Warfarin Therapy for Livedoid Vasculopathy Associated With Cryofibrinogenemia and Hyperhomocysteinemia

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Background: Livedoid vasculopathy is an idiopathic, chronic disorder manifested by painful, purpuric macules on the lower extremities that superficially ulcerate, resulting in atrophic, stellate scars with peripheral telangiectasias and hyperpigmentation.

Observations: A 50-year-old man presented with recurrent, painful ulcerations on the medial aspect of his malleoli and calves. The clinical presentation, histologic findings, and results of laboratory evaluation confirmed the diagnosis of livedoid vasculopathy in this case. Despite being refractory to treatment with multiple other medications, the lesions responded dramatically to oral warfarin sodium therapy.

Conclusion: Treatment with warfarin may be a beneficial therapy for patients with livedoid vasculopathy.

LIVEDOID VASCULOPATHY (also known as atrophie blanche, livedo vasculitis, segmental hyalinizing vasculitis, and livedo reticularis with summer/winter ulceration) is an idiopathic disorder that was first described by Bard and Winkelmann in 1967. Although this uncommon chronic condition has previously been classified as a localized vasculitic process, it appears instead to be a cutaneous vasculopathy. The disorder most commonly affects young to middle-age women, with a male-female ratio of 1:3. The earliest lesions consist of painful, purpuric macules that are primarily located on the lower extremities. The lesions then superficially ulcerate and slowly heal over 3 to 4 months, leaving atrophic, stellate scars with surrounding telangiectasias. Histologically, deposition of homogeneous, fibrinoid material within superficial dermal blood vessels is observed along with occasional extravasation of erythrocytes. There is no evidence of leukocytoclastic vasculitis.

Although the etiology is unknown, microcirculatory or thrombotic mechanisms have been implicated in the pathogenesis owing to the relative success of fibrinolytic and antiplatelet therapies. However, livedoid vasculopathy remains a difficult condition to manage, with no clearly defined treatment of choice. Herein, we provide a retrospective analysis of a case of livedoid vasculopathy that responded dramatically to warfarin therapy despite being refractory to treatment with multiple other systemic medications.

REPORT OF A CASE

A 50-year-old man presented with a 2-year history of recurrent, painful ulcerations that were affecting the medial aspect of his malleoli and calves. His medical history was significant for hypertension, which was adequately controlled with diet and exercise. He had been evaluated by a dermatologist 2 years earlier. A biopsy specimen obtained at the time reportedly showed leukocytoclastic vasculitis. Also, the patient’s initial workup revealed a weak positivity for anticardiolipin antibody. Based on these results, anticardiolipin syndrome with thrombotic vasculopathy was initially diagnosed. Treatment with nonsteroidal anti-inflammatory medications and oral prednisone resulted in no significant improvement.

A rheumatologist also assessed the patient because of his preliminary diagnosis of possible primary antiphospholipid antibody syndrome. The results of the following laboratory investigations were negative or normal: complete blood cell count, comprehensive metabolic panel, and tests...
for lupus anticoagulant, ant cardiolipin antibody, antinuclear antibody, and complement levels. The findings of noninvasive vascular studies (venous and arterial Doppler studies) were also within normal limits. The patient was subsequently referred (to J.P.C.) for additional evaluation and recommendations regarding treatment.

Physical examination revealed erythematous ulcerations with hemorrhagic crust on the medial aspect of both malleoli (Figure 1). His lower extremities also exhibited vascular engorgement in a livedoid pattern that extended from his shins to the plantar aspect of both feet (Figure 2). Blood chemistry tests were positive for cryofibrinogen. Also, serologic tests were positive for β2-glycoprotein IgA antibody but did not demonstrate similar IgM or IgG antibodies. Results of the following laboratory investigations were negative or normal: complete blood cell count, comprehensive metabolic panel, erythrocyte sedimentation rate, protein electrophoresis, and tests for ant cardiolipin antibody, antineutrophil cytoplasmic antibody, anti-Ro/SS-A and anti-La/SS-B antibodies, antinuclear antibody, anti–double-stranded DNA antibody, rapid plasma reagin, hepatitis C antibody, and factor V Leiden mutation. The tissue specimen from the patient’s original biopsy was also reviewed and revealed a vaso-occlusive disorder with secondary epidermal necrosis. The histopathologic findings supported a vasculopathic reaction rather than a vasculitic process due to a larger proportion of fibrinous vascular occlusion than associated inflammation. A chest x-ray film and an echocardiogram showed no significant abnormalities other than mild left ventricular hypertrophy. Given the patient’s clinical presentation, the review of previous histopathologic findings, and the results of laboratory evaluation, livedoid vasculopathy related to the fibrinogen positivity was diagnosed.

