Livedoid Vasculopathy
—Report of One Case Treated with Warfarin—

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Livedoid vasculopathy is a chronic disorder characterized clinically by recurrent painful ulcers of the feet, ankles and legs that heal with residual white atrophic scars and histologically by intravascular deposition of fibrin. We report a 42-year-old man who had recurrent multiple painful, deep-crusted ulcerations with erythematous bases over bilateral lower legs for one and a half years. Therapeutic response to dipyridamole, pentoxiphylline and aspirin was very poor. Oral anticoagulant, warfarin was administered at 3.75mg/day and maintained for 2 months. New lesions have not recurred and existing lesions have improved after 2 months. (Dermatol Sinica 20: 51-56, 2002)

Key words: Livedoid vasculopathy, Warfarin

Introduction

Livedoid vasculopathy is also known as livedo vasculitis, livedo reticularis with summer or winter ulceration or atrophia blanche. It is a chronic disorder manifested as recurrent painful and non-healing ulcers, predominantly localized in lower legs. Women are more affected than man with the male to female ratio of 1:4. It may
occur at any age with a peak incidence ranges from 30-60 years. Although the course and precise pathophysiology are not entirely known, the deposition of fibrinoid material in dermal and/or subcutaneous vessels with secondary ischemic change of the overlying skin suggests an underlying thrombo-occlusive process. Recent studies implicated that livedoid vasculopathy can be regarded as the superficial counterpart of deep-vein thrombosis with similar pathophysiology. The mainstay of treatment at present includes oral aspirin, dipyridamole, pentoxiphylline, subcutaneous heparin and danazol with variable response. On the bases of recent investigations indicating hypercoagulable status may be the cause of livedoid vasculopathy, we choose to treat the lesions with warfarin, an inexpensive and easy-to-use oral anticoagulant.

CASE REPORT
A 42 year-old man suffered from recurrent multiple painful, deep crusted ulcerations with erythematous to violaceous bases over bilateral lower legs of one and a half years duration. Despite of various treatment regimens including topical corticosteroid, Duoderm, oral dipyridamole, aspirin, prednisolone, and pentoxiphylline administered at different hospitals, the disease progressed with further development of purple papules and ulcerations. He was admitted to TMUH. Physical examination revealed BT: 36.3°C, HR: 80 bpm and RR: 18 times/min. There were multiple ulcers with crust formation and violaceous papules on bilateral lower legs, ankles and feet (Fig. 1a). His medical history was not significant. The following laboratory studies were within normal limits: complete blood count, erythrocyte sedimentation rate, C reactive protein, liver function test, renal function test, electrolytes, prothrombin time, activated partial thromboplastin time, antiphospholipid antibody, anticardiolipin antibody, anti-nuclear antibody, protein C, and antithrombin III. Histopathologic study showed atrophic epidermis with ulceration and focal necrosis, fibrinoid necrosis of blood vessels with fibrin thrombi and thickened vascular wall in the dermis and subcutis, red blood cells extravasation, and mild lymphocytic infiltration. No nuclear dusts or intramural neutrophil infiltration was noted (Fig. 2a, b).

After admission, oral anticoagulant warfarin was administered with the initial dose of 2.5 mg per day. The dosage of warfarin was adjusted according to the prolongation of prothrombin time. No new skin lesions developed after the administration of warfarin and original skin ulcerations healed gradually within the next 2 months (Fig. 1b). No adverse side effect was noted during the course of treatment.

DISCUSSION
Livedoid vasculopathy is a chronic recurrent disease with painful ulceration of the feet, ankles and legs. It is characterized by purpuric papules and plaques that undergo superficial necrosis and heal with residual white atrophic scarring. The histopathologic hallmark is segmental hyalinization, endothelial proliferation, fibrin deposition, and thrombus formation in superficial and deep dermal vessels with minimal perivascular lymphocytic infiltration. For many years, livedoid vasculopathy has been considered to be a primary vasculitic process. Recently, however, a new school of thought considers hypercoagulable state with resulting occlusive vasculopathy as its etiology. McClamont et al. found elevated level of fibrinopeptide A, a peptide resulting from the cleavage of thrombin. Proteins C and S are two vitamin K-dependent proteins characterized by their activities of inhibiting coagulation cofactors Va and VIIIa. Thus, deficiency of protein C or S allows coagulation to proceed relatively unchecked and predisposes one to a thrombotic tendency. Boyrat et al. reported two cases of livedoid vasculopathy associated with heterozygous protein C deficiency. Papi et al. found platelet and lymphocyte activation present in livedoid vasculopathy, whereas the levels of inflammatory mediators are within the normal range. Antiphospholipid antibody syndrome is an acquired multi-system disorder of hypercoagula-
tion in which venous or arterial thrombi, or both, develop. Acland et al.\(^9\) reported four patients with livedoid vasculopathy associated with increased levels of anticardiolipin antibodies without systemic manifestations. Factor XII is the initiator of the intrinsic coagulation cascade system and is regarded as a coagulation factor in the past. However, recent studies\(^{10-11}\) have indicated that factor XII may be more important as a fibrinolytic activator and that its deficiency may be a risk for thrombosis. Superficial migratory thrombophlebitis\(^9\) and leg ulcer\(^9\) have been documented as skin manifestations of factor XII deficiency. Matsumura et al.\(^14\) demonstrated factor XII deficiency to be a possible cause of livedoid vasculopathy in two patients and found the ulceration healed with the oral anticoagulant, warfarin. Coagulation factor Va is inactivated by activated protein C. A single point mutation (Factor V Leiden) renders factor Va resistant to inactivation by activated protein C.\(^15\) As a result, Factor V Leiden has been associated with thrombotic episodes and is reported to be the single most common cause of congenital thrombophilia. Tilo et al.\(^16\) has reported a case of livedoid vasculopathy associated with factor V mutation (Leiden). Homocysteinemia has been reported to be associated with arterial and venous thromboembolic events at an early age.\(^17\) Gibson et al.\(^18\) found elevated homocysteine levels among patients with livedoid vasculopathy. However, the actual correlation between homocysteine and livedoid vasculopathy needs further studies. Based on the above findings, we speculate that livedoid vasculopathy is a final presentation of different etiologies leading to hypercoagulability. In the past, hypercoagulability has more often been considered in patients with deep-vein thrombosis, a veno-occlusive disorder of the deep veins of the lower extremities. Vaso-occlusion of dermal and subcutaneous vessels, such as livedoid vasculopathy, can be regarded as the superficial counterpart of deep-vein thrombosis. Therefore, patients suffer from a similar pathophysiology except for the rare incidence of systemic embolization. An interesting question arises as to why thrombosis of the same mechanism affects vessels of different sizes and results in various clinical manifestations. We think the endothelial cells of various sized vessels play different roles in these two similar diseases.

