Livedoid Vasculopathy: Review of Pathogenesis, Clinical Presentation, Diagnostic Workup, and Treatment

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We report the case of a patient with livedoid vasculopathy that had been undiagnosed and inadequately treated for more than 10 years. To improve disease recognition and management, we review the pathogenesis, typical clinical presentation, diagnostic workup, and treatment options for livedoid vasculopathy.

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Case Report

A 71-year-old man presented with a history of painful sores on both legs of more than 10 years' duration. The patient reported that he had previously consulted with multiple dermatologists and had "been told many things," but he claimed no one had helped him with his condition.

The patient's medical history was remarkable for hypertension, hypercholesterolemia, macrocytic anemia, gastroesophageal reflux disease, androgenetic alopecia, attention-deficit/hyperactivity disorder, depression, and a 4-vessel coronary artery bypass graft performed 10 years prior. His current medications included simvastatin (40 mg daily), valsartan (80 mg daily), clopidogrel bisulfate (75 mg daily), ketoprofen (200 mg daily), omeprazole (20 mg daily), finasteride (1 mg daily), folic acid-cyanocobalamin-pyridoxine 2.5-25-2 mg daily), amphetamine-dextroamphetamine (40 mg daily), paroxetine hydrochloride (30 mg daily), venlafaxine hydrochloride extended release (225 mg daily), bupropion hydrochloride (300 mg daily), zinc (50 mg daily), selenium (200 mg daily), calcium (800 mg daily), and omega-3 (2 g daily). The patient reported no known drug allergies. His family history was remarkable for myocardial infarction in his father and 6 of 11 siblings as well as cerebrovascular accident in his mother; no relatives reported experiencing symptoms similar to the patient's current presentation. He denied a history of smoking or use of alcohol or illegal drugs. A review of systems was positive for easy bruising but otherwise was negative. The patient denied any history of lower extremity deep vein thrombosis or thrombophlebitis.

On physical examination the lower extremities revealed 3+ pitting edema, palpable posterior tibial and dorsalis pedis artery pulses, and a capillary refill time of less than 3 seconds. Hair growth was noted on the bilateral lower legs but was absent on the bilateral feet and toes. Plantar sensation to monofilament was intact (10/10) bilaterally. Tender punched out ulcers and stellate atrophic hypopigmented plaques (Figure 1) with peripheral hyperpigmentation, erythema, and telangiectasia (Figure 2) were seen bilaterally. In total, 6 ulcers of variable size were found on the shins and surrounding the malleoli.

Venous ultrasound of the bilateral lower extremities showed no evidence of deep vein thrombosis. The ankle brachial index was normal (left, 1.04; right, 1.05). Wound cultures were negative. A 4-mm punch biopsy was taken from the left calf. The histologic findings demonstrated a mild perivascular infiltrate with red blood cell extravasation. The walls of the dermal vessels showed thickening and hyalinization of the tunica intima (Figure 3). These findings were consistent with a diagnosis of livedoid vasculopathy.

The patient was referred to our wound care center and was treated with compression therapy. The ulcerations were covered with a silver-impregnated dressing and 2-layer knee-high elastic compression wraps. The patient attended weekly follow-up appointments for dressing changes; by the third follow-up the

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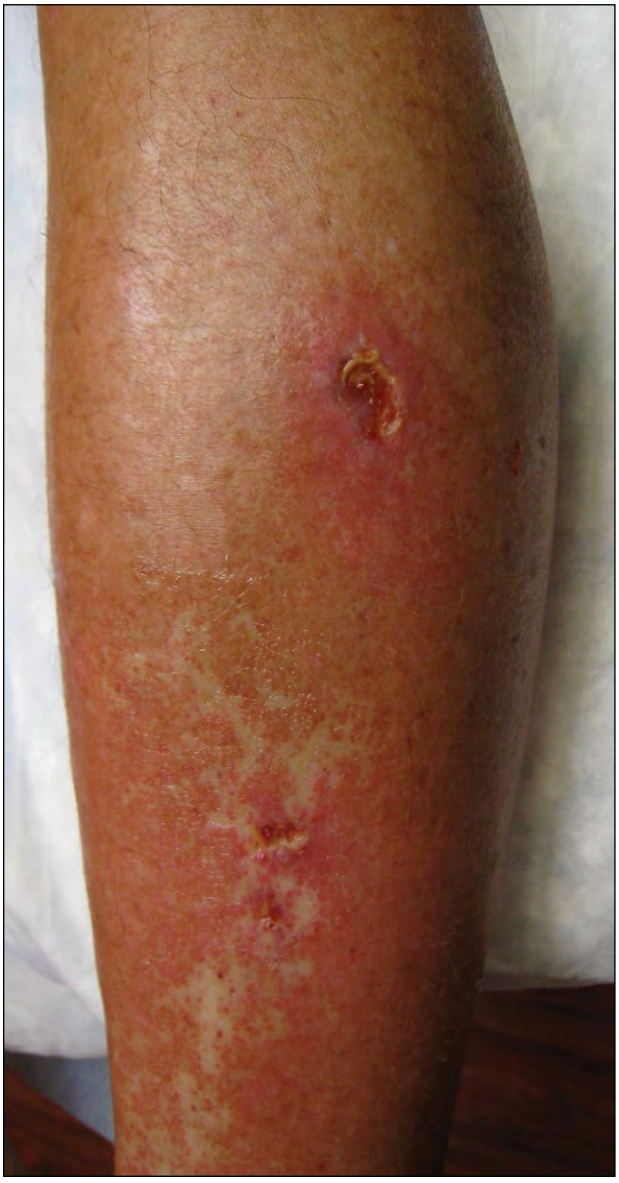

