Severe cutaneous necrosis associated with type I cryoglobulinemia

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INTRODUCTION

Cryoglobulins are circulating immunoglobulins that aggregate and precipitate in cold temperatures in vitro, and can be asymptomatic or cause a variety of manifestations in the skin, nerves, and kidneys in vivo. The distinction between type I and mixed cryoglobulinemias relates to pathologic mechanisms at the tissue level. Here we present the case of a healthy woman who had severe infarctive skin necrosis associated with type I cryoglobulinemia. This case serves to alert the clinician to the utility of skin biopsy in differentiating type I cryoglobulinemia from the other causes of thrombotic vasculopathy.[1-4]

Abbreviations used:

CS: corticosteroids
PAS: periodic acid–Schiff

CASE REPORT

A previously healthy 58-year-old woman presented to her local hospital with a 1-month history of painful retiform purpura on her bilateral lower extremities that rapidly progressed to extensive gangrenous necrosis with black eschars involving large areas of the body. The patient denied fever, anorexia, arthralgias, or fatigue. On examination, the patient was in no acute distress with normal vital signs. Her skin examination was notable for a retiform purpuric rash with extensive gangrenous necrosis with large black eschars on the bilateral lower extremities, buttocks, posterior upper arms, anterior forearms, and cheeks (Fig 1).

Laboratory testing at her local hospital found multiple positive qualitative cryoglobulin tests, negative cryofibrinogen, low complement C4, and borderline elevated rheumatoid factor. Renal function, liver function, and complete blood counts were normal other than mild anemia of chronic disease thought to be related to her presenting illness. Initial infectious, malignancy, and standard hypercoagulability workups were negative. A skin biopsy was obtained, and the patient was treated with corticosteroids (CS), plasmapheresis, and 1 dose of rituximab before transfer to an academic institution where further testing was obtained.

Biopsy of a pretreatment skin lesion found necrosis of the epidermis with prominent eosinophilic homogenous material within dermal vessels (Fig 2). This material was positive for both periodic acid–Schiff (PAS) and phosphotungstic acid–hematoxylin stains, suggesting that the material contained both immunoglobulin and fibrin, respectively (Fig 3). The material was also positive for IgM immunostain (Fig 4). There was prominent dermal hemorrhage but no significant inflammation. There were no changes to suggest vasculitis or calciphylaxis.

Complete hypercoagulability workup was normal, including testing for activated partial thromboplastin time, prothrombin time, fibrinogen, protein C, protein S, antithrombin III, factor V Leiden mutation, lupus anticoagulant, β-2 glycoprotein 1 antibody, and anticardiolipin antibodies. A thorough internal malignancy workup proved negative, including positron emission tomography scan, bone marrow biopsy, multiple serum and urine protein electrophoresis and immunofixations, and testing for Bence Jones proteins. Workup for underlying systemic autoimmune disease as etiology for vasculitis was negative including antinuclear antibody, antineutrophil cytoplasmic antibodies, SSA,

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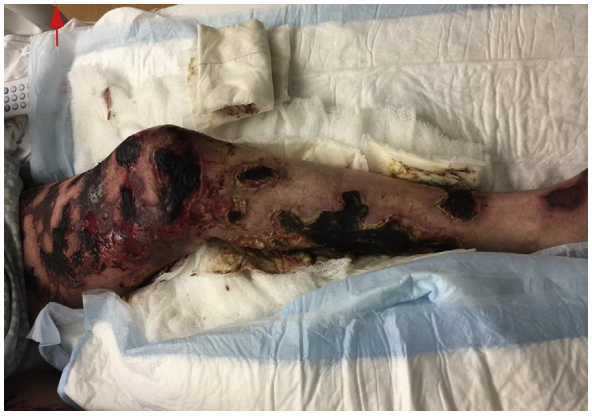

Fig 1. Patient with type I cryoglobulinemia with extensive irregular necrotic ulcers on the skin.

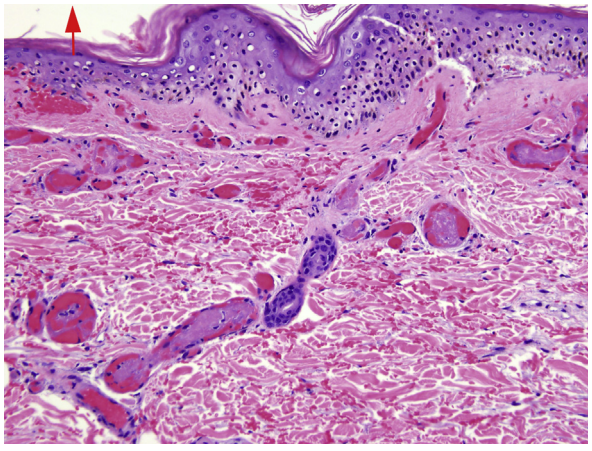

Fig 2. Skin biopsy result shows dermal blood vessels with eosinophilic homogenous material in the lumina. (Hematoxylin-eosin stain; original magnification: ×100.)

