CRYOGLOBULINEMIA

by Sue Herms

Cryoglobulinemia ("cryo") literally means "cold antibody in the blood" and refers to the fact that those antibodies involved precipitate at a temperature below 37°C (body temperature) and then re-dissolve upon warming. Cryo may develop due to unknown causes or may be associated with an underlying disease such as Waldenstrom's. There are three types of cryo, based on the type of antibody present.

Type I cryo (simple cryo) is usually a single monoclonal IgM, less frequently a monoclonal IgG or IgA. This type may be related to the presence of a lymphoid cancer such as Waldenstrom's, multiple myeloma, or chronic lymphocytic leukemia. Frequently, Type I does not cause symptoms until the concentration of monoclonal antibody reaches high levels. At that point it can produce a variety of symptoms because the precipitated antibody physically obstructs smaller blood vessels. If present, symptoms can include blueness of hands and feet from the cold, Raynaud's phenomenon (whiteness and numbness of the fingers and toes from the cold), purpura (purple skin marks), bleeding conditions, and ulcers and gangrene of the fingers and toes.

Type II cryo is also called mixed cryo because, unlike Type I, it is a combination of two antibody types – monoclonal rheumatoid factor (an antibody that can attach to other antibodies and cause inflammation) and polyclonal IgG. These two antibodies form immune complexes and activate an immune system protein called complement that causes injury, primarily to the blood vessels. Type II cryo has been closely associated with the presence of chronic hepatitis C infection, although it can have other causes. Patients with Type II may develop a B-cell cancer such as Waldenstrom's several years after the cryo diagnosis. It has been suggested that a single clone of IgM-secreting cells develops as a result of chronic stimulation of the immune system by a disease such as hepatitis C and that the clonal cells become malignant over time. Type II cryo can manifest many of the same symptoms as TypeI, but the inflammation from deposition of the immune complexes in Type II can also cause more severe problems such as kidney disease, peripheral neuropathy, fatigue, joint and muscle pain, abdominal pain, and liver and lung involvement.

Type III cryo is also characterized as mixed cryo. It is a combination of polyclonal rheumatoid factor and polyclonal IgG – there is no monoclonal antibody present with this type. A large number of infectious diseases and autoimmune diseases, such as lupus, exhibit Type III cryo; however, lymphoid cancers are not typically associated with this type. The symptoms associated with Type III are similar to those observed in Type II.

Waldenstrom's patients should be tested for cryoglobulinemia at diagnosis, since it can not only complicate treatment, but can also affect the results of other lab testing used in the management of WM. It has been estimated from some studies that up to 20% of Waldenstrom's patients have some degree of cryo. For the cryo test, a blood specimen is collected in warm (37°C) vials and kept warm while the serum is removed by centrifugation. The serum sample is then incubated at 4°C and observed for the development of a precipitate. Type I tends to produce a precipitate within 24 hours, while Type III can take up to 7 days. Other tests can help to characterize the type and severity of cryoglobulinemia. These include rheumatoid factor and other auto-antibodies, serum filters for viral and other infections, urinalysis, complement evaluation, serum protein electrophoresis, serum viscosity, liver function studies, and tissue biopsy.

Fay Langer, a WM patient who has Type I cryo, suggests that serum viscosity testing requires special handling of the blood specimen if the patient also has cryo, especially if the specimen has to be sent to an off-site reference lab. If the blood is not collected, transported, and processed at a warm temperature, the precipitation of the cryo can cause an inaccurate result.

Treatment for cryoglobulinemia can depend upon whether an associated disease is present. Asymptomatic cryo does not usually require treatment. Patients with mild symptoms are treated with low-dose steroids and NSAIDs (non- steroidal anti-inflammatory drugs). Those with severe problems may receive high-dose steroids with or without cyclophosphamide. If it is determined that chronic hepatitis C is present, the main aim of therapy is the attempted eradication of the virus with interferon and/or ribavirin. Plasmapharesis (plasma exchange) may be helpful when serum cryo levels are very high, but special handling is needed since the blood circulating during this process must be kept warm. Rituximab therapy has also alleviated symptoms in many cases because of its action against CD20+ lymphocytes that are known to manufacture antibodies.

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*, (Spring 2007) page 8.