

Clinical Profile and Treatment Outcome of Livedoid Vasculitis: A Case Series

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Abstract

Introduction: Livedoid vasculitis is a painful ulcerative condition affecting the legs that is often difficult to treat. In this case series, the clinical profile of 6 patients with livedoid vasculitis and their treatment response to aspirin and pentoxifylline are reported. **Materials and Methods:** This is an open trial. Investigations to exclude secondary causes of livedoid vasculitis were done. Skin biopsies were performed for histology and direct immunofluorescence. Four patients were treated with pentoxifylline and 2 with aspirin. Response to treatment was assessed at the third and sixth weeks. Thereafter, treatment was individualised according to each patient's clinical response. **Results:** Only 1 out of 6 patients had a good response. This patient was treated with pentoxifylline. Most patients required treatment with drugs such as prednisolone, colchicine and azathioprine to control disease activity after the trial period. **Conclusion:** Pentoxifylline or aspirin did not result in significant improvement for most of our patients when used alone. Combination with immunosuppressive treatment yielded better results.

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Key words: Aspirin, Immunosuppressive, Lymphocytic vasculitis, Pentoxifylline, Prothrombotic

Introduction

Livedoid vasculitis is a clinicopathological entity that has variously been referred to as atrophie blanche, livedoid vasculopathy or segmental hyalinising vasculitis.^{1,2} It presents with purpuric lesions and recurrent, painful ulcerations of the lower limbs which result in depressed, atrophic white scars. This disease commonly affects middle-aged women. Histologic features, though varying with age of the lesion, are mainly characterised by hyalinising vascular changes and luminal occlusion by fibrin thrombi.³

Various treatment modalities have been used in livedoid vasculitis. Aspirin, an antiplatelet agent, inactivates platelet prostaglandin cyclooxygenase. Prostaglandin and thromboxane A₂ synthesis are inhibited, resulting in inhibition of platelet aggregation and thrombin formation.⁴ It has been used successfully in relieving pain and progression of lesions of livedoid vasculitis.⁵ Pentoxifylline, a methylxanthine derivative, has also been used in livedoid vasculitis with success.^{6,7} Its immunomodulatory actions include increasing leukocyte deformability, decreasing endothelial leukocyte adhesion and inhibition of T and B lymphocyte activation. It improves hypercoagulable states by decreasing platelet aggregation and adhesion, and enhancing fibrinolysis.⁸

This is a case series of the clinical profile of 6 patients with livedoid vasculitis and their response to 6 weeks of either aspirin or pentoxifylline therapy. Thereafter, they were given treatment as deemed appropriate by the attending physician.

Patients and Methods

The recruitment period was from August 1998 to March 2000. Six patients with recurrent, painful lower limb purpura and ulcers that healed with stellate scarring (Fig. 1), and whose biopsy was consistent with livedoid vasculitis, were recruited.

Exclusion criteria were any history of peptic ulceration, bleeding disorder, recent acute myocardial infarction, cerebral or retinal haemorrhage in the last 6 months, severe hypertension defined as diastolic blood pressure of more than 110 mmHg, pregnancy, renal or hepatic disease, and asthma (for aspirin treatment arm patients only).

Investigations were done to exclude secondary causes. These included full blood count, erythrocyte sedimentation rate, serum urea, electrolytes and creatinine, serum antistreptolysin-O titres, urine analysis, hepatitis B surface antigen, hepatitis C antibody (IgG), antinuclear antibodies, cryoglobulins, lupus anticoagulant, anticardiolipin

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antibodies and serum protein electrophoresis.

Of the 6 patients, 4 received pentoxifylline 400 mg thrice a day for 6 weeks, while the other 2 patients received aspirin 300 mg thrice a day for 6 weeks. There was a washout period of 2 weeks prior to initiation of therapy. Therapeutic response was assessed by subjective pain score (none, mild, moderate or severe) and number of ulcers, at 0, 3 and 6 weeks of therapy. The final therapeutic response was then graded as none, partial or good by the observer.

Each patient's biopsy specimen for histology and direct immunofluorescence studies were reviewed.

Results

Of the 6 patients, 5 were female. All were Chinese with a mean age of 39 years (range, 21 to 52 years). Duration of symptoms ranged from 9 months to 40 years. Two patients had livedo reticularis. No patient experienced Raynaud's phenomenon. The previous treatment they received were varied. Four patients received non-steroidal anti-inflammatory drugs (NSAIDs), 2 received dapsone, 3 received colchicine, 2 had prednisolone, and 1 patient was given daflon and vasteral before.

