Three Cases of Livedoid Vasculitis Improved by Low-dose Danazol

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Livedoid vasculitis is characterized clinically by smooth or depressed ivory-white scars surrounded by hyperpigmentation and telangiectasia with or without preceding purpuric infiltrated papules and plaques and histologically by intravascular deposition of fibrin. Its pathophysiology is still obscure. Many treatment modalities have been used, but results are not satisfactory.

Recently, there have been experiences of successful treatments with danazol, a synthetic androgen. We used danazol in three patients who presented with livedoid vasculitis and were relatively resistant to treatments with aspirin and/or pentoxifylline. After 4 to 8 weeks, there was remarkable clinical improvement in all three patients.

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Key Words : Danazol, Livedoid vasculitis

Livedoid vasculitis is a chronic disorder with periodic painful skin eruptions, leaving atropic ivory-white scars on the lower extremities. This disease mainly affects young and middle-aged women and is usually not associated with any underlying systemic diseases. Its incidence in Korea is still unknown but it is considered not rare. Livedoid vasculitis is still obscure in its precise pathophysiology and is very difficult to treat. Many treatment modalities have been used, but there is no consistently effective treatment method.

Danazol, a synthetic androgen with a potential fibrinolytic effect, has been used in the management of endometriosis, hereditary angioedema, and fibrocystic disease of the breast, and was also reported to be effective in livedoid vasculitis at low-dose.

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CASE REPORT

Case 1

A 16-year-old woman was presented with a 3-year history of recurrent painful ulcers on both lower legs. Her skin lesions were exacerbated especially during summer. Black crusted ulcers with peripheral brownish pigmentation were observed(Fig. 1). Her past medical history and family history were not contributory. On laboratory examinations including CBC, LFT, BUN/Cr, U/A, VDRL, fibrinogen, plasminogen, and antithrombin III, there were no abnormalities except positive anticardiolipin antibody. On histopathologic examination, there was a fibrinoid deposition at the lumen and the wall of small blood vessels(Fig. 2) and perivascular lymphohistiocytic infiltration in the dermis. At first we treated her with aspirin 400mg/day, but after 4 weeks her skin lesions were aggravated. Therefore we increased the dose of aspirin(600mg/day) and she showed clinical improvement after 4 weeks. Next summer her skin lesions were aggravated and we used aspirin(400mg/day) and pentoxifylline(1200mg/day). After 12 weeks her skin lesions improved but were exacerbated next summer. At that time we used danazol(200mg/day), and clinical improvement was observed after 8

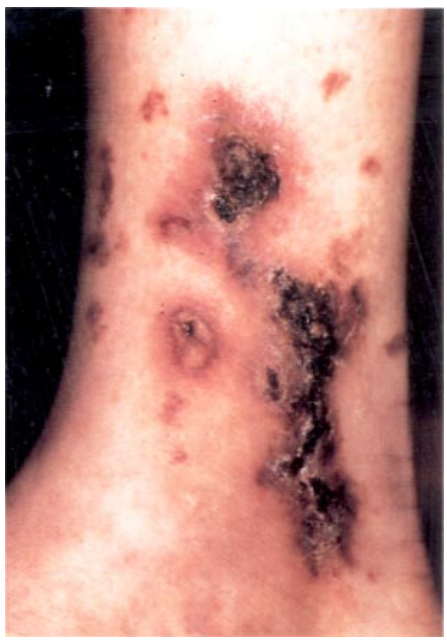

Fig. 1. Black crusted ulcers with peripheral brownish pigmentation were shown on both lower legs.

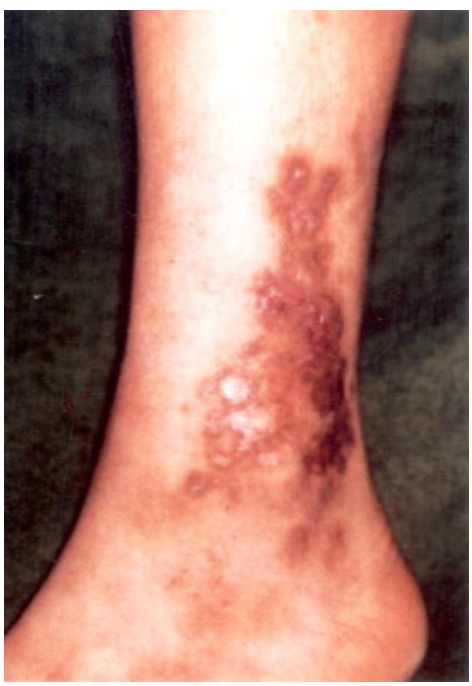

Fig. 3. There was remarkable improvement after 8-week treatment with danazol.

weeks(Fig. 3). There was no evidence of recurrence in the following 15 months.

Case 2

A 27-year-old woman was presented with a 4-year history of recurrent painful ulcers with peripheral brownish mottling on the lower legs. The lesions were exacerbated in summer. The clinical manifestation and histopathologic findings were consistent with livedoid vasculitis. On laboratory examination, there were no abnormalities except positive ANCA. We treated her with aspirin and pentoxifylline for 16 weeks, but there was no improvement. We used danazol(200mg/day) and clinical improvement was observed after 6 weeks. There was no recurrence in the following 12 months.

