REVIEW

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Cryoglobulinemia Vasculitis

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ABSTRACT

Cryoglobulinemic vasculitis (CryoVas) is a small-vessel vasculitis involving mainly the skin, the joints, the peripheral nervous system, and the kidneys. Type I CryoVas is single monoclonal immunoglobulins related to an underlying B-cell lymphoproliferative disorder. Type II and III cryoglobulins, often referred to as mixed cryoglobulinemia, consist of polyclonal immunoglobulin (Ig)G with or without monoclonal IgM with rheumatoid factor activity. Hepatitis C virus (HCV) infection represents the main cause of mixed CryoVas. The 10-year survival rates are 63%, 65%, and 87% in HCV-positive mixed CryoVas, HCV-negative mixed CryoVas, and type I CryoVas patients, respectively. In HCV-positive patients, baseline poor prognostic factors include the presence of severe liver fibrosis, and central nervous system, kidney, and heart involvement. Treatment with antivirals is associated with a good prognosis, whereas use of immunosuppressants (including corticosteroids) is associated with a poor outcome. In HCV-negative patients, pulmonary and gastrointestinal involvement, renal insufficiency, and age $>$ 65 years are independently associated with death. Increased risk of lymphoma also should be underlined. Treatment of type I CryoVas is that of the hemopathy; specific treatment also includes plasma exchange, corticosteroids, rituximab, and ilomedine. In HCV-CryoVas with mild-to-moderate disease, an optimal antiviral treatment should be given. For HCV-CryoVas with severe vasculitis (ie, worsening of renal function, mononeuritis multiplex, extensive skin disease, intestinal ischemia…) control of disease with rituximab, with or without plasmapheresis, is required before initiation of antiviral therapy. Other immunosuppressants should be given only in case of refractory forms of CryoVas, frequently associated with underlying B-cell lymphoma.

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KEYWORDS: Cryoglobulinemia vasculitis; Cryoglobulins; HCV; Prognosis; Treatment

Cryoglobulins are immune complexes that may induce systemic vasculitis, a small-vessel vasculitis involving mainly the skin, the joints, the peripheral nervous system, and the kidneys. During the last 25 years, major progress has been made since the discovery of the hepatitis C virus (HCV), which represents the main cause of cryoglobulins.[1-4]

CRYOGLOBULINEMIA SPECTRUM AND DIAGNOSTIC TESTS

Cryoglobulins are defined by the presence of circulating immunoglobulins that precipitate as serum is cooled below core body temperature and resolubilize when rewarmed. Cryoglobulinemia is confirmed by the detection of protein that

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precipitates in the patient's serum maintained at 4°C during at least 7 days, and which dissolved when heated at 37°C. In most expert centers, patients are considered to have a significant cryoglobulin level when > 0.05 g/L on 2 determinations.[4-6] The benefit of the detection of cryoglobulinemia is the excellent diagnostic performance for cryoglobulinemic vasculitis in the context of clinical symptoms evocative of vasculitis, such as purpura, peripheral neuropathy, or glomerulonephritis. After detection, cryoglobulinemia is categorized by immunochemical analysis into 3 types.[4] Type I cryoglobulins are single monoclonal immunoglobulins always linked to a B-cell lymphoproliferative disorder.[7] Type II cryoglobulins consist of polyclonal immunoglobulin (Ig)G with monoclonal IgM with rheumatoid factor activity. Type III cryoglobulins are comprised of polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Types II and III are referred to often as mixed cryoglobulinemia. Some laboratories characterize cryoglobulinemia using immunofixation or immunoelectrophoresis, and quantify the cryoglobulin level by determining the cryocrit as the percentage of the total volume (by using appropriate tube). The use of immunoblotting for immunochemical characterization is a sensitive and specific method allowing a full identification in 98%, in comparison with immunofixation and immunoelectrophoresis in which identification is possible in only 54% and 28%, respectively. A limitation of testing methods is that each of the immunochemical assays previously described may be influenced by artifacts arising from ex vivo cryoprecipitation after blood drawing. In consequence, when a cryoglobulin is suspected, serum should be kept warm, and tests should be carried out at 37°C.

Other laboratory surrogate markers, easier to detect than cryoglobulins, may provide indirect evidence of the presence of cryoglobulinemia, such as low C4 serum complement fraction, decreased total hemolytic complement levels, or presence of a monoclonal immunoglobulin or rheumatoid factor activity. Also, serum cryoglobulin may interfere with a variety of laboratory tests and have been associated with spurious quantitation of plasma proteins and erythrocyte sedimentation rate, pseudoleukocytosis, pseudothrombocytosis, or pseudomacrocytosis.

MAIN FEATURES OF CRYOGLOBULINEMIC VASCULITIS

The disease expression is variable, ranging from mild clinical symptoms (fatigue, purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis) (Table 1).[1-3,6]

Fatigue is the main symptom, noted in 80%-90% of patients. The main cutaneous sign is a palpable purpura, which is reported in 70%-90% of patients, but cutaneous ulcers may occur. It always begins at the lower limbs and may extend to the abdominal area, less frequently to the trunk and upper limbs. It persists 3-10 days with a residual brownish pigmentation. Raynaud's syndrome and acrocyanosis, which may evolve to digital ulcerations, can occur. Arthralgia is reported in 40%-60% of patients. Joint pains are bilateral and symmetric, nondeforming, and involve mainly knees and hands, more seldom elbows and ankles. Frank arthritis is reported in < 10% of patients. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex (60%-70%). The most frequently described form is a distal sensory or sensorymotor polyneuropathy. Polyneuropathy usually presents with painful, asymmetric paresthesia, which later becomes symmetric. Motor deficit is inconstant and mainly affects the lower limbs, appearing a few months to a few years after sensory symptoms. Involvement of the

CLINICAL SIGNIFICANCE

- In hepatitis C virus (HCV)-negative patients with cryoglobulinemic vasculitis (CryoVas), pulmonary, gastrointestinal, and renal involvement, and age > 65 years are associated with death.
- In HCV-positive patients with CryoVas, antivirals are associated with a good prognosis, whereas use of immunosuppressant is associated with a poor outcome.
- Increased risk of lymphoma exists in both forms.
- For HCV patients with severe vasculitis, rituximab, with or without plasmapheresis, is required before initiation of antiviral therapy.

Table 1 Main Demographic and Clinical Features of Patients with Cryoglobulinemia Vasculitis According to Hepatitis C Virus (HCV) Status and Immunochemical Type of the Cryoglobulin[1]

HCV Status	HCV Negative		HCV Positive
Type of cryoglobulin	Monoclonal	Mixed	Mixed
Number of patients	64	242	165
Age, y	65	63	60
Female (%)	56	69	54
Clinical features (%)			
Skin	86	83	76
Purpura	69	75	71
Necrosis	28	16	1
Ulcers	27	14	4
Livedo	13	2	4
Joints	28	40	53
Peripheral neuropathy	44	52	74
Central nervous system	0	2	9
Kidney	30	35	34
Gastrointestinal	0	5	7
Biological features (g/L)			
Cryoglobulin	1.55	0.94	1.04
C4	0.09	0.07	0.09