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Intravascular Crystal Deposition: An Early Clue to the Diagnosis of Type 1 Cryoglobulinemic Vasculitis

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Abstract

Cutaneous small vessel vasculitis (CSVV) is a nonspecific finding with an extensive differential diagnosis. It is critically important to distinguish skin-limited presentations of CSVV from severe life-threatening systemic vasculitides presenting with CSVV as an initial manifestation. It can be challenging to determine which patients presenting with CSVV are at risk for systemic disease. Standard histopathologic evaluation, direct immunofluorescence, and serologic evaluation is typically required to exclude a systemic vasculitis. Type 1 cryoglobulinemia may rarely present with CSVV. Herein, we report a case of type 1 cryoglobulinemia in the setting of occult multiple myeloma. CSVV with prominent intravascular crystal formation was noted. The presence of intravascular crystals in the setting of CSVV may represent an important early clue to the diagnosis of type 1 cryoglobulinemic vasculitis.

Keywords

leukocytoclastic vasculitis; cryoglobulinemia; multiple myeloma; intravascular crystals; cutaneous small vessel vasculitis

INTRODUCTION

Cutaneous small vessel vasculitis (CSVV) is a nonspecific finding with an extensive differential diagnosis. It is critically important to distinguish the largely short-lived, benign, skin-limited presentations of CSVV from severe life-threatening systemic vasculitides presenting with CSVV as an initial manifestation. Half of patients with systemic disease will have cutaneous involvement at some point in their disease course.¹ It has been reported that involvement of both the superficial and deep dermal vessels is more frequently associated with systemic disease than is CSVV limited to the superficial dermal vessels.² Others, however, have reported that findings of patients with CSVV are indistinguishable from systemic vasculitis.¹ Particularly troubling is the series of patients with CSVV in whom 43% subsequently developed renal disease due to Henoch–Schönlein purpura, microscopic polyangiitis, or Wegener granulomatosis.³

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Classifying the vasculitis by vessel size and extent of involvement, that is, superficial, superficial and deep, or subcutaneous vessels provides a means of expediently honing the differential diagnosis.^{1,4,5} Further narrowing the differential diagnosis requires performance of direct immunofluorescence and assay for antineutrophil cytoplasmic antibodies, at a minimum. Despite these measures, it often remains challenging to determine which patients presenting with CSVV are at risk for systemic disease. Delay in diagnosis and treatment of a systemic vasculitis results in further vascular and end organ damage that ultimately could result in death.

Herein, we report a case of type 1 cryoglobulinemic vasculitis presenting with CSVV. Prominent intravascular crystal formation was noted, representing an important clue to the diagnosis of type 1 cryoglobulinemic vasculitis due to an occult plasma cell dyscrasia.

MATERIALS AND METHODS

Biopsy specimens were fixed in 10% buffered formalin, and sections were routinely processed and embedded in paraffin. Serial 4- μ m-thick sections were cut for hematoxylin and eosin staining.

REPORT OF A CASE

A 56-year-old white female with a past medical history significant for hypothyroidism, hypertension, and monoclonal gammopathy of undetermined significance diagnosed 16 years prior presented with a 1-week history of painful erythematous to purpuric papules on the distal digits. The papules initially involved the right foot but progressed to involve both feet and the left hand. Due to progressive pain, the patient presented to the emergency department. Her review of systems at presentation was remarkable for progressive upper back pain over the week before admission, but was otherwise negative.

On examination, the patient was noted to have retiform purpura involving the forefoot and toes (Fig. 1) and purpuric periungual papules on the left hand. Lesions were exquisitely tender to palpation. Punch biopsy of the right third toe demonstrated an unremarkable epidermis overlying a superficial and deep mixed perivascular infiltrate. Fibrin thrombi were noted to be plugging the small dermal blood vessels (Fig. 2A, $\times 40$). Higher power examination revealed prominent leukocytoclastic vasculitis, characterized by hemorrhage, fibrin deposition, nuclear debris, and transmural migration of neutrophils (Fig. 2B, $\times 200$). Polygonal nonpolarizable eosinophilic crystals were noted within the vascular lumen of several vessels (Fig. 2C, $\times 400$). Direct immunofluorescence demonstrated intravascular and perivascular immunoglobulin G (IgG), C3, and fibrinogen (not shown).

