

# Livedoid vasculopathy and its association with factor V Leiden mutation

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**ABSTRACT** Livedoid vasculopathy is a rare chronic relapsing disorder characterised by recurrent painful thrombotic and vasculitic ulcers on the legs. We present the cases of two Indian women with livedoid vasculopathy that were found to be associated with an underlying factor V Leiden heterozygous mutation. There were no other thrombotic manifestations, and livedoid vasculopathy was the sole presenting feature of the factor V Leiden mutation, although this could also be coincidental. Initial treatment with high-dose immunosuppressive therapy was suboptimal, and the addition of pentoxifylline and antiplatelet therapy was crucial in achieving disease control and remission. These cases highlight the possible association with an underlying prothrombotic disorder, such as factor V Leiden mutation, in patients with livedoid vasculopathy. Although this association is relatively uncommon, it is more relevant to Indian patients, as the presence of factor V Leiden mutation is highest in this ethnicity as compared to the local Malay and Chinese populations.

*Keywords:* antiplatelet therapy, atrophie blanche, factor V Leiden mutation, livedoid vasculopathy, vasculitic ulcers  
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## INTRODUCTION

Livedoid vasculopathy (LV) is a rare chronic relapsing ulcerative vascular disorder with a predilection for middle-aged women. Characterised by severely painful and recurrent thrombotic ulceration of the feet and legs, LV can result in high patient morbidity and scarring. There has been recent recognition that underlying hypercoagulable disorders may have a crucial role in the pathogenesis of this condition.<sup>(1,2)</sup> We present two patients with LV who were found to have an underlying heterozygous factor V Leiden (FVL) mutation to highlight this rare association in our local population and the implications for therapy in such patients.

## CASE REPORTS

### Case 1

A 36-year-old Indian woman presented with a one-year history of recurrent painful ulcers over both ankles and feet. Clinically, there were multiple tender, dusky, necrotic ulcers and depigmented atrophic blanche scars over the dorsum of her feet and lateral ankles bilaterally (Fig. 1). The lesional skin biopsy performed was consistent with LV, with the presence of red blood cell thrombi within the vascular lumina, fibrinoid material within the vessel walls and a sparse perivascular lymphocytic infiltrate (Fig. 2). Initial investigations, including full blood count, C-reactive protein, erythrocyte sedimentation rate, complement levels, hepatitis B and C serologies, and cryoglobulins were either normal or negative. There was a positive antinuclear antibody titre of 1:320, but other autoimmune markers, including extractable nuclear antigen antibodies, antineutrophil cytoplasmic antibodies, anti-double-stranded DNA antibodies and anticardiolipin antibodies, were negative.



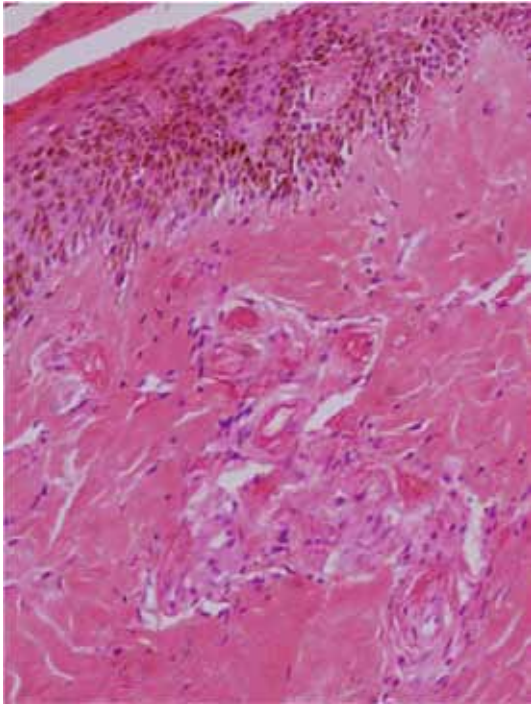
**Fig. 1** Photograph shows new ulcers, along with surrounding atrophie blanche and hyperpigmentation over the dorsum of both feet, and lateral malleoli in Patient 1.

The patient was initially treated with various combinations of anti-inflammatory and immunosuppressive agents, including prednisolone, dapsone, hydroxychloroquine, methotrexate, mycophenolate mofetil and intravenous cyclophosphamide, but with limited sustained clinical response. Subsequent workups done, including a full thrombophilia screen, revealed heterozygous FVL mutation with activated protein C resistance. She was then started on a combination of aspirin, pentoxifylline, prednisolone and azathioprine. Within four weeks of this new combination, she had notable improvement with a decrease in pain and formation of new ulcers. The patient remains well currently and the dose of prednisolone has been gradually tapered down successfully.

### Case 2

A 31-year-old Indian woman first presented in 2006 with recurrent tender erythematous plaques on the dorsum of her feet and legs for six weeks, associated with peripheral sensory loss over both

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**Fig. 2** Photomicrograph of the skin biopsy taken from Patient 1 shows vessels with red cell thrombi plugging the vascular lumina and blood vessels with segmental fibrin deposits within the vessel walls (Haematoxylin & eosin,  $\times 200$ ).

her lower limbs. The initial skin biopsy showed fibrinoid necrosis of the upper dermal capillaries, extravasated red cells, perivascular infiltrate of lymphocytes and minimal nuclear dust. Direct immunofluorescence (DIF) was negative. Electromyography and sural nerve biopsy were consistent with vasculitic neuropathy. A diagnosis of leukocytoclastic vasculitis with mononeuritis multiplex was made, and she was treated with prednisolone, mycophenolate mofetil and methotrexate, with improvement.

