Autopsy Case Reports

Letter to the Editor

# Livedoid vasculopathy: a compelling diagnosis

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**How to cite:** Freitas TQ, Halpern I, Criado PR. Livedoid vasculopathy: a compelling diagnosis. Autops Case Report [Internet]. 2018;8(3):e2018034. http://dx.doi.org/10.4322/acr.2018.034

## DEAR EDITOR

The goal of our letter is to catch the medical community's eye regarding an unusual diagnosis, which may be overlooked or diagnosed late because of lack of familiarity or even knowledge on the part of the vast majority of clinicians and general practitioners.

Livedoid vasculopathy (LV) is a rare disease, with an estimated incidence of 1:100,000 per year with a male to female ratio of 1:3, particularly from 15 to 50 years old.[1-3] The most relevant epidemiologic characteristic is the 5-year delay of accurate diagnosis and treatment.[2]

In 1955, Feldaker et al.[1] first described the entity and named it livedo reticularis with summer ulcerations. Since then, segmental hyalinizing vasculitis and Milian's atrophie blanche are among many other recognized synonymy. However, it is accepted that "livedoid vasculopathy" is an appropriate name due to its descriptive labeling, since its focal vascular occlusions are not caused by vasculitis.[2]

The clinical manifestations are recurrent and begin with a focal non-inflammatory thrombosis of the venulae of the superior superficial and medium dermis, especially on the lower extremities, bilaterally; however, involvement of the upper extremities has also been reported.[3] Such thrombosis leads to blood and pressure build-up in the superficial veins of the dermis, which manifests as livedo racemosa or, less frequently, livedo reticularis.[4] As a consequence of the blood flow obstruction, the oxygen partial pressure in the skin diminishes, which starts a cutaneous response that is manifested as pruritus with painful papules and erythematous-violaceous, purpuric plaques.[3] They rapidly evolve into hemorrhagic vesicles or bullae that, when ruptured, become painful small ulcers of roughly 5 mm in diameter, which tend to merge into reticulate, confluent, geometric, and painful ulcerations[3] (Figure 1A and 1B). During the disease activity, lesions in different stages coexist, and early treatment may halt the development of new lesions.[2] During a period of 3 to 4 months, the ulcerations change to a porcelain-white atrophic scarring tissue with punctate telangiectasia: the so-called Milian's atrophie blanche or capillaritis alba (Figure 1B).[3,4]

The main acute complications are pain and secondary infection due to the exposure of the tissue. LV also results in several chronic complications, such as atrophic scars, residual hyperpigmentation, mononeuritis multiplex due to vasa nervorum thrombosis, and cutaneous hemosiderosis in the lower extremities because of erythrocytes pouring out from the high-pressure regimen veins, due to hemosiderin deposits in the skin.[3]

Differential diagnoses that must be excluded are (i) gangrenous pyoderma, especially when a secondary infection is present; (ii) factitious

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dermatitis, which presents only with ulcerations (without papules or vesicles); and (iii) cutaneous polyarteritis nodosa, which typically starts with painful subcutaneous nodules. Other differential diagnoses include leukocytoclastic vasculitis, pseudo-Kaposi sarcoma or acroangiodermatitis of Mali, Degos disease, and chronic venous stasis.[2,3]

Even though the clinical manifestation may seem fairly characteristic, the diagnosis is histopathological.

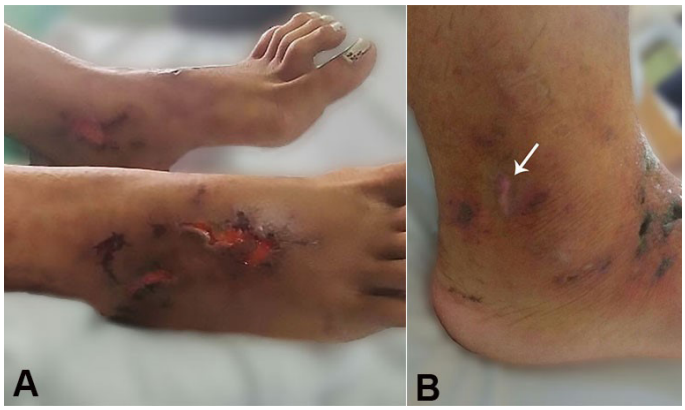


**Figure 1.** Gross view of the livedoid vasculopathy lesions. **A –** Note the presence of purpuric plaques that merged forming ulcerating lesions, and the coexistence of varying-degree lesions; **B –** The purpuric lesions are surrounded by an erythematous ring; the arrow points to the porcelain-white atrophic scarring tissue.

It is believed that the benefits of a skin biopsy outweigh the theoretic possibility of an ulcerous formation in its place, since it prompts earlier treatment.[3] A deep punch or excisional biopsy should be performed in an active lesion avoiding the necrotic areas. Initially, histology shows fibrin thrombi inside the lumina of small vessels without evidence of inflammation (Figure 2).

