Multiple myeloma presenting as cryoglobulinemic vasculitis

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INTRODUCTION

Type I cryoglobulinemic vasculitis (CryoVas) is a rare entity occurring in the context of an existing lymphoproliferative disorder and often exhibiting severe cutaneous involvement.[1] Cutaneous clinical manifestations include palpable purpura with necrosis and ulceration. Importantly, few reports of Type I CryoVas exist in the literature, and characteristic histopathologic features are not well-characterized. Herein, we present the clinical and histopathologic features of a case of recurrent Type I CryoVas in the setting of multiple myeloma.

Abbreviations used:

CryoVas: cryoglobulinemic vasculitis
LCV: leukocytoclastic vasculitis

CASE REPORT

A 62-year-old woman presented with painful, worsening, reticulated, and angulated purpuric plaques with necrotic ulcers on her extremities (Fig 1). These lesions had emerged approximately 1 year earlier and were associated with fatigue, arthralgias, and myalgias. Skin biopsy revealed leukocytoclastic vasculitis (Fig 2) with few vessels showing intraluminal cryoglobulin (Fig 3). On further evaluation, she was found to have IgG lambda cryoglobulinemia and multiple myeloma (bone marrow exam revealed 60% monoclonal plasma cells with a serum kappa/lambda free light chain ratio of 0.02), and her vasculitis was attributed to cryoglobulinemic vasculitis. Her symptoms worsened despite treatment of her multiple myeloma with a single dose of bortezomib and dexamethasone, and she was transferred to our institution.

Repeat biopsy of a representative lesion revealed intraluminal cryoglobulins and vasculitis in small- and medium-sized vessels, including fibrin thrombi, extravasated erythrocytes, and fibrinous degeneration of vascular walls. A serum cryoglobulin assay was positive for IgG lambda monoclonal cryoglobulins. Tissue cultures were negative, renal function was unimpaired, and a vasculopathy work-up was otherwise unremarkable. Specifically, her complement levels (C3 and C4), prothrombin time, and partial thromboplastin time were within normal limits. She was negative for proteinase 3 antibody, myeloperoxidase antibody, rheumatoid factor, hepatitis B, hepatitis C, and HIV.

Her complete blood cell count was notable for mild leukocytosis and mild anemia, and a complete metabolic panel revealed a mildly elevated glucose and alanine transaminase. Her fibrinogen level was elevated at 555 mg/dL.

A diagnosis of Type I CryoVas was made based on the recent diagnosis of multiple myeloma with monoclonal cryoglobulins and vasculitis. Plasmapheresis was performed, and the patient was given intravenous methylprednisolone, leading to improvement of her skin lesions and pain. The patient subsequently received carfilzomib, lenalidomide, and dexamethasone followed by autologous hematopoietic stem cell transplantation, leading to remission of both the multiple myeloma and the CryoVas.

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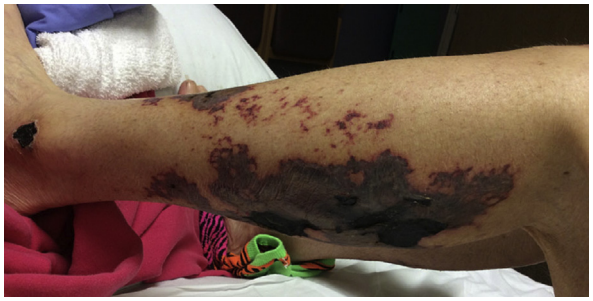

Fig 1. Cryoglobulinemic vasculitis. Reticulated, angulated purpura and necrotic ulcers were found on bilateral lower extremities.

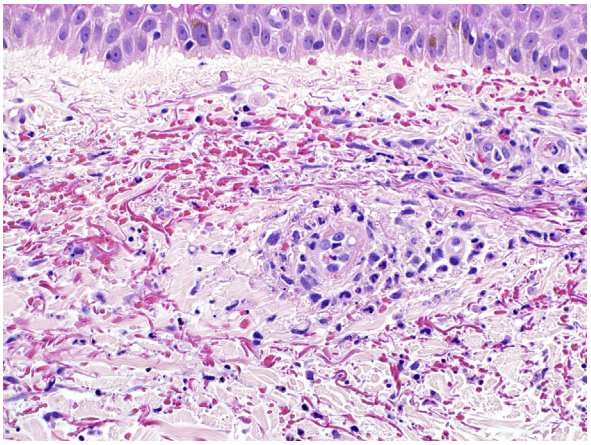

Fig 2. Cryoglobulinemic vasculitis. Vessels reveal fibrinous degeneration of vascular walls with associated neutrophils, karyorrhectic debris, and extravasated erythrocytes (Original magnification, ×400).

