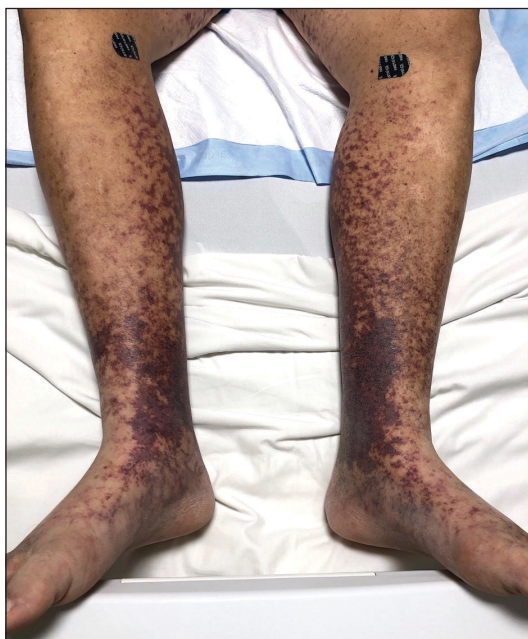


Retiform Purpura on the Lower Legs

Beau Sitton, BS; Benjamin H. Kaffenberger, MD; Abraham M. Korman, MD



A 58-year-old man presented with a petechial and purpuric rash limited to the lower extremities. He reported that the rash had been present for months but worsened acutely over the last 3 days with new-onset dark urine, joint pain, and edema limiting his ability to walk. Physical examination showed areas of violaceous macules and papules on the legs and dorsal feet in a reticular distribution. Laboratory findings were remarkable for an elevated serum creatinine level of 2.75 mg/dL (reference range, 0.70–1.30 mg/dL), and serum immunofixation revealed the presence of markedly elevated IgG lambda monoclonal proteins. He was afebrile and his vital signs were stable. Dermatology, nephrology, and rheumatology services were consulted.

WHAT'S YOUR DIAGNOSIS?

- a. angioinvasive fungal infection
- b. antiphospholipid antibody syndrome
- c. calciphylaxis
- d. livedoid vasculopathy
- e. type I cryoglobulinemia

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THE DIAGNOSIS: Type I Cryoglobulinemia

Retiform purpura with overlying necrosis subsequently developed over the course of a week following presentation (Figure 1). A skin biopsy showed fibrin thrombi and congestion of small- and medium-sized blood vessels, consistent with vasculopathy (Figure 2). Urinalysis revealed hematuria and proteinuria. A renal biopsy performed due to a continually elevated serum creatinine level revealed glomerulonephritis with numerous IgG1 lambda-restricted glomerular capillary hyaline thrombi, compatible with a lymphoproliferative disorder-associated type I cryoglobulinemia. A serum cryoglobulin immunofixation test confirmed type I cryoglobulinemia involving monoclonal IgG lambda. The combination of cutaneous, renal, and hematologic findings was consistent with type I cryoglobulinemia. A subsequent bone marrow biopsy demonstrated a CD20⁺ lambda-restricted plasma cell neoplasm. Initial treatment with high-dose corticosteroids followed by targeted treatment of the underlying hematologic condition with bortezomib, rituximab, and dexamethasone improved the skin disease.

Cryoglobulins are abnormal immunoglobulins that precipitate at temperatures below 37 °C. The persistent presence of cryoglobulins in the serum is termed *cryoglobulinemia*.¹ Type I cryoglobulinemia is distinguished from mixed cryoglobulinemia—types II and III—by the presence of a single monoclonal immunoglobulin, typically IgM or IgG. It is associated with lymphoproliferative disorders, most commonly monoclonal gammopathy of undetermined significance and B-cell malignancies such as Waldenström macroglobulinemia, multiple myeloma, or chronic lymphocytic leukemia. Histopathology shows occlusion of small vessel lumina with homogenous eosinophilic material containing the monoclonal cryoprecipitate.² Disease manifestations are caused by small vessel occlusion, which leads to ischemia and tissue damage.