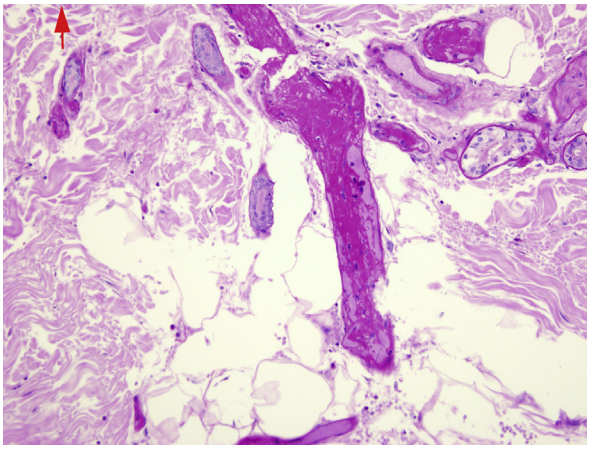

Fig 3. Intraluminal material within vessels is positive with PAS stain, consistent with the presence of cryoglobulins. (Original magnification: ×100.)

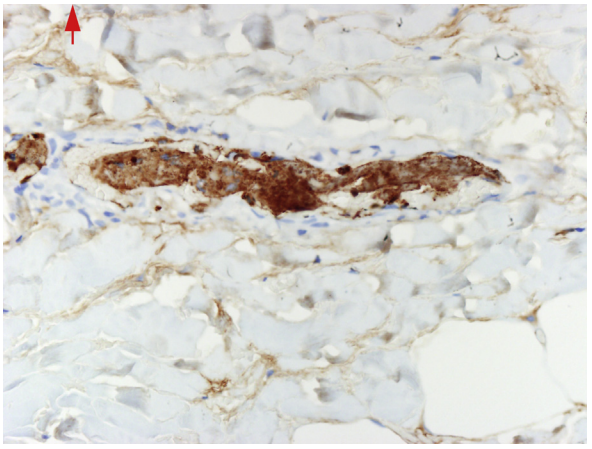

Fig 4. Immunostain for IgM confirms the presence of immunoglobulin within vessels. (Original magnification: ×200.)

SSB, complement C3, and direct Coombs testing. Levamisole-induced vasculitis was considered, and although serum levamisole was not specifically obtained, urine drug screen was negative, and autoantibodies such as antineutrophil cytoplasmic antibodies, antinuclear antibody and antiphospholipid antibodies, which are frequently seen with levamisole-induced vasculitis, were negative. Infectious workup was negative, including HIV; hepatitis A, B, and C serologies; and tuberculosis testing.

The patient completed treatment with CS, 4 doses of rituximab (375 mg/m^2 per dose), and ultimately became dependent on plasmapheresis multiple times per week until receiving cyclophosphamide. Eventually, CS and plasmapheresis were tapered. Anticoagulation with warfarin therapy was initiated given the findings of vessel thrombosis and her lack of response to immunosuppressive therapy. On this treatment regimen, the patient responded well and had slow improvement of her skin lesions over 4 months. However, in the ensuing months, her course was complicated by recurrent infections, presumably from cutaneous sources, to which she eventually succumbed.

DISCUSSION

This patient's case highlights a severe presentation of type I cryoglobulinemia presenting with significant skin necrosis, PAS-positive thrombotic vasculopathy confirmed on biopsy, positive cryoglobulin testing, and low C4. A thorough workup excluded other hypercoagulable, autoimmune, malignant, and infectious causes of her presentation. We speculate that the initiation of aggressive

treatment at the outside hospital may have affected the subsequent quantification of cryoglobulins, making the skin biopsy critically important for diagnosis. Cryoglobulins are immunoglobulins that aggregate and precipitate or gel at temperatures less than 37°C, a phenomenon that is reversed when the specimen temperature is increased. If a cryoglobulin is found, it is further characterized by washing, eluting, and measuring the concentration of immunoglobulins, rheumatoid factor, and total protein in the 37°C sample. Immunofixation of the cryoglobulin elution is performed, and the results of cryoprecipitate testing (negative, trace, present) are reported at 48 hours and at 7 days.[5] Type I cryoglobulinemia is typically associated with an underlying lymphoproliferative disorder, or. less commonly, cold agglutinin disease or amyloidosis. We were unable to identify any associated lymphoproliferative disorder in our patient; however, this finding is not exceptional. Similar patients have been described. Close clinical monitoring for the potential development of lymphoproliferative disease seems prudent.[1-4,6-9]

This case serves to alert the clinician to the severe infarctive skin necrosis that may be seen with type I cryoglobulinemia. Skin biopsy identifying PAS-positive noninflammatory thrombi can be helpful in differentiating type I cryoglobulinemia from the other cause of thrombotic vasculopathy.

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