None of the patients had abnormal findings in the investigations to exclude secondary causes of livedoid vasculitis.

Biopsy specimens were taken from active, painful lesions. These included purpuric lesions or active ulcer edges. These showed 2 main histological patterns. Fibrinoid necrosis and thrombo-occlusion of small dermal vessels with or without involvement of subcutaneous blood vessels were seen in acute lesions (Fig. 2), while more chronic lesions showed neovascularisation in the upper dermis with scarring in the dermis and/or subcutis. A sparse perivascular infiltrate of lymphocytes with or without

neutrophils was often seen. Lymphocytes were also present in the wall of an arteriole in 1 case (Fig. 3). There was no evidence of leukocytoclasia.

Immunofluorescence of biopsy specimens showed that C3 and fibrinogen were fairly constant features in vessel walls. Immunoglobulin deposition of mainly IgM with occasional IgA was seen. Two patients had luminal deposits of fibrinogen and immunoglobulin.

Of the 4 patients treated with pentoxifylline, only 1 patient had a good response at the end of 6 weeks (Case 1). However, this patient developed diffuse alopecia after the third week of treatment, and pentoxifylline was stopped after the 6-week treatment period. One patient had a partial response (Case 2), and the other 2 had no response to pentoxifylline (Cases 3 and 4). One of the patients who had no response was subsequently lost to follow-up (Case 3). Of the 2 patients treated with aspirin, 1 had only a partial response (Case 5), while the other had no response

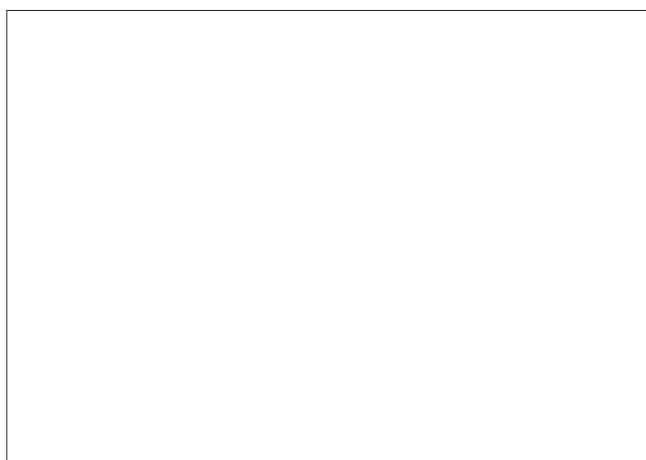


Fig. 1. Atrophie blanche: painful ulcers and atrophic scars with surrounding telangiectasia and hyperpigmentation over both feet.

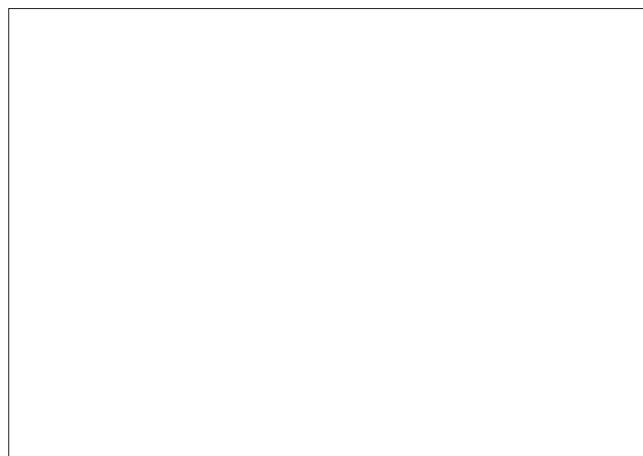


Fig. 2. Case 4—histology showing small dermal blood vessels occluded by fibrin thrombi. The epidermis is necrotic as a result of infarction. Haematoxylin and eosin stain x100.

