Cold Hard Facts of Cryoglobulinemia

Updates on Clinical Features and Treatment Advances

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KEYWORDS

• Cryoglobulinemia • Cryoglobulinemic • Vasculitis • Rituximab • HCV • Diagnosis • Treatment

KEY POINTS

- Cryoglobulins can be grouped by the Brouet classification criteria into 3 categories based on their immunoglobulin clonality. These categories have differing clinical presentations and treatment responses.
- Skin, peripheral nerves, and kidneys are the most commonly affected organs in mixed cryoglobulinemic vasculitis.
- Treatment of cryoglobulinemic vasculitis must take into account the cause of the cryoglobulins, the mechanism of damage, and the severity of symptoms.
- Most cases of cryoglobulinemic vasculitis are caused by hepatitis C virus (HCV) and advances in the identification and treatment of HCV have led to major progress in the treatment of cryoglobulinemic vasculitis.
- Mixed cryoglobulinemic vasculitis is associated with B-cell proliferation and rituximab is highly effective in the treatment of severe cases.

INTRODUCTION

Cryoglobulins consist of proteins (primarily immunoglobulins) that precipitate at temperatures less than 37°C and resolubilize when blood is heated to more than 37°C. They develop secondary to underlying inflammatory, infectious, and malignant processes but rarely can occur without an identifiable cause (ie, essential cryoglobulinemia). Cryoglobulins cause pathologic findings through 2 principal mechanisms: hyperviscosity and immune complex deposition leading to complement fixation and

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vascular inflammation. When vasculitis is present, the disease is termed cryoglobulinemic vasculitis (CryoVas). A variety of organs can be affected, leading to complex management decisions spanning gastroenterology, hematology, infectious disease, internal medicine, nephrology, neurology, and rheumatology.

BROUET CLASSIFICATION

The Brouet classification groups cryoglobulins based on their immunoglobulin clonality into 3 broad categories.[1] Types II and III consist of a polyclonal or mixed population, so they are frequently termed mixed cryoglobulins.

Type I

Type I cryoglobulinemia consists of a pure monoclonal immunoglobin[1–3] and is almost always associated with B-cell–proliferative disorders. Immunoglobulin G (IgG) and immunoglobulin M (IgM) are the most common immunoglobulins, but immunoglobulin A has been reported. Malignancies including Waldenström macroglobulinemia and multiple myeloma are the most common associations; however, monoclonal gammopathy of unclear significance can also cause disease.[4] It is the least common of the cryoglobulinemias, accounting for 10% to 15% of cases.[5]

Type II

Type II cryoglobulinemia consists of a polyclonal IgG with a monoclonal IgM directed against the polyclonal IgG.[1–3] Because a rheumatoid factor (RF) is an antibody associated with the Fc portion of IgG, patients with type II CG typically also display the RF. It is the most common type of cryoglobulinemia and is associated with hepatitis C virus (HCV) infection in 80% to 98% of cases.[6,7] Less frequent associations include hepatitis B virus (HBV)[8,9] and human immunodeficiency virus (HIV).[10]

Type III

Type III cryoglobulinemia consists of a polyclonal IgG with a polyclonal IgM and RF directed against the polyclonal IgG.[1–3] Patients usually have a background of autoimmune diseases, including lupus or Sjögren disease; however, it can also be seen secondary to HCV and lymphoproliferative disorders.[11]

EPIDEMIOLOGY

The prevalence of CryoVas is not well known; however, it is presumed to parallel the rates of local HCV infection. CryoVas presents most commonly in middle-aged individuals and is more common in women than men, with a ratio of approximately 3:1.[12] Approximately half of all patients infected with HCV have cryoglobulinemia[13,14] but only a small percentage (5%–10%) develop vasculitis.[15] Cryoglobulins can similarly be detected in the serum of patients with HBV (15%),[16] HIV (17%),[10] or connective tissue diseases (15%–25%), including systemic lupus erythematosus[17] and Sjögren syndrome,[18] but not all patients develop vasculitis.

PATHOGENESIS

The pathogenesis of type I cryoglobulinemia differs from that of mixed CryoVas. In type I, damage occurs because of hyperviscosity from high concentrations of paraproteins, resulting in sludging and eventually vascular occlusion.[19]

In contrast, B-cell stimulation and expansion are essential to the pathogenesis of mixed CryoVas. Because HCV infection is responsible for most cases, much of the