Cold agglutinin disease: An update on pathogenesis and future prospects on therapy

Sigbjørn Berentsen

Haugesund Hospital, Norway

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia and a low-proliferating clonal bone marrow lymphoproliferative disorder. CAD is a well-defined clinico-pathologic entity that should be distinguished from cold agglutinin syndrome (CAS), which occurs secondary to specific infections or aggressive lymphoma and will not be further addressed here. The typical clinical features of CAD are hemolytic anemia, cold-induced circulatory symptoms, fatigue (only partly explained by the anemia), and, often, exacerbations during diseases with acute phase reaction. The causative autoantibodies in CAD, cold agglutinins, are monoclonal, most often IgM kappa. Hemolysis is mostly extravascular and entirely mediated by complement classical pathway activation. Not all patients need drug treatment. Corticosteroids should not be used to treat CAD. First-line therapy is rituximab plus bendamustine or rituximab monotherapy, depending on individual patient characteristics. Newer B-cell directed treatments have also yielded promising results, in particular Bruton tyrosine kinase inhibitors. An alternative, attractive approach is upstream classical pathway inhibition, which has shown favorable results when using the C1s inhibitor sutimlimab. Other classical pathway inhibitors are also promising. Thus, several treatment options are currently available or will appear in the near future, and the choice of therapy should be individualized. Patients with CAD requiring therapy should be considered for prospective trials if available.