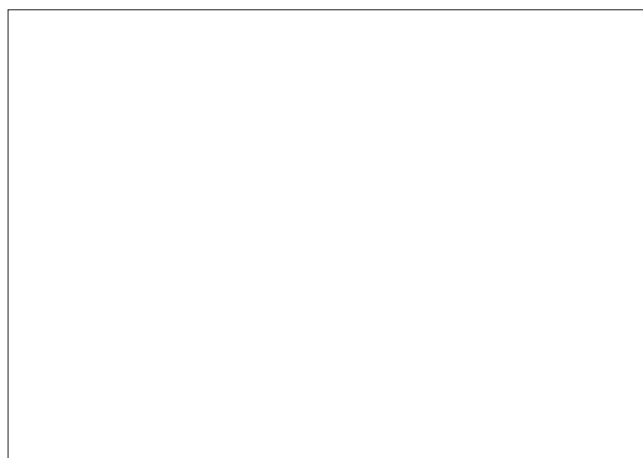


Fig. 3. Case 1—intimal hyperplasia of vessel wall, with lymphocytes infiltrating the wall of a muscular medium-sized blood vessel. Haematoxylin and eosin stain x200.

(Case 6). Subsequent treatment for all these patients required addition of immunosuppressants such as prednisolone, azathioprine and colchicine for control of disease activity.

Pentoxifylline Treatment Arm

Case 1: This 52-year-old Chinese lady had recurrent painful lower limb ulcers for 40 years. Clinically, there was atrophie blanche with keloidal scars, pupura and multiple ulcers over the legs and dorsum of both feet. Lower limb pulses were present. She was treated with dapsone in the past but defaulted follow-up for 7 years. Investigations were normal except for a high erythrocyte sedimentation rate of 60 mm/h. Skin biopsy from the edge of an active purpuric ulcer on the left leg showed proliferation of small blood vessels in the upper dermis, intimal thickening with fibrinoid deposits and lymphocytes within the wall of a subcutaneous blood vessel (Fig. 3), and a scattered lymphocytic infiltrate, consistent with atrophie blanche. Direct immunofluorescence showed deposits of C3 in the walls of several mid-dermal blood vessels. At the start of pentoxifylline treatment, she graded the pain intensity of the ulcers as severe. There were 15 ulcers on both limbs. Three weeks into treatment, the pain intensity improved and was graded as mild. The number of ulcers had decreased to 3. However, she complained of alopecia, and subsequently took only pentoxifylline 400 mg every other day on her own. At week 6, there was no more pain and the number of ulcers reduced to 3. The response to pentoxifylline was graded as good. As the alopecia was bothering her, a decision to stop pentoxifylline was made. She was given aspirin, but developed angioedema and urticaria. Prednisolone 10 mg per day and colchicine 0.5 mg thrice a day were prescribed. At week 7, 1 week after stopping pentoxifylline, she continued to have hair fall. Hair studies showed a reversal of anagen to telogen hair ratio (10%: 90%) consistent with telogen effluvium. Iron studies showed a borderline low iron level of 9 $\mu\text{mol/L}$ and a normal level of total iron binding capacity of 55 $\mu\text{mol/L}$. She was given iron supplements. At 3 months, she had no more alopecia, and was continued on a tailing down dose of prednisolone and colchicine. At 5 months, the ulcers had healed completely and prednisolone was taken off. Colchicine was taken off 7 months later. The patient had no relapse since.

Case 2: This 21-year-old Chinese lady, a student undergoing tertiary education, presented with recurrent painful lower limb ulcers associated with purpura and livedo reticularis for two and a half years. She did not experience Raynaud's phenomenon and peripheral pulses were felt. Skin biopsy taken from an active ulcer edge of the right medial malleolus showed acanthosis, dilated capillaries and vessels present in the dermal papillae and upper dermis with haemosiderin deposits. Marked fibrosis with thick

walled vessels in the fibrotic subcutis was observed. These features were consistent with atrophie blanche. Direct immunofluorescence revealed deposits of IgM, C3 and C1q in the walls of the superficial and mid-dermal blood vessels, and fibrinogen deposits within the lumen of several upper dermal blood vessels. She was variously treated with indomethacin, colchicine, dapsone, prednisolone and aspirin. At the start of the pentoxifylline treatment, she graded the pain intensity of the ulcers as severe. There were 10 ulcers. Three weeks later, the pain intensity had decreased to moderate but the number of ulcers remained at 10. At 6 weeks, the pain intensity remained at moderate but ulcers had now decreased to 7. Response to pentoxifylline was graded as partial. Pentoxifylline was continued but at week 9, the lesions worsened and prednisolone was added for control. The lesions improved; but upon tailing down the prednisolone dose, the lesions flared again. Pentoxifylline was replaced by colchicine with better control, but the patient was still steroid-dependant. Dapsone and indomethacin were also used but lesions flared when prednisolone was tapered to about 10 mg per day. Azathioprine was able to control the ulcers, and prednisolone was taken off after a year. Her lesions are currently quiescent.

