% of cases,[4] with the remainder occurring in the setting of an underlying malignant, autoimmune, infectious, or drug triggers. For idiopathic warm AIHA, females are more commonly affected than males and are generally affected in their fourth or fifth decade.[4] The demographic prevalence of secondary causes varies widely and is primarily driven by the underlying disease.

DIAGNOSIS

Clinical Symptoms

AIHA is a clinicopathologic diagnosis that requires the presence of clinical features of hemolysis as well as serologic positivity for RBC-directed antibodies and/or complement fractions. The clinical spectrum of disease in warm AIHA is wide, with some patients presenting with mild, asymptomatic anemia and others presenting with a life-threatening hemolytic crisis. Common features include symptoms related to the degree of anemia, such as fatigue, weakness, pallor, and dyspnea on exertion, and symptoms related to hemolysis, such as jaundice, hemoglobinuria, or splenic fullness.

Laboratory Evaluation

Serologic diagnosis of warm AIHA requires confirmation of hemolytic anemia and pathologic anti-RBC immunoglobulins with or without RBC-bound complement. The hemolysis associated with warm AIHA is classically extravascular, or occurring in the spleen, although intravascular hemolysis is also common and may account for many of the fulminant cases of warm AIHA.[4] Near universal laboratory features of hemolysis include low hemoglobin, elevated reticulocyte count, and elevated lactate dehydrogenase levels. Depleted haptoglobin levels and elevated indirect bilirubin