Oral dipyridamole, pentoxyphylline, aspirin and low-dose subcutaneous heparin are the mainstay of treatment for patients with livedoid vasculopathy at present. Danazol\(^15\) and calcium channel blocker\(^19\) are also recently reported to be effective. Among the treatment modalities, subcutaneous low-dose heparin seems to be the most promising, and it is reasonable to use anticoagulants for an underlying hypercoagulability. Heparin and warfarin are widely used anticoagulants with different mechanisms for the treatment of deep-vein thrombosis. However, intravenous or subcutaneous drug administration may be uncomfortable or even intolerable for some patients based on the chronicity of the disease. Due to the above reasons, we chose to give the patient oral warfarin as it is an inexpensive, convenient and long-lasting way to treat livedoid vasculopathy.

Warfarin, a vitamin K antagonist, reduces hepatic production of vitamin K-dependent coagulation factors II, VII, IX and X, and protein C.\(^20\) It is widely used in some hereditary and acquired hypercoagulable disorders such as protein C and S deficiency and antithrombin deficiency to prevent venous thromboembolism. It is usually administered following intravenous heparin to maintain anticoagulability in patients with thromboembolic disease. The doses are adjusted according to prothrombin time expressed in international normalized ratio (INR). The therapeutic range of INR is 2.0-3.0; higher values are associated with greater bleeding tendency, but no greater efficacy. Warfarin causes the plasma concentrations of functional factor VII and protein C to fall quickly because of their short half lives (6-8 hours), whereas decreases in other clotting factors are delayed for 24-48 hours. Therefore, when warfarin therapy begins, the initial anticoagulant effect is
preceded by a transient hypercoagulable state because protein C concentrations are concomitantly low. This is why warfarin-induced skin necrosis occurred. Contraindications for warfarin usage include active bleeding, genitourinary/gastrointestinal bleeding within 10 days, active peptic ulcer disease, recent major trauma, defective hemostasis, invasive surgical procedure within 10 days, and the first trimester of pregnancy due to the possibility of teratogenicity. In patients with protein C and S deficiency, the initial dose should be lower.

In the case presented herein, the skin lesions progressed despite the combination of dipyramole and pentoxyphylline treatment for one and a half years. Warfarin was administered at an initial dose of 2.5 mg/day, and then adjusted to maintain the INR between 2.0 and 3.0. Local treatment included wet dressing three times per day. No new skin lesions were found after warfarin use, and old ulcers gradually healed. The investigation for hypercoagulation, protein C, antithrombin, antiphospholipid antibody, and anticardiolipin antibody were all
within normal limits. However, this could not exclude the absence of hypercoagulability. In our patient, as in many other individuals, the definable cause of hypercoagulability cannot be determined by present laboratory investigations. The fact that the disease activity persisted for many months despite various aggressive treatments but subsided after the administration of warfarin supports our hypothesis.

In conclusion, when evaluating a patient with livedoid vasculopathy, the possibility of hypercoagulation should be extensively investigated to determine the underlying etiology. Oral dipyridamole and pentoxyphylline can be administered first. If the response is poor, more-aggressive treatment such as anticoagulants can then be given. Oral anticoagulant warfarin serves as a relatively safe and convenient treatment modality under the guise of prothrombin time measurement. Hospitalization is needed only to determine the loading of warfarin and for adjusting the maintenance dosage. However, the optimal duration of anticoagulation administration in patients with livedoid vasculopathy needs to be determined by further prospective studies.

REFERENCES