Case 3: This 33-year-old Chinese male had recurrent painful ulcers with atrophie blanche on both ankles and feet for 10 years. He was previously treated with daflon and vasteral with no improvement. Skin biopsy from an ulcer edge showed acanthosis, superficial and deep perivascular dermatitis and neovascularisation at the upper dermis with a lymphocytic infiltrate, consistent with a healing lesion of atrophie blanche. Direct immunofluorescence showed deposits of fibrinogen and C3 in the walls of upper and mid-dermal blood vessels. At the start of the study, he had 6 ulcers and experienced mild pain over the lesions. Three weeks into treatment, the pain severity remained at mild, the number of ulcers did not change. At week 6, pain severity had not changed but there were now 7 ulcers. The response was graded as none. The patient subsequently defaulted follow-up.

Case 4: This 40-year-old Chinese lady, working as a merchandiser, presented with lower limb ulcers with atrophie blanche and purpura for 9 months. She was treated with colchicine and indomethacin previously. Skin biopsy from a purpuric lesion on the leg revealed a necrotic epidermis, superficial and deep dermal blood vessels with fibrinoid material within the vessel walls and lumen, a relatively sparse perivascular infiltrate and some neutrophils seen in the walls of a few upper dermal vessels and in the necrotic epidermis, consistent with livedoid vasculitis (Fig. 2). Direct immunofluorescence showed the presence of fibrinogen, IgM and C3 in the walls' dermal blood vessels. In addition, IgM and fibrinogen were also noted in the

lumen of the vessels. She came back early after 1 week of treatment complaining of severe, intolerable pain over the lower limb lesions. Indomethacin was added for pain relief. At the third week, lesions improved to only 1 ulcer and pain severity improved to only mild. However, at the sixth week, there was an increase in lesions to 4 ulcers, and an increase in pain severity back to moderate. Response was graded as none. Prednisolone and colchicine were given subsequently with fair control, but lesions worsened when prednisolone was tailed down to below 10 mg per day. Dapsone and aspirin were added later, but dapsone was taken off because of increased haemolysis, and aspirin was stopped because of gastric ulcerations. There was worsening of lesions when prednisolone was tailed down to below 10 mg per day.

Azathioprine was added with improvement of lesions and prednisolone is currently being tapered.

Aspirin Treatment Arm

Case 5: This 47-year-old Chinese lady, a fashion designer, presented with painful, recurrent lower limb ulcers and purpura that healed with stellate white scars for a year. There were no precipitating factors. A Doppler study of the lower limb veins was normal. She was treated with mefenamic acid for the lower limb lesions before with no improvement. Skin biopsy of a painful purpuric macule over the foot revealed acanthosis, hyaline thrombi in the upper dermal blood vessels, fibrin deposits in the walls and in the lumen of vessels in the upper subcutis and red cell extravasate, consistent with livedoid vasculitis. Direct immunofluorescence showed deposits of IgA, IgM and C3 in the walls of the upper and mid dermal blood vessels. At the start of aspirin therapy, pain severity was graded as severe and there were 23 ulcers. At 3 weeks, pain severity was improved and graded as mild, but the number of ulcers had increased to 27. At 6 weeks, pain severity had increased to moderate but the number of ulcers had decreased to 21. Response was graded as partial. However, at week 9 she started to develop new, painful ulcers. Pentoxifylline was used instead, but lesions continued to worsen and 5 weeks later, colchicine 0.5 mg thrice a day and low dose aspirin (150 mg daily) were added, with better control of the lesions. However, when she stopped taking colchicine for 2 weeks on her own, lesions flared up again. She has since been given just colchicine alone with good control of the lesions. She is currently on colchicine 0.5 mg once a day with no recurrence of lower limb ulcers for a year.

Case 6: This is a 41-year-old Chinese lady with painful lower limb ulcers since 1988 for which she variously received indomethacin, colchicine and prednisolone for treatment. She was well from 1994 onwards till 1999, when she presented with 4 months' history of recurrent painful ulcers on the lower limbs. Clinically, there were leg ulcers associated with livedo reticularis, atrophie blanche and

stasis changes. Skin biopsy from an active ulcer edge showed fibrin thrombi within the lumen of upper dermal vessels, associated with some neutrophils. Direct immunofluorescence showed IgM, IgA, C3 and fibrinogen in the walls of the upper dermal blood vessels. At the start of aspirin therapy, there were 6 ulcers and the pain intensity was moderate. At week 3, pain was still moderate but ulcers had decreased to 3. By week 6, pain intensity was severe and ulcers had increased to 7. Response was graded as none. Aspirin was stopped and prednisolone (20 mg daily) and pentoxifylline were given. However, lesions flared when prednisolone was tapered. Colchicine and dapsone were subsequently added for better control. She was lesion-free 3 months after taking off pentoxifylline and dapsone, and was maintained on just colchicine and a tapering dose of prednisolone.