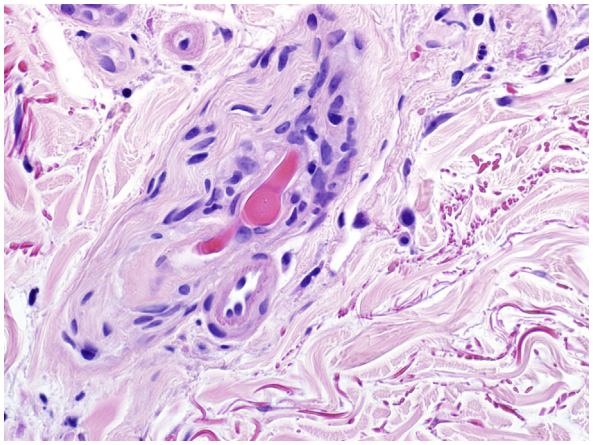

Fig 3. Cryoglobulinemic vasculitis. Vessels demonstrating densely eosinophilic, periodic acid—Schiff-positive, hyaline material, compatible with cryoglobulin (Original magnification, ×400).

DISCUSSION

Type I cryoglobulinemia is defined as the presence of circulating monoclonal immunoglobulins that characteristically precipitate in cold temperatures and dissolve with rewarming. It arises in the setting of a B-cell lymphoproliferative disorder, most often monoclonal gammopathy of undetermined significance (MGUS), Waldenström macroglobulinemia, or multiple myeloma, and occurs due to aberrant production of a monoclonal cryoglobulin by neoplastic cells.[1-3] Rarely, Type I cryoglobulinemia is associated with systemic small-vessel vasculitis (CryoVas). Type I CryoVas is the least frequent Type of CryoVas, making up approximately 10% of CryoVas cases.[1,4]

Most patients with Type I CryoVas present with cutaneous findings, including palpable purpura, acrocyanosis, necrosis, ulceration, livedo reticularis, and cold urticaria.[1,5] Lesions usually begin on the lower extremities and may progress to involve the abdomen, trunk and upper extremities.[5] Typically, patients with Type I CryoVas have severe cutaneous disease with extensive necrosis and ulceration.[1] Patients also commonly have peripheral neuropathy, renal involvement, and arthralgias/arthritis.

Histopathologic confirmation of CryoVas relies on the identification of vasculitis and may also reveal cryoglobulins, the latter appearing as hyaline material within vessel lumina. Periodic acid—Schiff with diastase staining may assist in recognition of cryoglobulins, as it stains cryoglobulins densely eosinophilic.[2] According to the rheumatology literature, histopathologic confirmation is not required for the diagnosis of CryoVas. Overt vasculitis may not be seen on biopsy, and/or cryoglobulins may be difficult to identify histopathologically. Clinical manifestations of vasculitis and laboratory evidence of a cryoglobulinemia is sufficient for the diagnosis of Type I CryoVas.[1,3,4,6]

Notably, some authors use the term "vasculitis" loosely. The 2 largest series on Type I CryoVas highlight the debate. Harel et al.[2] doubt the presence of a true leukocytoclastic vasculitis (LCV) in Type I CryoVas, attributing the findings instead to a thrombotic vasculopathy.[2] In contrast, Terrier et al.[1] found histopathologic confirmation of a vasculitis in the majority of the cases; however, they did not provide histopathologic details of the vasculitis. Our case highlights an overt LCV in the setting of Type I CryoVas, suggesting that at least some cases of Type I cryoglobulinemia include LCV. The underlying mechanism in Type I CryoVas is not entirely clear. Classically, the clinical manifestations of Type I CryoVas have been attributed to vascular occlusion by cryoglobulins in contrast to the immune complex

deposition causing Type II and III CryoVas, and which leads to LCV without cryoprecipitates.[3] However, some have proposed that Type I cryoglobulin aggregates may include complement and lead to inflammation when deposited on small-vessel endothelium.[3]

As Type I CryoVas occurs within the context of existing lymphoproliferative diseases, recognition of signs and symptoms of CryoVas and a monoclonal cryoglobulin should prompt an evaluation for a systemic lymphoproliferative disorder. As in this case, CryoVas can be the presenting manifestation of an underlying hematopoietic neoplasm, which must be treated for the CryoVas to resolve. Importantly, Type I CryoVas can be life threatening, both due to the severity of the vasculitis and the underlying hematopoietic neoplasm.[1] In addition to chemotherapy targeting the hematopoietic neoplasm, patients may also benefit from plasmapheresis and iloprost.[4] While they must be urgently treated, patients with Type I CryoVas have been reported to have an improved survival compared with those who have types II or III.[5] Moreover, MGUS patients with Type I CryoVas have been found to have a more favorable prognosis compared to those with an overt hematologic malignancy.[1]

In summary, our case expands the literature on the clinical and histopathologic findings in Type I CryoVas. It also highlights that CryoVas may rarely be seen in Type I cryoglobulinemia and may herald the diagnosis of an underlying B-cell lymphoproliferative disorder.

Conflicts of interest

None disclosed.

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