However, she relapsed in 2009 with severely painful left leg ulcers (Fig. 3), atrophie blanche and livedo reticularis over the forearms. A repeat skin biopsy found neovascularisation, intravascular fibrin thrombi, vessel wall thickening and red cell extravasation, which were consistent with LV. DIF showed granular deposits of immunoglobulin M, Complement 3 and fibrinogen around the vessels. Repeat workup for systemic inflammatory and autoimmune diseases was negative. A full thrombophilia screen showed a low protein S level (46%) and genetic testing found a heterozygous FVL mutation.

The patient was treated with a combination of prednisolone, cyclophosphamide, pentoxifylline and aspirin. Her condition improved with a significant reduction in pain and complete healing of the existing ulcer after two months. She currently remains well with no new ulcer formation, and the dose of prednisolone has been gradually tapered down successfully.

## DISCUSSION

This case report highlights two patients with LV and heterozygous FVL mutation. It is noteworthy that the patients' first and only clinical manifestation of their underlying FVL mutation was the development of LV. In contrast, the major clinical manifestation



**Fig. 3** Photograph shows a 4 cm  $\times$  1.5 cm ulcer over the left medial malleolus of Patient 2.

of FVL is usually deep vein thrombosis or pulmonary embolism.<sup>(3)</sup> Other thrombotic manifestations reported include cerebral, superficial vein, mesenteric, portal vein and postsurgical thromboses, as well as pregnancy loss.<sup>(3)</sup>

However, the pathogenesis of LV is still unclear. While there is evidence that LV may have an autoimmune basis because of its frequent association with systemic connective tissue disease, such as antiphospholipid antibody syndrome and systemic lupus erythematosus, there is increasing recognition of the possibility that a prothrombotic aetiology may play an important role in the pathogenesis of this condition.<sup>(1)</sup> It has been postulated that an alteration in the local or systemic control of coagulation, with the formation of fibrin thrombi within the superficial dermal blood vessels, leads to recurrent painful ulceration.<sup>(2)</sup> This is supported by histological findings of occlusion of dermal vessels by intravascular fibrin, segmental hyalinisation and endothelial proliferation, as seen in these cases.

Apart from FVL, LV has been associated with other thrombophilic conditions such as protein C and S deficiencies, antithrombin deficiency, prothrombin gene mutation and hyperhomocysteinaemia.<sup>(1,4,5)</sup> In a cohort of American patients with LV, heterozygous FVL mutation was detected in 22.2% of the patients tested,<sup>(2)</sup> but there have been no reports on the prevalence of FVL in Asian LV patients. FVL is the most common cause of inherited thrombophilia in the West, accounting for 40%–50% of cases.<sup>(6)</sup> The prevalence of heterozygous FVL mutation in European, Jewish, Arab and Indian populations ranges from 1%–8.5%,<sup>(7)</sup> and this prevalence is highest in Greece, Sweden and Lebanon, approximating 15% in some areas.<sup>(8)</sup> On the other hand, the prevalence of FVL in Asian patients has not been well studied. In a retrospective analysis of the positive detection rate of FVL mutation among Malay, Chinese and Indian patients in Singapore, heterozygous FVL mutation was detected in 10.7% of

Indians, 0.4% of Chinese and 1.8% of Malays,<sup>(9)</sup> thus highlighting the rarity of this condition in Chinese and Malays.<sup>(7,9,10)</sup> It is important to point out that this study may not be representative of the general population, as the tests were exclusively ordered for patients with venous thrombotic events that required further thrombophilia screening. In a cohort of LV patients seen in our centre, there has been no other cases of FVL in Chinese or Malay patients with LV to our knowledge.

There is no single effective therapy for LV – both antithrombotic and immunosuppressive drugs play crucial roles in the management of this condition. Although a prothrombotic aetiology is strongly favoured in the pathogenesis of LV, some patients may also require aggressive immunosuppressive treatment for the arrest of disease activity in the initial active phase, which would lend support to a concomitant inflammatory process. In a previous local study, monotherapy with either aspirin or pentoxifylline alone did not engender a good response and most patients required the addition of immunosuppressive drugs, such as prednisolone and azathioprine, for better control of disease activity.<sup>(11)</sup> This provides evidence that optimal control of the disease may be better achieved with a combination of antithrombotic and immunosuppressive agents.

As highlighted in these cases, in patients suffering from LV associated with a heterozygous FVL mutation with no other major thrombotic complications attributable to FVL, a reasonable initial approach would be to combine therapy with antiplatelet agents, such as aspirin, clopidogrel and/or pentoxifylline, together with immunosuppressive agents. In previous case reports, there has been success with the use of varying combinations of prednisolone, pulsed methylprednisolone, azathioprine and hydroxychloroquine with antithrombotic agents.<sup>(12,13)</sup> The successful management of our two patients with a combination of antiplatelet agents, pentoxifylline and immunosuppressants highlights the synergistic effect of such an approach. The use of warfarin for anticoagulation should be reserved for refractory cases,<sup>(14)</sup> or in LV patients with other major thrombotic events attributable to FVL.

As FVL is not common among the Chinese and Malay populations in Singapore, routine testing for FVL in Chinese and

Malay patients with venous thromboembolism has not been recommended.<sup>(10)</sup> Likewise, we propose that FVL mutation need not be routinely screened in all LV patients, except in patients with a significant history of recurrent thrombosis, or in Indian or Caucasian patients in whom there is a higher prevalence of FVL mutation.

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