COLD AGGLUTININ DISEASE

A Variant of Autoimmune Hemolytic Anemia

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Cold agglutinin disease is an autoimmune disorder characterized by antibodies that react at cold temperatures with proteins on the surface membrane of red blood cells.

What are Agglutinins?

Agglutinins are antibodies. In 1903 the physician Landsteiner reported the presence of agglutinins that were able to react with or agglutinate (precipitate or clump with) red blood cells (RBCs). The autoimmune disorder known as cold agglutinin disease (CAD) or cold antibody disease is an acquired form of autoimmune hemolytic anemia (AIHA) characterized by high titers of cold-reacting antibodies that target certain antigens, usually the antigen I, found on the surface of red blood cells.

Cold antibodies, which are usually immunoglobulin M (IgM) or immunoglobulin A (IgA) and rarely immunoglobulin G (IgG) antibodies, bind to the target RBC antigens causing premature destruction (hemolysis) of the RBCs. This cell destruction is caused by activation of the immune system chemical known as complement.

Primary or Secondary Conditions

In primary cold agglutinin disease, there is no underlying systemic disease associated with the development of cold antibodies. Primary cold agglutinin disease is usually associated with monoclonal (reacting with one antigen) autoantibodies. Secondary cold agglutinin disease may be associated with monoclonal or polyclonal (reacting with several antigens) autoantibodies and is primarily caused by infection and lymphoproliferative disorders, such as Waldenstrom’s macroglobulinemia.

Who is Affected?

Primary cold agglutinin disease is chronic and generally occurs after the fifth decade of life with a peak incidence around 70 to 80 years of age. Secondary cold agglutinin disease primarily occurs in children and young adults, occurring as a transient condition following an infection, typically mycoplasma pneumonia, Epstein-Barr Virus, cytomegalovirus (CMV), rubella or infectious mononucleosis.

Women and affected slightly more often than men. Overall, approximately 7-25 percent of cases of autoimmune hemolytic anemia are caused by cold agglutinins alone. In some instances of AIHA, both cold and warm agglutinins are present.

Symptoms and Disease Course
Most cold agglutinins only react at temperatures lower than body temperature and affect the cooler parts of the body that can be exposed to the cold, such as the fingers, nose and ears by causing reduced blood flow. Occasionally, peripheral gangrene and, rarely, fatalities, have occurred after inadvertent prolonged exposure to cold temperatures.

Usually, however, the affected RBCs in cold agglutinin disease merely stimulate complement production. Residual complement can result in a process leading to hemolysis. However, with the depletion of complement, hemolysis becomes self-limited. Likewise, temporary increases in complement due to febrile illnesses can increase hemolysis.

In laboratory tests, cold agglutinins often interfere with laboratory assays, particularly red blood cell indices and blood typing procedures. Cold agglutinins that react at body temperatures can cause Blood Bank crossmatching problems, moderate to severe hemolysis and lead to anemia.

In its classic presentation, in which it occurs together with hemolytic anemia and Raynaud syndrome, CAD is usually idiopathic. Similar to the process in most chronic autoimmune diseases, stimulated B lymphocytes begin to produce pathogenic antibodies against an antigen normally present in human tissue. In this disease, the antibody is an IgM, usually monoclonal antibody, with kappa or lambda light chains.

**Cold Antibodies**

Cold antibodies occur naturally in most people at low titers and usually only react at temperatures in the refrigerator range of 4 degrees Celsius. In people with cold agglutinin disease, titers of cold antibodies are very high, usually greater than 1:1000 and they may react at temperatures as high as 37 degrees Celsius (body temperature).

**Resources:**


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