Treatment of Livedoid Vasculopathy With Low-Molecular-Weight Heparin

Report of 2 Cases

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 23-year-old man who was otherwise healthy had a 5-year history of recalcitrant ulcers of the lower extremities. The ulcers worsened in warm weather and during periods of increased physical activity. The ulcers were painful and interfered with his participation in sports, including soccer and basketball. Shallow ulcers and crusting with stellate, porcelain-white scarring and surrounding hyperpigmentation on the lower extremities and dorsal feet were noted on examination (Figure 1).

Noninvasive vascular testing, including continuous-wave venous Doppler imaging and measurements of the ankle-brachial index and transcutaneous oximetry (TcPO2), revealed moderately to severely reduced TcPO2 levels but no evidence of venous insufficiency. Histopathologic analysis of a skin biopsy specimen from the left ankle was notable for hyalinization of dermal blood vessels in the papillary and superficial reticular dermis and minimal perivascular lymphocytic infiltrate (Figure 2). Direct immunofluorescence study showed superficial vessel deposition of IgG, IgM, and C3 conjugates with patchy deposition of fibrin. Results of laboratory studies, including an extensive screen for coagulation abnormalities, were normal. Taken together, these findings were consistent with a diagnosis of livedoid vasculopathy. Several treatment approaches had been ineffective in controlling ulceration. These approaches included topical corticosteroids, compression therapy, stanozolol, and a triple regimen of pentoxifylline (400 mg, 3 times daily for 29 months), nifedipine (30 mg/d for 21 months), and aspirin (81 mg/d for 29 months).

CASE 2

A 59-year-old man had been treated for seasonal, painful ulcers of the lower extremities for 4 years. His history was also notable for a low-grade B-cell lymphoproliferative disorder. His skin lesions were pruritic and started in the warm months of spring and summer. The ulcers were painful and interfered with his participation in sports, including soccer and basketball. Shallow ulcers and crusting with stellate, porcelain-white scarring and surrounding hyperpigmentation on the lower extremities and dorsal feet were noted on examination (Figure 3).

Noninvasive vascular testing, including continuous-wave venous Doppler imaging and measurements of the ankle-brachial index and transcutaneous oximetry (TcPO2), revealed moderately to severely reduced TcPO2 levels but no evidence of venous insufficiency. Histopathologic analysis of a skin biopsy specimen from the left ankle was notable for hyalinization of dermal blood vessels in the papillary and superficial reticular dermis and minimal perivascular lymphocytic infiltrate (Figure 4). Direct immunofluorescence study showed superficial vessel deposition of IgG, IgM, and C3 conjugates with patchy deposition of fibrin. Results of laboratory studies, including an extensive screen for coagulation abnormalities, were normal. Taken together, these findings were consistent with a diagnosis of livedoid vasculopathy. Several treatment approaches had been ineffective in controlling ulceration. These approaches included topical corticosteroids, compression therapy, stanozolol, and a triple regimen of pentoxifylline (400 mg, 3 times daily for 29 months), nifedipine (30 mg/d for 21 months), and aspirin (81 mg/d for 29 months).
liferative disorder (IgG λ monoclonal protein) previously treated with rituximab. The ulcerative disease did not improve during the course of rituximab treatment. Physical examination revealed shallow, crusted ulcers and surrounding stellate white scars with telangiectases and hyperpigmentation on the anterior shins and dorsal feet.

Noninvasive vascular testing, including continuous-wave venous Doppler imaging and measurements of the ankle-brachial index and TcPo2, showed moderately to severely reduced TcPo2 of the anterior part of both legs and the left dorsal foot. A skin biopsy specimen from the lower extremity revealed ulceration with hyalinizing, fibrinoid changes of the small to medium dermal blood vessels without marked inflammation. A direct immunofluorescence study of the skin specimen demonstrated vascular staining with C3 and fibrinogen. Taken together, these findings were consistent with a diagnosis of livedo reticuloid vasculopathy. An extensive coagulation screen and polymerase chain reaction analysis revealed heterozygosity for the factor V R506Q (Leiden) mutation.

Because of the refractory nature of his active ulcers and secondary pain, the patient was hospitalized on the inpatient dermatology service and treated with topical corticosteroids, topical antibiotics, and wet dressings. Initially after hospitalization, his condition improved while receiving a regimen of niacin (500 mg, 3 times daily for 8 months), pentoxifylline (400 mg, 3 times daily for 8 months), and aspirin (81 mg/d for 8 months). Treatment with these medications was discontinued by the patient, who continued topical corticosteroid therapy. The ulcerations recurred within 6 months and were recalcitrant to reintroduction of his previous regimen.

Treatment with these medications was discontinued by the patient, who continued topical corticosteroid therapy. The ulcerations recurred within 6 months and were recalcitrant to reintroduction of his previous regimen. Warfarin was considered; however, it was not an appropriate therapy for him because his residence in a rural area had previously made it difficult to maintain a therapeutic international normalized ratio.

**THERAPEUTIC CHALLENGE**

As outlined in the clinical cases, numerous therapies had been undertaken without success in healing the extensive, painful, and scarring ulcers of livedoid vasculopathy. Our challenge was to treat these recalcitrant lesions with an alternative agent that would lead to improvement in physical manifestations and alleviation of the pain associated with the ulcers.

