COLD AGGLUTININ DISEASE

by Sue Herms

Cold agglutinin disease (CAD) is sometimes confused with cryoglobulinemia because both conditions involve antibodies (usually of the IgM-type) that react at lower temperatures. However, the antibodies responsible for cold agglutinin disease are specifically directed against antigens on one's own red blood cells. This characteristic is responsible for one of CAD's primary symptoms, namely hemolytic anemia.

Cold agglutinins occur naturally in nearly everyone but at low levels. High concentrations can cause anemia because red blood cells are destroyed faster than the bone marrow can replace them.

CAD may be primary (or idiopathic), meaning that the cause is unknown. This type is chronic and usually occurs in older people, with a peak incidence at approximately 70 years of age. Secondary CAD is associated with an underlying condition, such as infection, autoimmune disorder, or lymphoma, as is the case with Waldenstrom's. Frequently, secondary CAD that occurs as a result of infection is transient and will resolve; however, secondary CAD associated with autoimmune disorders and lymphomas is chronic in nature.

In both types of cold agglutinin disease, the antibody forms an immune complex with complement (an immune system protein) and attaches to the red blood cell membrane at low temperature. This causes the red blood cells to agglutinate (clump). The clumping can reduce circulation in the extremities. Because the red blood cells are altered with complement, the liver may remove them prematurely from the circulating blood. This is called extravascular hemolysis because destruction of the cells occurs outside of the bloodstream. In extreme cases, the red blood cells will actually lyse (burst) inside the blood vessels; this is referred to as *intra*vascular hemolysis.

Symptoms of CAD vary according to its severity. They include Raynaud's phenomenon (color changes in the skin of the fingers, toes, nose, and ears in response to cold), painful fingers and toes, anemia, fatigue, shortness of breath, jaundice, and dark urine caused by the presence of hemoglobin. A few of these symptoms, such as Raynaud's, are similar to those of cryoglobulinemia because both conditions can affect the circulation, but hemolytic anemia is not a consequence of cryo.

Several tests are used to diagnose cold agglutinin disease and determine any possible associated condition. These include acomplete blood count, reticulocyte (immature red blood cell) count, urinalysis, cold agglutinin titer, serum chemistries, and direct antiglobulin test (also called DAT or direct Coombs test). Further testing can involve serology for infectious and autoimmune diseases, serum protein electrophoresis, bone marrow aspiration and biopsy, and flow cytometry. Some of these tests are affected if performed at room temperature in the laboratory and may have to be repeated after warming the blood samples.

Therapy for cold agglutinin disease depends upon the presence of underlying conditions. Primary or idiopathic CAD is usually fairly benign and characterized by flare- ups and remissions; it may not require aggressive treatment. Secondary CAD due to infection is frequently self-limiting and requires supportive care during the acute phase.

For both kinds of CAD, avoiding exposure to cold is often helpful. Folic acid supplements are advisable to meet the demand for increased red blood cell production in the bone marrow. Splenectomy is usually not helpful because most of the extravascular hemolysis in CAD occurs in the liver; however, in cases where an enlarged spleen is associated with an underlying condition such as lymphoma, splenectomy may be of benefit. Transfusion should be used sparingly. Typing and cross matching of blood in the laboratory may be difficult unless performed at 37°C (body temperature). Transfusion must be started slowly, and the blood should be warmed during the process. Patients undergoing operative procedures should be kept warm in order to avoid acute episodes of hemolysis. If an associated autoimmune or malignant disease is present, chemotherapy, rituximab therapy and/or plasmapheresis will usually help to control cold agglutinin disease.

IWMF Board Member Sue Herms is chair of the Publications Committee, member of the Research Committee, and Associate Editor of the Torch. Her column Medical News Roundup appears in every issue of the IWMF newsletter. Sue Herms holds degrees in Zoology and in Medical Technology from Ohio University and from the Medical University of South Carolina, respectively, and is affiliated with Roper Hospital in Charleston, South Carolina.

This article was published in the IWMF *Torch*, (Summer 2007) page 5.