Retiform purpura, livedo reticularis/racemosa, and necrosis leading to ulcers are the most common cutaneous clinical findings. Extracutaneous signs include peripheral neuropathy, arthralgia, Raynaud phenomenon, and acrocyanosis. Renal involvement, most commonly glomerulonephritis with associated proteinuria, is noted in 14% to 20% of cases.^{3,4} An elevated cryocrit can lead to symptoms of hyperviscosity syndrome.²

Treatment is difficult and primarily is focused on addressing the underlying hematologic condition, which is responsible for synthesis of the cryoglobulin. Decreasing cryoglobulin production leads to decreased occlusion of blood vessels, thus alleviating the ischemia and skin damage. Monoclonal gammopathy of undetermined significance-related type I cryoglobulinemia initially is treated with corticosteroids followed by rituximab if a

CD20⁺ B-cell clone is identified.² Bortezomib is recommended for cases associated with Waldenström macroglobulinemia and cases associated with multiple myeloma with concurrent renal failure. In patients with neuropathy, a lenalidomide-based treatment can be employed. Patients should be instructed to keep extremities warm.² Diabetic foot care guidelines should be followed to prevent wound complications.

The differential diagnosis for type I cryoglobulinemia includes other causes of retiform purpura—like angioinvasive fungal infection, antiphospholipid antibody syndrome, calciphylaxis, and livedoid vasculopathy.⁵ Angioinvasive fungal infections are caused by *Candida*, *Aspergillus*, and *Mucorales* species, as well as other hyaline molds. They typically occur in immunocompromised patients and invade the blood vessels via direct inoculation or dissemination.⁶ Patients present with retiform purpura but typically will be acutely ill with fevers and vital sign abnormalities. Histopathology with special stains



FIGURE 1. Retiform purpura with central necrosis and eschar.

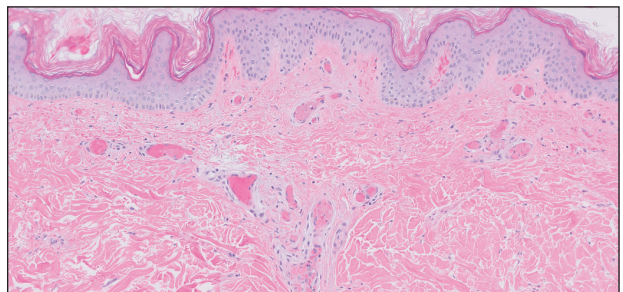


FIGURE 2. Occlusion of small-caliber dermal blood vessels by homogenous eosinophilic hyaline material (H&E, original magnification $\times 20$).

often will identify the fungal organisms in the dermis or inside blood vessel walls with vessel wall destruction and hemorrhage.⁷ Accurate diagnosis is essential to selecting appropriate antifungal agents. If angioinvasive fungal infection is clinically suspected, treatment should begin before culture and histopathologic data are available.⁷

Antiphospholipid antibody syndrome is an autoimmune thrombophilia that can occur as primary disease or in association with other autoimmune conditions, most commonly systemic lupus erythematosus. Diagnosis requires the presence of antiphospholipid antibodies, such as lupus anticoagulant, anticardiolipin antibody, anti- β 2-glycoprotein-1 antibody, with arterial or venous thrombosis and/or recurrent pregnancy loss. Paraproteinemia is not seen. The most common cutaneous finding is livedo reticularis, with livedo racemosa being a more distinctive finding.⁸ Small vessel thrombosis is seen histopathologically. Treatment includes antiplatelet and anticoagulant medications. Patients with refractory disease may benefit from additional therapy with hydroxychloroquine or intravenous immunoglobulins.⁸

Calciphylaxis is a rare depositional vasculopathy that often occurs in patients with end-stage renal disease on dialysis. Patients present with painful and poor-healing skin lesions including indurated nodules, violaceous plaques, and retiform purpura that typically affect areas of high adiposity such as the thighs, abdomen, and buttocks.⁹ Ulceration and superimposed infections are common complications. Histopathologically, small dermal and subcutaneous vessels demonstrate calcification, microthrombosis, and fibrointimal hyperplasia.⁹ Wound management is critically important in patients with calciphylaxis. Treatment with intravenous sodium thiosulfate is typical, but prognosis remains poor.

Although livedoid vasculopathy may present with retiform purpura in the ankles, paraproteinemia is not seen and patients frequently present with punched-out ulcerations that tend to heal into atrophie blanche.¹⁰

Livedoid vasculopathy has been associated with underlying hypercoagulable states, connective tissue diseases, and chronic venous hypertension. Hypercoagulability and endothelial cell damage contribute to the formation of fibrin thrombi in the superficial dermal blood vessels. Histopathology demonstrates thickening of vessel walls and intraluminal hyaline thrombi. Successful treatment in most cases is achieved with anticoagulation therapy, typically rivaroxaban, especially in patients with underlying hypercoagulability. Antiplatelet therapy also may be considered, while anabolic agents have been shown to be helpful in patients with connective tissue disease.¹⁰

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