Figure 1. Punched out ulcers and stellate atrophie blanche.

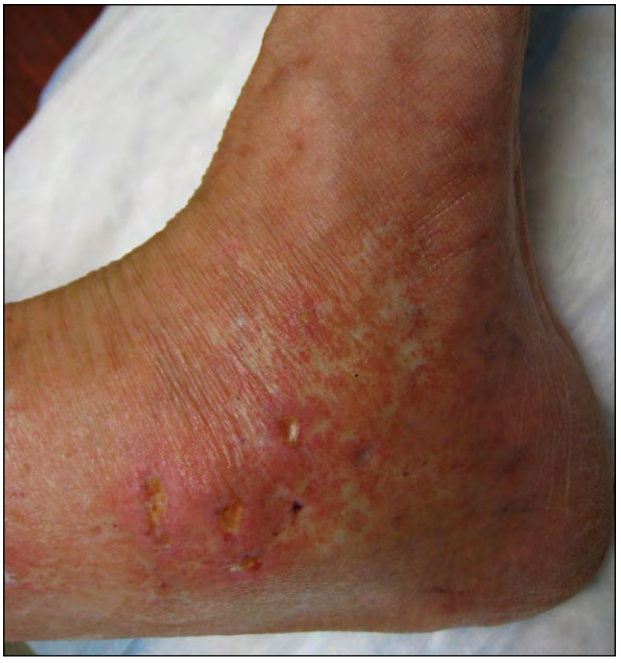

Figure 2. Reticulated atrophie blanche with peripheral hyperpigmentation, erythema, and telangiectasia.

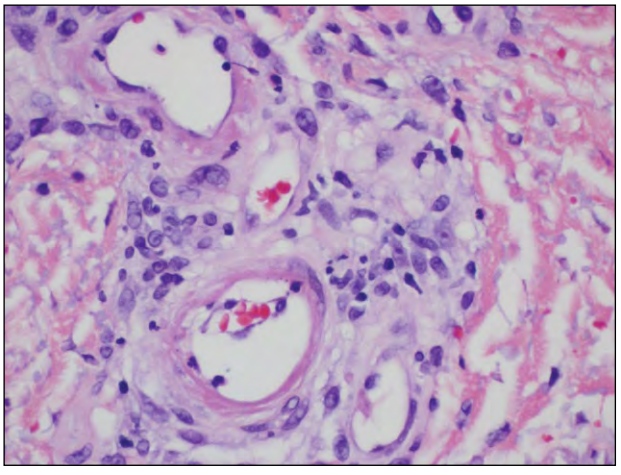

Figure 3. Mild perivascular infiltrate with red blood cell extravasation and thickening of vessel walls with hyalinization of the tunica intima (H&E, original magnification ×60).

ulcers had completely epithelialized. The patient subsequently refused workup for underlying systemic coagulopathy.

Comment

Livedoid vasculopathy is a disorder of the blood vessels most commonly seen in adult women. The pathogenesis is not well understood but is believed to involve alteration of local or systemic control of coagulation, causing formation of fibrin thrombi focally within the superficial dermal blood vessels. Thrombosis causes superficial tissue ischemia and necrosis with resulting pain and ulceration.[1]

Patients with livedoid vasculopathy clinically present with chronic painful ulceration and scarring of the lower extremities. The ulcers favor the distal lower extremities, particularly around the malleoli. Ulcers are punched out and slowly heal to form stellate, reticulated, atrophic scars known as atrophie blanche. Peripheral telangiectasia, erythema, hyperpigmentation, and/or purpura may be present. It also is common for livedoid vasculopathy to

present as chronic atrophie blanche with no history of ulceration.[2]