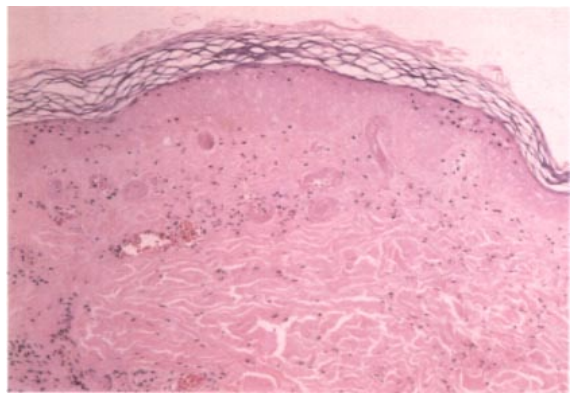

Fig. 2. Fibrinoid deposition at the lumen and the wall of small blood vessels in the upper dermis(H&E, × 200).

Case 3

A 31-year-old woman visited our department because of her lower leg lesions. She had recurrent painful ulceration for 5 years, especially in summer. Her clinical manifestation and histopathologic findings were consistent with livedoid vasculitis. Laboratory examinations showed no abnormalities. Her leg lesions improved after 8 weeks with pentoxifylline 1200mg/day, but recurred 10 months later. At that time, we used danazol 200mg/day and her lesions improved after 4 weeks. She has been free of lesions following 8 months.

DISCUSSION

Livedoid vasculitis, also known as livedo vasculitis, livedo reticularis with summer and/or winter ulceration, segmental hyalinizing vasculitis, or atrophie blanche, is a chronic disorder manifested as

recurrent, painful skin eruptions of the lower extremities. It is characterized by the presence of smooth or depressed ivory-white lesions surrounded by hyperpigmentation and telangiectasia with or without preceding purpuric infiltrated papules and plaques. Mainly affecting young and middle-aged women, it is usually not associated with any underlying systemic disease process[1,2].

The histopathologic findings are nonspecific and vary with the stage of the lesion. However, in all stages, vascular changes are present. The fibrinoid material may be noted in the vessel wall and vessel lumen in early lesions. In late atrophic lesions, the epithelium is thinned and the dermis is sclerotic. The walls of the dermal vessels may show thickening and hyalinization and fibrinoid material may be seen[3].

Though the cause and precise pathophysiology are unknown, 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. The factors that initiate this fibrin deposition are not completely understood. Defects in endothelial cell synthesis of tissue plasminogen activator and prostacyclin, dysfunction of platelets or erythrocytes, dysregulation of coagulation and fibrinolysis, vasospasm, and change in hydrostatic pressure are all possible causes. Agents that can reverse or stop the tendency of clot formation might be helpful in the treatment of livedoid vasculitis[1,2].

Many treatment modalities such as conservative methods(bed rest with leg elevation, saline soaking, elastic stockings), many drugs(sympathetic blocking agents, systemic steroids or other immunosuppressants, vasodilators, sulfasalazine, fibrinolytic agents, antiplatelet agents, dextran infusion, pentoxifylline, heparin, prostacyclin and tissue plasminogen activator), and surgical methods(lumbar sympathectomy) have been used. However, no consistent benefits have been found with any particular treatment modalities[1,2].

Danazol, a synthetic, attenuated, androgenic steroid, has been used in the treatment of endometriosis, fibrocystic breast disease, and hereditary angioedema. Recently it was tried in the management of hypoplasminogenemia, protein C deficiency, and venous thrombosis, possibly through inhibiting coagulation and enhancing fibrinolysis. Al-momen et al4 insisted that low-dose danazol(5-7mg/kg) was effective in venous thrombosis and enhanced fibrinolytic activity. Therefore it is possible to use danazol in the treatment of livedo vasculitis. Danazol induces significant changes in a large number of plasma proteins. The mechanism by which danazol exerts its effect is related to competitive receptor binding at the hepatocyte[5]. The most frequent adverse effects of danazol are androgenic effects and rarely, clitorial hypertrophy. Thus danazol should be used cautiously in patients before adolescence. But low-dose danazol is known to be free of side effects except menstrual irregularity and weight gain. Danazol may cause fetal harm, such as spontaneous abortion and congenital anomalies, when administered to pregnant women. Women of childbearing age should be instructed to use an effective, nonhormonal method of contraception during danazol therapy, and be informed of potential hazard to the fetus should they become pregnant during therapy. Danazol is also contraindicated in patients with abnormal genital bleeding and in those patients with markedly impaired hepatic, renal, or cardiac functions. In the previous reports on the use of low-dose danazol in livedo vasculitis, there have not been any side effects, except for menstrual irregularities and weight gain6-8. Amenorrhea occurs during danazol therapy in most female subjects, but menstruation usually resumes within 2 to 3 months following discontinuation of drug therapy.

Hsiao et al[1,2] insisted that low-dose danazol(200mg/day, 3-5mg/kg/day) was effective in livedoid vasculitis, and decline of fibrinogen level and disappearance of pain/tenderness were good indicators for discontinuance of the therapy. Moon and Cho[9] used danazol in nine patients with livedoid vasculitis and obtained good results after 4 to 8 weeks without significant side effects in eight patients. Only one female patient experienced amenorrhea in their study.

Recently, prostaglandin E1 and PUVA was reported to be effective in the treatment of livedoid vasculitis[10,11]. But prostaglandin E1 costs too much and PUVA needs more study on the mechanism of its action and long-term effect.

In our cases, patients had experienced spontaneous improvement to some degree in autumn or winter. But they improved more rapidly and more completely with the use of danazol than with other treatments or without treatment. And during the fol-

low-up period, there was no evidence of recurrence. There was no evidence of side effects in our cases. Thus low-dose danazol was supposed to be an effective method of treatment in livedoid vasculitis.

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