Extensive laboratory evaluation was remarkable for a negative HIV, viral hepatitis, antinuclear antibody, and rheumatoid factor assays. Complete blood count was remarkable for a mild macrocytic anemia. Peripheral blood smear demonstrated moderate polychromasia and occasional rouleaux formation. Complete metabolic panel demonstrated elevated total protein at 10.3 g/dL (6.0–9.0) and serum globulin at 6.8 g/dL (2.0–5.0). Serum cryoprotein was 17% and 13% in the plasma at 72 hours. Serum-free light chain assay demonstrated elevated free kappa light chain at 4.2 mg/dL (0.3–2.0) and normal lambda

light chain. Serum protein electrophoresis demonstrated an abnormal band of 1.7 g/dL determined on serum immunofixation to be monoclonal IgG. Bone marrow biopsy was diagnostic for plasma cell myeloma with 20% kappa-restricted plasma cells.

The patient was diagnosed with IgG kappa multiple myeloma complicated by type 1 cryoglobulinemic vasculitis. She was initially treated with high-dose corticosteroids, followed by initiation of cytotoxic chemotherapy with dexamethasone, bortezomib, and cyclophosphamide.

DISCUSSION

Type 1 cryoglobulinemia is a rare cause of vasculitis. Cryoglobulins are divided into 3 types, as delineated by Brouet et al.⁶ Type 1 cryoglobulins are a single class of monoclonal immunoglobulins produced by an underlying B-cell lymphoproliferative disorder. Type 2 cryoglobulins consist of a polyclonal IgG and a monoclonal IgM with rheumatoid factor activity, whereas type 3 consists of a polyclonal IgG and polyclonal IgM with rheumatoid factor activity. Types 2 and 3 are referred to as mixed cryoglobulins. Approximately, 80% of cases of cryoglobulinemic vasculitis are due to mixed cryoglobulinemia associated with hepatitis C virus.⁷ When compared with mixed cryoglobulinemia, type 1 cryoglobulinemic vasculitis results in more severe skin involvement and can be life threatening.⁷ Aggressive multiagent chemotherapy is often required, and early diagnosis is essential in limiting progressive vessel disease and end organ damage.

Immunoglobulin crystal formation is an important clue to an underlying plasma cell dyscrasia. Crystallized immunoglobulin has previously been reported in the peripheral blood smear of a patient with type 1 cryoglobulinemia in whom assays for cryoglobulins were repeatedly negative despite appropriate collection technique.⁸ Similarly, intra-articular cryoglobulin crystal formation has been reported to be an early diagnostic clue to the diagnosis of multiple myeloma in a patient presenting with seronegative arthritis.⁹ Slender needleshaped immunoglobulin crystals have been reported in the ascitic fluid, peritoneum, liver, and bone marrow of a patient with an indolent plasma cell dyscrasia.¹⁰ Intravascular immunoglobulin crystals were identified in the bowel resection of a patient with ischemia-induced small bowel perforation in the setting of multiple myeloma.^{11,12} Importantly, assays for cryoglobulinemia were negative in both reports.^{11,12} Cytoplasmic crystal deposition is also rarely observed in association with plasma cell dyscrasias. Crystal storing histiocytosis is a rare phenomenon in which intracytoplasmic crystal deposition is noted within histiocytes. The majority of crystal storing histiocytosis is associated with multiple myeloma or monoclonal gammopathy of undetermined significance, but may also rarely be associated with clofazamine.¹³

To our knowledge, intravascular crystal formation in the setting of CSVV has not been previously reported. Immunoglobulin crystals are invariably reported in association with a monoclonal gammopathy or frank multiple myeloma.⁸⁻¹¹ It is unclear if the observed histopathologic findings in this case are related to the underlying plasma cell dyscrasia or the presence of cryoglobulin activity in the elaborated protein. However, in patients presenting

with CSVV, the presence of intravascular crystals may represent an opportunity for early diagnosis and treatment of an underlying plasma cell dyscrasia.

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FIGURE 1.

The patient presented with a 1-week history of painful erythematous to violaceous papules and retiform patches on the bilateral dorsal feet and left hand.

FIGURE 2.

Punch biopsy of the right third toe demonstrates a superficial and deep perivascular infiltrate. A, Fibrin thrombi were noted within the lumen of small dermal blood vessels ($\times 40$). B, Higher power examination revealed prominent leukocytoclastic vasculitis, characterized by hemorrhage, fibrin deposition, nuclear debris, and transmigration of neutrophils ($\times 200$). C, Polygonal eosinophilic crystals were noted within the vascular lumen of several vessels ($\times 600$).