The differential diagnosis of ulceration on the legs is broad, and atrophie blanche is not specific to livedoid vasculopathy. Ulceration also can result from vasculitides such as small-vessel vasculitis, microscopic polyarteritis, polyarteritis nodosa, and granulomatous vasculitis, as well as peripheral vascular disease resulting from venous or arterial insufficiency.[3,4] Leg ulceration is a possible complication from treatment with hydroxyurea.[3] Various systemic coagulopathies have been observed in patients with livedoid vasculopathy, suggesting that dermal thrombosis plays a primary role in the disease pathogenesis.[5] These coagulopathies include the antiphospholipid syndrome,[6-9] dysproteinemias,[3] genetic thrombophilic disorders such as factor V Leiden (R506Q) mutation,[1] deficiency in protein C or S,[10,11] hyperhomocysteinemia,[12] sickle cell anemia, and other disorders of abnormal platelet activation or fibrinolysis.[13-16]

A thorough clinical history that rules out other common causes of atrophie blanche as well as a tissue biopsy may help to definitively diagnose livedoid vasculopathy. Because biopsy sites typically have a prolonged healing time, repeat biopsies are discouraged.[3,5] Characteristic findings include intraluminal thrombosis, fibrin deposition, endothelial proliferation, hyalinized degeneration of the subintimal layer of superficial dermal vessels with extravasated red blood cells, and mild perivascular lymphocytic infiltrates.[17] The term *vasculopathy* is preferred over *vasculitis*, as the inflammatory component is minimal.[1] Immunofluorescence findings are nonspecific and include superficial vessel deposition of immunoglobulins, complement components, and fibrin, suggesting a possible immune-mediated component to the pathogenesis.[3,18]

The diagnostic workup should first rule out common causes of atrophie blanche such as venous insufficiency. Although our patient's symptoms were not directly caused by venous disease, we feel it did aggravate the underlying livedoid vasculopathy. Venous insufficiency is easily treated with compression therapy. Although venous stasis is the most common cause of atrophie blanche, livedoid vasculopathy is not diagnosed without a component of dermal intravascular thrombosis. The physician also can search for an underlying systemic coagulation defect; however, we do not feel it is necessary to order the entire coagulopathy profile unless systemic symptoms suggest otherwise.

Various treatment modalities for livedoid vasculopathy have been documented.[19] Basic wound care including zinc oxide, glycerin, gelatin bandages should be employed. Physical modalities such as leg elevation and compression stockings also are extremely effective.[1,20] Any underlying coagulation disorder should be specifically addressed. Elevated levels of homocysteine or a mutation of methylenetetrahydrofolate reductase respond to treatment with folic acid and possibly vitamin B complex[21,22]; idiopathic cryofibrinogenemia responds to treatment with anabolic steroids such as danazol, stanozolol, or ethylestrenol.[23-26] Tissue plasminogen activator and other antithrombotics have been shown to be efficacious in some patients[14,27,28]; however, the potential benefits must be weighed against the risk for complications as well as the high cost of treatment and necessity for inpatient administration. Antiplatelet agents such as aspirin, dipyridamole, ticlopidine, pentoxifylline, ketanserin, and prostacyclin analogues iloprost and beraprost have been successfully used.[7,15,29-37] Vitamin K antagonists such as warfarin and heparin are effective in some patients when used as monotherapies.[4,38-46] Low-molecular-weight heparin (enoxaparin sodium) is recommended for use only in patients who are refractory to antiplatelet and vitamin K antagonists due to cost, compliance with injections, and the long-term risk for osteoporosis.[44,46] Corticosteroids have a fibrinolytic effect, but additional benefit from an anti-inflammatory component cannot be excluded.[27] Psoralen plus UVA light therapy has helped some patients.[47,48] Antimalarial drugs such as hydroxychloroquine have been utilized in patients with lupus or antiphospholipid antibodies and atrophie blanche. Patients with atrophie blanche–like lesions who currently are taking hydroxyurea may need a trial period off the drug, as hydroxyurea may mimic this syndrome through unknown mechanisms.[3] Other treatment options include hyperbaric oxygen,[49,50] intravenous immunoglobulins,[51,52] niacin,[2] dihydropyridine calcium channel blockers such as nifedipine,[46] and immunosuppressive therapies.[53] Combination therapies also have been reported to be effective.[3,46] Smoking cessation also should be encouraged.[3]

Conclusion

Livedoid vasculopathy is a clinical syndrome of chronic painful ulceration of the lower extremities and atrophie blanche in the context of histologic evidence of intraluminal thrombosis of dermal vessels and is commonly seen in conjunction with systemic coagulation abnormalities. Underdiagnosis and inappropriate management of the disorder have been the result of numerous challenges in diagnosis, including a nebulous etymology, broad differential diagnosis of leg ulceration and atrophie blanche, concomitant systemic coagulopathies, and lack of standard treatment guidelines. Treatment options are varied and include managing specific underlying coagulation

disorders, platelet activation, and fibrinolysis. Proper wound care in patients with livedoid vasculopathy is essential. With the addition of the correct dressing to maintain an effective environment for healing in combination with compression therapy, our patient had dramatic improvement. In our experience, systemic medications such as aspirin, pentoxifylline, and danazol are helpful and may be added if symptoms do not improve or worsen.

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