Discussion

The typical clinical profile of a patient with livedoid vasculitis is a female in the third or fourth decade of life, as has also been shown in other reports. The 2 histological patterns of prominent vascular plugging by fibrin thrombi of the dermal vessels, with or without subcutaneous involvement, and scarring in the presence of neo-vascularisation as seen in our patients, no doubt are related to the varying ages of the lesions. Although neutrophils can be present in some of the biopsies, there is an absence of nuclear dusting and vessel infiltration by neutrophils, which are characteristic of leukocytoclastic vasculitis. Luminal thickening and occlusion of the subcutaneous vessels were also observed in 2 cases. In polyarteritis nodosa, which affects both medium sized and small dermal vessels, prominent vascular occlusion of dermal vessels by fibrin thrombi is not a feature.

The immunofluorescence pattern of immunoglobulin deposits suggests secondary trapping of immune reactants by fibrin thrombi rather than a primary immune complex mechanism. Our finding is consistent with the findings of various investigators that the pattern of immunofluorescence is non-specific, and this condition is not primarily an immune-complex mediated vasculitis.^{2,9}

We investigated extensively to exclude secondary causes of livedoid vasculitis. Although in this small series of 6 patients no secondary causes were found, it is nevertheless important to search for treatable causes such as the antiphospholipid syndrome. Clues pointing to an underlying systemic disease include absence of associated chronic venous insufficiency and presence of livedo reticularis.^{9,10}

The original concept of the pathogenesis of livedoid vasculitis was based on evidence that there are disturbances in coagulation and fibrinolysis resulting in a thrombogenic vasculopathy. Shornick et al⁹ observed that deposition of

fibrin in blood vessel lumina resulted in vascular occlusion. Elevated blood levels of fibrinopeptide A were found in this condition by McCalmont et al, and clinical improvement after use of antiplatelet and anticoagulant therapy further supported the theory of a thrombogenic vasculopathy.^{2,5,9,11,12} However, despite histopathological features of prominent thrombo-occlusion, pentoxifylline or aspirin did not result in significant improvement for most of our patients when used alone. Disease activity was better controlled after combining with immunosuppressive therapy, such as prednisolone, colchicine and azathioprine. This is compatible with the experience of some other investigators. Sauer⁷ felt that, in his experience, prednisone therapy was often required for better control of the painful ulcers. Colchicine has occasionally been shown to improve lesions.⁹ There are isolated case reports of improvement after dapsone of skin lesions of livedoid vasculitis in patients with the antiphospholipid syndrome and protein C deficiency.^{13,14} Could livedoid vasculitis be a form of lymphocytic vasculitis giving rise to a prothrombogenic state? Recently, this has been suggested, and there has been evidence in support of this novel concept.¹⁵ Variable numbers of lymphocytes have been observed perivascularly, and increased levels of interleukin 2 and soluble interleukin 2 receptor levels, which are markers of lymphocyte activation, were found by Papi et al.¹⁶ The poor response to antifibrinolytic and antiplatelet agents in our patients, who almost invariably required immunosuppressive treatment with prednisolone for control, lends support to the concept of livedoid vasculitis being a lymphocytic vasculitis. Another possible explanation for the disappointing response of aspirin or pentoxifylline in our patients, as compared to other reports, could be due to the phase of disease. In the initial active phase, it is conceivable that patients may require aggressive immunosuppressive treatment for arrest of disease activity. It is when the secondary procoagulant effects of lymphocytic vasculitis set in that anti-thrombotic therapy may be useful. However, even in our patients who had prominent thrombo-occlusion by fibrin thrombi, aspirin or pentoxifylline monotherapy did not result in any clinical response. It is possible that combined treatment with immunosuppressive treatment may be synergistic.

Conclusion

Disease control of livedoid vasculitis often requires immunosuppressive therapy. Fibrinolytic or antiplatelet

therapy used alone is often not sufficient for full control of disease activity. Whether they have synergistic effects when used with corticosteroids or other immunosuppressives need further study.

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