Cold Agglutinin-Mediated Autoimmune Hemolytic Anemia

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KEYWORDS

• Autoimmune hemolytic anemia • B lymphocytes • Cold agglutinin
• Cold agglutinin disease • Cold agglutinin syndrome • Complement
• Lymphoproliferative disorders • Therapy

KEY POINTS

- Primary chronic cold agglutinin disease (CAD) is a clonal lymphoproliferative disorder and a distinct clinicopathologic entity.
- Secondary cold agglutinin syndrome (CAS) occasionally complicates specific infections or aggressive lymphomas.
- In both CAD and CAS, hemolysis is entirely complement dependent.
- Hemolysis is predominantly extravascular, mediated by the classical complement pathway.
- Targeting the pathogenic B-lymphocyte clone has resulted in successful therapy for CAD. Complement modulation is promising in specific situations, but has to be further developed and documented before clinical use.

INTRODUCTION

Cold antibody types account for approximately 25% of autoimmune hemolytic anemias (AIHA) and are classified as shown in **Box 1**.[1–3] Most cold-reactive autoantibodies are cold agglutinins (CA). CA are antibodies that bind to erythrocyte surface antigens at low temperatures, causing agglutination and complement-mediated hemolysis. We review the etiology, pathogenesis, clinical features, and therapy of CA-mediated AIHA, highlighting the role of complement involvement. Paroxysmal cold hemoglobinuria is not addressed, because it is described elsewhere in this issue and the involved autoantibodies are not agglutinins.

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Box 1
Autoimmune hemolytic anemia

- Warm antibody type
  - Primary
  - Secondary
- Cold antibody type
  - Primary chronic cold agglutinin disease
  - Secondary cold agglutinin syndrome
    - Associated with malignant disease
    - Acute, infection associated
  - Paroxysmal cold hemoglobinuria
- Mixed cold and warm antibody type

Data from Refs.[1–3]

COLD AGGLUTININS

Cold hemagglutination was first described in 1903.[4] CA are determined semiquantitatively by their titer, based on their ability to agglutinate erythrocytes at 4°C.[5] A proportion of the adult population has demonstrable CA in serum without any evidence of hemolysis or disease; a frequency of positive screening tests at 0.3% has been reported in a cohort of patients with nonrelated disorders.[6,7] These normally occurring CA are polyclonal and are found in low titers, usually below 64 and rarely exceeding 256.[6,8] In 172 consecutive individuals with monoclonal immunoglobulin (Ig)M in serum, on the other hand, significant CA activity was found in 8.5% with titers between 512 and 65,500, and all individuals with detectable CA had hemolysis.[9] Thus, monoclonal CA are generally far more pathogenic than polyclonal CA.

The thermal amplitude is defined as the highest temperature at which the CA reacts with the antigen. In general, the pathogenicity of CA depends more on the thermal amplitude than on the titer.[10–12] The normally occurring CA have low thermal amplitudes. If the thermal amplitude exceeds 28°C or 30°C, erythrocytes agglutinate in the circulation in acral parts of the body, even at mild ambient temperatures and, often, complement fixation and complement-mediated hemolysis ensues. CA should not be confused with cryoglobulins. In rare cases, however, the cryoprotein can have both CA and cryoglobulin properties.[13,14]

Most CAs are directed against the Ii blood group system.[5,15] The I and i antigens are carbohydrate macromolecules and the density of these antigens on the erythrocyte surface are inversely proportional. Neonatal red blood cells almost exclusively express the i antigen, whereas the I antigen predominates in individuals of 18 months of age and older.[16] Therefore, CA with anti-I specificity are more pathogenic in children as well as adults than those specific for the i antigen. Occasionally, CA show specificity against the erythrocyte surface protein antigen designated Pr and such CA can be highly pathogenic.[17,18] Other specificities have been reported, but are probably very rare.[8] More than 90% of pathogenic CA are of the IgM class and these IgM macromolecules can be pentameric or hexameric.[19–21] Hexameric IgM is more pathogenic than pentameric IgM.[20]

The terms *cold agglutinin disease* (CAD) and *cold agglutinin syndrome* (CAS) have been used in the literature in a rather random way. We should distinguish, however,