**SOLUTION**

A trial of subcutaneous injectable enoxaparin, a low-molecular-weight heparin, was initiated in our patients after patient education in self-administration. In both cases, the patients were maintained on their current oral regimens (pentoxifylline, extended-release nifedipine, and aspirin in case 1; extended-release niacin, pentoxifylline, and aspirin in case 2). Two dosing regimens were used. Patient 1 received enoxaparin, 1 mg/kg by subcutaneous injection every 12 hours, which is the dosage of enoxaparin used to treat active thrombosis.1 Patient 2 was treated with 30 mg by subcutaneous injection every 12 hours, which is the perioperative prophylactic dose against deep venous thrombosis.1 Patient 1 noted no further ulceration after initiating the injections and had dramatic healing of his ulcers within 4 months (Figure 3). Repeated TcPo2 measurements of the lower extremities 9 months after initiation of therapy revealed marked improvement in oxygenation with normalization of previously reduced levels. His discomfort also was controlled on the regimen without further need for daily pain medications. After 6 months of therapy, his dosage was decreased to 1 mg/kg once daily with continued benefit. Patient 2 also had improvement in his ulcers in his 7 months on the enoxaparin regimen.

**COMMENT**

Livedoid vasculopathy, or livedoid vasculitis, is a disease characterized by ulceration of the lower extremities. Smooth, ivory-white plaquelike areas with surrounding telangiectases and hyperpigmentation (atrophie blanche) are commonly identified. The histopathologic features are distinctive, although not pathognomonic, and analysis usually reveals a segmental hyalinizing vascular pattern involving the dermal blood vessels, with vessel thickening, endothelial proliferation, and focal thrombosis without leukocytoclasis.2 Direct immunofluorescence staining typically demonstrates immunoglobulin and complement components in the superficial, mid-dermal, and deep dermal vasculature.3 The underlying cause is not yet fully understood; however, the disease has been reported in individuals with altered coagulation, including factor V Leiden mutation,4 protein C deficiency,5 antiphospholipid antibody syndrome,6 increased plasma homocysteine levels,7 abnormalities in fibrinolysis,8 and increased platelet activation.9

Because potential thrombogenic mechanisms may be involved in the disease pathogenesis,10,11 anticoagulant therapy is often tried. The Table lists anticoagulant and fibrinolytic therapies that have been reported in the English-language medical literature as treatments for livedoid vasculopathy.12-24 Anticoagulant therapy with warfarin is another option. Treatment at our institution has shown nicotinic acid to be helpful.25 Psoralen plus UV-A has also been reported as an effective treatment modality.26,27

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Figure 3. Marked improvement in the ulcers of the dorsal feet (patient 1 after 4 months of treatment with enoxaparin).
Our cases illustrate the use of enoxaparin as a potential therapy for livedoid vasculopathy. Patient 1 is an otherwise healthy young man with ulcers refractory to standard therapies. He has had dramatic and sustained clinical improvement as he continues with the subcutaneous injections. Levels of TcPO2, once moderately to severely reduced, are within the normal range. His pain management has been markedly improved as well. Patient 2 may have an underlying thrombotic diathesis with the factor V Leiden mutation, in addition to his chronic low-grade B-cell lymphoproliferative disorder. This patient was maintained on the therapy during the summer months, when his disease was usually more severe, and had an improved response compared with that obtained with previous treatments. His lymphoproliferative process was stable during the heparin therapy. He had flaring of his disease in the late summer months because of increased activity and bacterial impetiginization, and his course was discontinued at that time. Patient 1, who received 1 mg/kg of enoxaparin twice daily, had a more effective and prolonged response to the medication. Benefits continued with a decrease in dosage to 1 mg/kg each day. Neither patient had any adverse effects or difficulties in compliance while receiving the enoxaparin regimen.

Enoxaparin is widely used perioperatively in the prevention of deep venous thrombosis in patients having orthopedic surgery; it is also used as treatment of acute deep venous thrombosis. Enoxaparin has been proven effective in the prevention of ischemic complications of unstable angina and non-Q-wave myocardial infarction. It acts by neutralizing factor Xa activity, assays of which may be monitored if necessary. Enoxaparin therapy may be an acceptable alternative for the patient with livedoid vasculopathy whose disease is refractory to other therapies, the patient in whom appropriate anticoagulation cannot be maintained with use of warfarin, or the patient who is hesitant to initiate advanced therapy such as the use of tissue plasminogen activator. The optimal dosage of low-molecular-weight heparin for treatment and management of livedoid vasculopathy has not been determined.

The adverse effects of enoxaparin are similar to those of unfractionated heparin. They include minor and major hemorrhages (including retroperitoneal or intracranial bleeding) and thrombocytopenia. However, a weight-adjusted dosage of enoxaparin is as efficacious as unfractionated heparin in the treatment of deep venous thrombosis and is more convenient for patients to use; monitoring of the activated partial thromboplastin time is not necessary. Similarly, enoxaparin does not require monitoring of the therapeutic international normalized ratio, as does warfarin. However, patients should be counseled regarding the risks of hemorrhage while they are receiving enoxaparin, and contraindications to anticoagulation should be fully reviewed before therapy is initiated. Candidates also should be screened for risk of osteoporosis, a potential complication of heparin therapy, and considered for calcium supplementation. Our patients were started on an aggressive regimen of enoxaparin in combination with their previous medications, including aspirin. Although the concomitant use of aspirin and anticoagulants is usually avoided because of the increased risk of bleeding, the severity of the disease in our patients warranted aggressive therapy; potential risks were appropriately reviewed with the patients before treatment.

Low-molecular-weight heparin is expensive compared with other therapies discussed in the treatment of this disease. However, for the patient with disease recalcitrant to other therapies, the benefits of treatment with low-molecular-weight heparin outweigh the costs by providing the potential for increased occupational productivity, decreased need for inpatient or wound care therapy, and improved quality of life.

Our cases demonstrate that enoxaparin may be considered a viable alternative in the treatment of livedoid vasculopathy. It may be of particular advantage in treating patients with documented coagulation abnormalities. It should be included on the list of potential anticoagulant therapies for patients with treatment-resistant livedoid vasculopathy.

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