Oral hydroxychloroquine sulfate (200 mg twice a day) and oral aspirin (325 mg/d) therapy was initiated. However, new ulcerations continued to develop, without significant improvement. Two months after the hydroxychloroquine therapy was begun, oral dipyridamole (75 mg 3 times per day) was added to the treatment regimen, also without clinical improvement. After 9 months of treatment with hydroxychloroquine without a significant change in the patient’s lesions, this therapy was discontinued and oral stanozolol therapy (2 mg twice a day) was initiated. The addition of stanozolol to the treatment regimen resulted in mild improvement of the lesions. An elevated homocysteine level was discovered on subsequent laboratory evaluation, and folic acid and nicotinamide were also added to the treatment regimen. Di agnostic studies performed throughout the patient’s care consistently revealed cryofibrinogen positivity, with no noted seasonal variation.

The patient was then referred to the dermatology department at Wake Forest University, Winston-Salem, NC, for additional evaluation. The physicians at the university concurred with the diagnosis of livedoid vasculopathy and added pentoxifylline (400 mg 3 times per day) to his treatment regimen. However, because of his complaints of sexual dysfunction related to the stanozolol therapy, the dosage of the therapy was tapered, after which his skin lesions worsened.

Approximately 18 months after his initial presentation to our clinic, he was hospitalized owing to the acute development of atrial fibrillation. His cardiologist elected to discontinue his stanozolol therapy, along with his other medications, and, as therapy for his cardiac condition, to prescribe warfarin sodium (3 mg/d) along with rate controlling medications (propafenone hydrochloride and metoprolol succinate). An echocardiogram again revealed left ventricular hypertrophy, which was unchanged from his previous study. He spontaneously reverted to a normal sinus rhythm before electric cardioversion. Within 1 month of the initiation of the warfarin therapy, there was dramatic improvement of his skin lesions, with complete resolution of the lower extremity ulcerations and no additional lesional development. The dosage of warfarin sodium therapy was increased (5 mg/d), with maintenance of the international normalized ratio between 1.5 and 2.0. The patient continued to experience quiescence of his disease, with only hyperpigmented, atrophic scars consistent with atrophie blanche during long-term warfarin therapy (Figure 3). After a disease-free interval of approximately 30 months, the dosage of his anticoagulant therapy was decreased. He promptly experienced a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions. Laboratory investigations revealed a relapse of his skin lesions.
Livedoid vasculopathy is a chronic occlusive vasculopathy characterized by recurrent, purpuric lesions of the lower extremities that progress to painful, irregularly shaped ulcerations. These ulcerations heal slowly and produce the distinctive porcelain, stellate scars with ectatic vessels of atrophie blanche. Although atrophie blanche is a consequence of the lesions of livedoid vasculopathy, it is not pathognomonic of this disorder and can occur in association with other conditions such as stasis dermatitis and collagen vascular diseases.

Although it is quite distinct from a vasculitis or immune-mediated process, livedoid vasculopathy has been confused with small vessel vasculitis in the past and can be misdiagnosed, as demonstrated by our patient’s diagnostic history. The term segmental hyalinizing vasculitis was commonly used to describe livedoid vasculopathy in the 1970s. The concept of a vasculitic pathogenesis was supported by the presence of fibrin, immunoglobulin, and complement in the vessel walls of the lesions. However, livedoid vasculopathy is an interesting disorder—the clinical presentation and the histopathologic features of the lesions temporally evolve. Histologic examination of early lesions clearly shows sole deposition of fibrin in the lumen of dermal vessels without associated immunoglobulin or complement. Also, the scarcity of polymorphonuclear leukocytes and the absence of leukocytoclasis argue against a primary vasculitic process.

