CASE REPORT

Refractory Livedoid Vasculopathy: Clinical Response to TNF-α Blocker in a Young Male Patient.

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Submitted: 02/12/2024. Revised edition: 29/01/2025. Accepted: 26/03/2025. Published online: 01/06/2025.

Abstract

Livedoid vasculopathy is a rare condition characterized by thrombosis of dermal vessels, predominantly affecting the ankles. The patient presented with a painful ulcer, which is usually chronic in nature with relapsing-remitting episodes. It may resemble other vasculitides disorders, such as microscopic polyangiitis and polyarteritis nodosa. Hence, diagnosis is mainly based on clinical and histopathological findings. Livedoid vasculopathy required antiplatelet and anticoagulant therapy, in contrast to vasculitides disorders. We describe a young man who presented with a recent onset of painful ulcers on both ankle regions, consistent with livedoid vasculopathy and supported by histopathological findings. Clinical remission was observed after treatment with subcutaneous adalimumab, after failing to respond to a combination of anticoagulant, corticosteroid, vasodilator, and antiplatelet agents.

Keywords: *Adalimumab, Anticoagulant Antiplatelet, Corticosteroid, Livedoid vasculopathy, Refractory, Thrombosis, Vasculitis, Vasodilator.*

Introduction

Livedoid vasculopathy (LV) is a rare disorder of thrombo-occlusive vasculopathy involving the vessels in the dermis layer [1]. It is characterized by painful, purpuric ulcers on the lower extremities. LV is more common in female than male (ratio of 3:1) with age range between 15 and 50 years [2, 3, 4]. The reported incidence rate is approximately 1 in 100,000 people [5]. The diagnosis is often delayed by about 5 years, according to previous epidemiological studies [6].

Although the term "atrophie blanche" (referring to atrophic ivory or porcelain-white stellate or retiform scars) is descriptive, it is commonly used to refer to one of the features of LV. The condition shares overlapping features with both vasculitis and vasculopathy, such as in granulomatous polyangiitis (GPA) and polyarteritis nodosa (PAN).

We report a case of a young, healthy man who presented with a first onset of typical LV features on both ankles. Remission was achieved with subcutaneous adalimumab after failure to respond to standard treatments, including corticosteroids, anticoagulants, vasodilators, and antiplatelet agents.

Case report

A 22-year-old Chinese man, previously well, developed a sudden onset of painful ulcers and rash on his ankles over the past 4 weeks, with more swelling on the right ankle than the left (Figure 1). He had no other rashes elsewhere and no fever, alopecia, mucosal ulcers, angina, or dyspnoea. He worked as a mechanic and denied any history of trauma. He occasionally smoked vape and drank alcohol. He had no significant contributory family or allergic history.

On physical examination, there were multiple cutaneous telangiectasias and 'atrophie blanche' on both malleoli, which were very tender (Figure 1). The dorsalis pedis and posterior tibialis pulses were present. The patient had tattoos on the dorsum of his right hand, knuckles, and shoulder. Other systems were unremarkable.

Laboratory investigations showed a C-reactive protein (CRP) level of 59 mg/L (normal < 5), an international normalized ratio (INR) of 1.04, and an activated partial thromboplastin time (aPTT) of 36.4 seconds (reference range: 25.6-35.2 seconds). The complete blood count, liver, and renal profiles were normal. Serological tests for HIV, Hepatitis B and C, and the Venereal Disease Research Laboratory (VDRL) test were non-reactive. The antinuclear antibody (ANA), anti-dsDNA, extractable nuclear antigen (ENA), rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), and anti-neutrophil cytoplasmic antibodies (ANCA) screenings were all negative. Lupus anticoagulant was present (first screening) but negative for cardiolipin antibodies (IgM, IgG, and IgA) and β2-glycoprotein 1 antibodies (IgM, IgG, and IgA). Protein S and C levels were normal, as were homocysteine (14.0 umol/L) and lipoprotein A (Lp(a)) levels (<10.2 mg/dL). Other thrombophilia tests, such as anti-thrombin, factor V Leiden, and factor VIII, were not performed. Doppler ultrasound showed no evidence of deep venous thrombosis (DVT) or arterial occlusive disease. Histopathological examination (HPE) of a skin biopsy demonstrated an inflammatory process in the epidermis, with the presence of fibrinoid necrosis, extensive capillary thrombosis, and mild neutrophil infiltration. Fibrosis was also present in the deep dermis, with intraluminal thrombosis noted in the medium-sized vessel. These HPE findings were consistent with LV (Figure 2). The immunofluorescence study was negative.