Other recent investigations have supported the theory of disordered coagulation as an etiologic factor by demonstrating elevated fibrinopeptide A, defective release of tissue plasminogen activator, and increased amounts of plasminogen activator inhibitor. Other reports indicate that abnormal platelet function may also play a pivotal role by showing that patients with livedoid vasculopathy exhibit increased levels of P-selectin. The favorable clinical response of patients to fibrinolytic, anticoagulant, and antiplatelet therapies is additional evidence for disordered coagulation or a thrombotic mechanism as the pathogenetic basis of livedoid vasculopathy.

Our patient also demonstrated cryofibrinogenemia along with elevated homocysteine levels, with no seasonal or temporal variation. Elevated homocysteine levels have been implicated as a risk factor for thrombotic events. The current treatment regimen for hyperhomocysteinemia is supplementation with vitamin B6, vitamin B12, and folate. Similarly, cryoglobulins have also been implicated in intravascular thrombotic processes that can result in skin infarction and necrosis. Cryoglobulinemia exhibits a myriad of cutaneous manifestations, including purpura, cold urticaria, Raynaud phenomenon, hemorrhagic crusts, and skin infarction and ulceration. The primary treatment for this disorder is immunosuppressive therapy, such as steroids, plasmapheresis, or cyclophosphamide. The use of warfarin in the management of skin lesions associated with cryofibrinogenemia has generated both successful and unsuccessful outcomes. Although our patient did exhibit both cryofibrinogenemia and hyperhomocysteinemia, we believed that these conditions were secondary to his livedoid vasculopathy.

As illustrated by our case, livedoid vasculopathy remains extremely difficult to treat. The most widely used initial treatments include aspirin, dipyridamole, subcutaneous heparin, and pentoxifylline. Also, clinical improvement has been achieved with the use of danazol, tissue plasminogen activator, nifedipine, sulfasalazine, ketanserin, intravenous immunoglobulin, and psoralen–UV-A. Our patient’s lesions were unresponsive to a variety of treatments, including aspirin, dipyridamole, pentoxifylline, hydroxychloroquine, and prednisone. His lesions were partially responsive to stanozolol therapy. However, he experienced dramatic clinical improvement after he began treatment with warfarin, which was incidentally prescribed as anticoagulant therapy after atrial fibrillation developed. Active disease progression was halted within just 1 month of sustained warfarin therapy, during which he experienced complete resolution of his ulcerations.

Although long-term warfarin therapy after the administration of tissue plasminogen activator has been reported in the literature as a successful treatment for livedoid vasculopathy, Francès and Barete recently discussed the efficacy of the use of vitamin K antagonists alone, specifically fluindione, in the treatment of refractory livedoid vasculopathy. The use of vitamin K antagonists in the treatment of this disorder is a logical choice because of the reported success of other antico-
agulant medications, such as heparin. Warfarin is a commonly used vitamin K antagonist that produces its anticoagulant effect by inhibiting the vitamin K conversion cycle that is necessary for the biologic activation of coagulation factors (factors II, VII, IX, and X) and proteins C and S via posttranslational carboxylation. The use of warfarin rather than heparin for long-term anticoagulation therapy has numerous advantages, including oral administration, once-daily administration, lower incidence of thrombocytopenia, and decreased cost.

Livedoid vasculopathy remains an uncommon disorder that can be difficult to manage effectively. Anticoagulant, antiplatelet, and fibrinolytic therapies have been used in the treatment of this disease, with varying degrees of success. Our patient exhibited livedoid vasculopathy that was unresponsive to treatment with a variety of agents but quickly improved with the administration of warfarin. Consequently, warfarin therapy may be considered a treatment option for patients with refractory livedoid vasculopathy.

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REFERENCES