The patient was initially treated with acetylsalicylic acid (aspirin) 150 mg daily, direct oral anticoagulant (DOAC) dabigatran 150 mg twice daily, and pentoxifylline 400 mg in three divided doses, which led to a gradual resolution of the lesions in the first few weeks. However, he developed new ulcers in the same area despite

treatment. Given the recurrent ulcers, subcutaneous adalimumab 40 mg every 2 weeks was initiated after appropriate counseling and negative screening for latent tuberculosis. All other medications were stopped. The patient received adalimumab for four months, after which the ulcers completely healed without recurrence (Figure 1B).

Discussion

LV is a rare disorder of unclear aetiopathogenesis characterized by painful purpuric ulcers that primarily affect the lower limbs. It is categorized into primary (idiopathic) and secondary forms, which the latter being associated with autoimmune diseases, malignancies or thrombophilia disorders including antiphospholipid antibody syndrome, Factor V Leiden mutation, protein C and S deficiencies, prothrombin mutation, antithrombin III deficiency, hyperhomocysteinemia, and elevated lipoprotein(a) levels [5].

Several hypercoagulable factors, coagulation disorders, fibrinolysis, rheumatological disorders, and endothelial dysfunction have been identified as playing roles in its pathogenesis. Genetic predisposition has also been demonstrated through polymorphisms in genes such as prothrombin G20210A, Factor V Leiden, plasminogen activator inhibitor-1 (PAI-1), and methylenetetrahydrofolate reductase (MTHFR) [7]. However, genetic study was not available for this patient.

The diagnosis of LV requires histopathological confirmation, even when clinical presentation is typical, as it is crucial to exclude other secondary aetiologies. Characteristic histological features include thickening or hyalinized degeneration of the subintimal layer of superficial dermal vessels, endothelial proliferation, intra-luminal fibrin deposits, thrombosis, red blood cell extravasation, and sparse perivascular lymphocytic infiltration, as observed in this patient [5, 8].

To date, there is no specific treatment for LV. The primary aim of treatment is to alleviate the symptoms such as pain, promote ulcer healing, and prevent relapses. Treatment responses vary due to several factors, including availability, accessibility, cost, comorbidities, and compliance. A systematic review by Micieli *et al.* demonstrated that the variability of treatment success depends on these factors [9]. LV is commonly managed with anticoagulants (e.g., rivaroxaban, warfarin, low molecular weight heparin), anabolic steroids (e.g., danazol), antiplatelets (e.g., aspirin, pentoxifylline, dipyramidole), and intravenous immunoglobulins [9]. Other treatment modalities include Psoralen and UV-A (PUVA) therapy and hyperbaric oxygen, either as monotherapy or in combination with other treatments. Unlike vasculitis, treatment of LV primarily focuses on preventing thrombosis or inducing vasodilation [10]. For refractory cases, immunosuppressants and biological agents including tumor necrosis factor α (TNF-α) blocker like adalimumab, have been used with reports of sustained remission [11, 12, 13].

The role of TNF- α blocker in LV is based on the mechanism of inflammation and thrombosis, the latter being associated with endothelial cell damage. TNF- α, a pro-inflammatory cytokine, contributes to pain in LV, which helps explain the therapeutic response to TNF- α blocker.

Conclusion

The diagnosis of livedoid vasculopathy (LV) remains a significant challenge due to its overlapping features with other vasculitides and autoimmune disorders, such as cutaneous polyarteritis nodosa (cPAN), systemic lupus erythematosus (SLE), scleroderma, and other causes of ulcers, including chronic venous ulcers. Histopathological examination (HPE) is crucial to differentiate these conditions. Standard LV treatment focuses on inhibiting thrombus

formation, promoting vasodilation, and stimulating fibrinolytic activity [10]. However, the presence of inflammatory infiltrates suggests a role for inflammatory cytokines, which may explain the observed response to anti-TNF blockers.

This patient's case is exceptionally rare given their young age and the absence of underlying autoimmune conditions or other contributing factors. Despite being refractory to standard treatments, the patient responded to adalimumab, consistent with previous case reports.

Authors' contribution

WS and HFBB were responsible for conceptualizing, collecting clinical data, writing, and finalizing the manuscript, while LBR handled histopathological analysis and report writing.

Acknowledgement

We want to express our gratitude to all healthcare providers involved in the care of this patient.

Conflict of interest: None

Funding: None

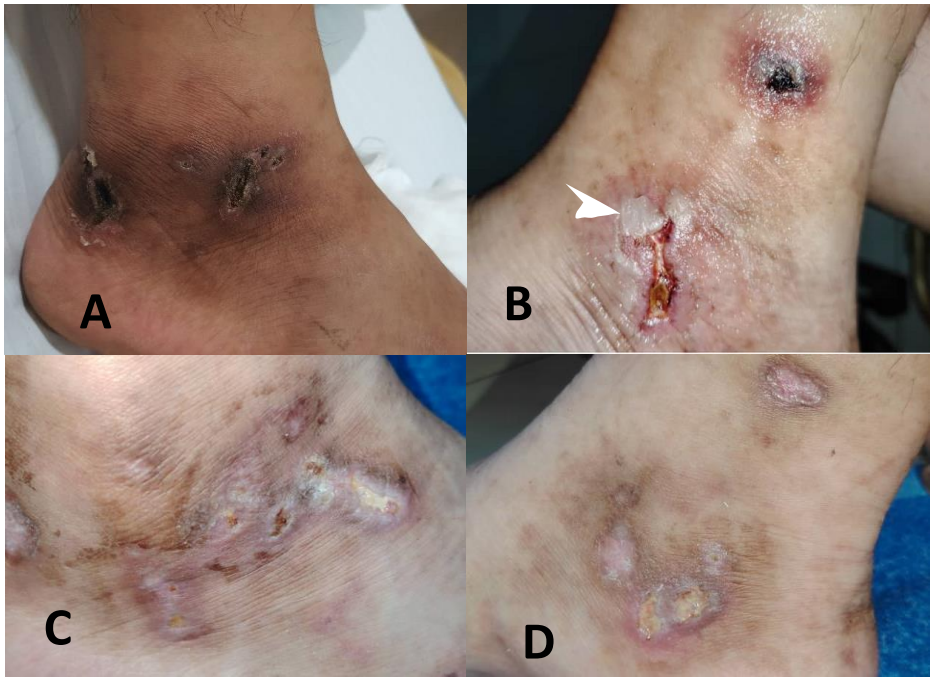

Figure 1. Typical features of livedoid vasculopathy are shown livedo racemosa, ulcers, and 'atrophie blanche' (arrowheads). (A: right foot; B: left foot). Note that the right ankle joint is also swollen. (C and D: healed ulcer after 4 weeks of adalimumab treatment.)

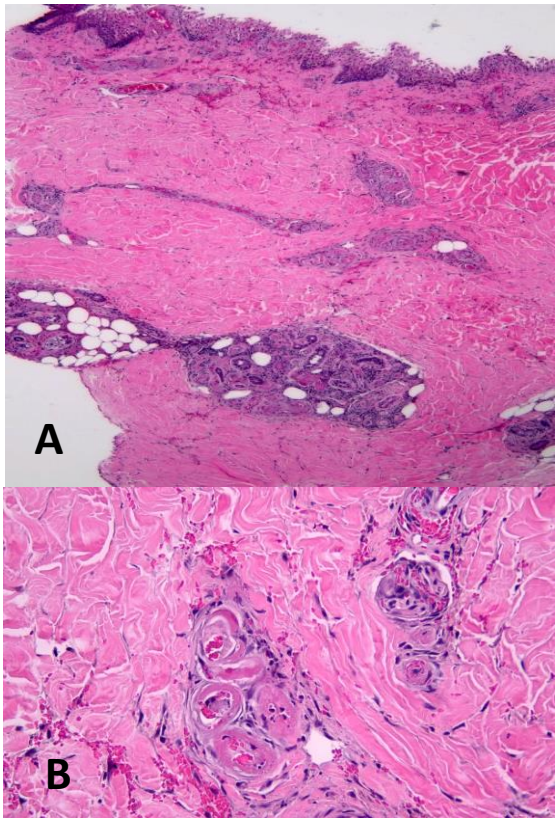

Figure 2. Histopathological examination of a skin biopsy shows the epidermis with spongiosis and neutrophil infiltration, along with acute on chronic inflammation in the underlying granulation tissue. Fibrinoid necrosis and extensive capillary thrombosis with mild neutrophil infiltration are observed (arrow). The deep dermis shows increased fibrosis, while the subcutaneous fat reveals medium-sized vessel thrombosis (arrow).

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