Later, more significant fibrin deposition in the lumen and in the vascular walls with secondary areas of infarction or ulceration are noted (Figure 3). At the periphery of the vessels, fibrin deposits can be present creating the characteristic hyalinized fibrin rings, with mild or absent lymphocytic infiltrate or signs of vasculitis.[2,3] Red blood cell extravasation and neutrophilic infiltrate secondary to the ulceration can be seen.[3]

Later, while maintaining the hyalinized fibrin thrombus, the walls of affected vessels thicken and endothelial cells proliferate in response.[3] The absence of exuberant neutrophil infiltration, perivascular nuclear fragmentation (leukocytoclasia), and fibrinoid necrosis of blood vessels define this pathology as a vasculopathy rather than vasculitis. Direct immunofluorescence exhibits non-specific fibrin, immunoglobulin, and complement deposition, but it does not provide any additional diagnostic information.[3]

LV should not be understood as a unique pathology, but rather as a cutaneous manifestation of many other

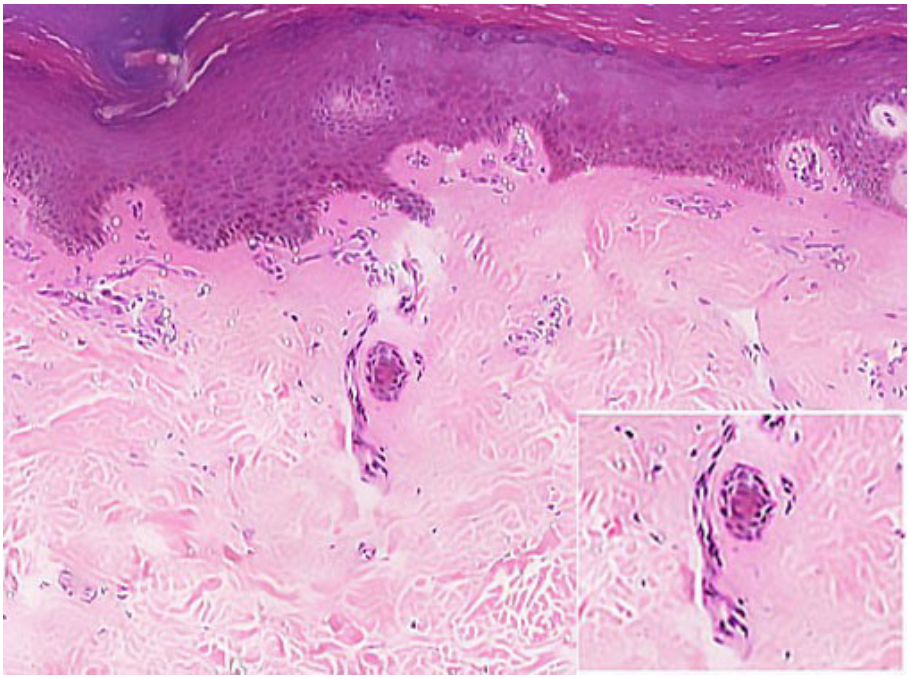

**Figure 2.** Photomicrography of the skin biopsy showing an intravascular thrombus (inset). Note the absence of perivascular inflammation and leukocytoclasia.

prothrombotic diseases that disturb any—or more than one—vertex of Virchow's triad. The disturbances in blood stasis are related to hyperviscosity syndromes, such as chronic myeloid leukemia, heavy chain diseases, and cryoglobulinemia.[3] Diseases associated with LV that cause endothelial injury are systemic erythematous lupus (anti-cardiolipin antibodies and lupus anticoagulant are found in a fraction of patients with LV),[2,3] as well rheumatoid arthritis, scleroderma, and hyperhomocysteinemia.[3] The Leiden factor V mutation, proteins C, S, Z, anti-thrombin deficiencies, elevated levels of plasminogen activator inhibitor type 1 (PAI-1), and lipoprotein(a) are entities that lead to hypercoagulability and may be associated with LV.[3]

Therefore, diagnostic investigation should not end with a conclusive biopsy. Serum complement and anti-neutrophil cytoplasmic antibodies are important because they are usually altered in most true vasculitis.[3] Screening for autoimmune diseases is also recommended with antinuclear antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies. Paraproteinemia should be excluded after normal serum protein electrophoresis, serum cryoglobulin levels, and negative proteinuria; testing for HIV plus hepatitis B and C is also important in such a context.[2,3] Dosing coagulation factors and their mutations are relevant for excluding hereditary and acquired thrombophilia.[2] However, even after a thorough laboratorial investigation, up to 20% of the cases of LV are stated as idiopathic.[3]

A systematic review on LV treatment was published in November 2017,[5] but it remains non-standardized because the evidence relies mostly on case reports and case series.[6] Anticoagulants are the most common monotherapy, particularly rivaroxaban, but unfractionated and low-molecular-weight heparin also can be used—all of which have bleeding as a common side effect. The second most common monotherapy is danazol because of its interference with the hepatic synthesis of coagulation factors. Glucocorticoids also are used, but have lower success rates,[5] which is probably due to the non-immune or pauci-immune characteristic of this entity, except for the cases related to other autoimmune or connective tissue diseases.[5] Anti-platelet agents are the drugs most often used for LV in Brazil, including acetylsalicylic acid, pentoxifylline, cilostazol,[3] and dipyridamole, which are administered either as monotherapy or combined. Recently, PAI-1 mutations related to LV were described, which prompted the use of thrombolytic drugs, such as the recombinant tissue plasminogen activator (rtPA),[5] which bypasses the inhibition of tPA by the mutated PAI-1,[3] with some promising outcomes. Other therapeutic agents, such as psolaren UV-A, hyperbaric oxygen, intravenous immunoglobulin, sulfasalazine, and nicotinic acid,[5] have been studied but show lower efficacy.

In clinical practice, vasculitis—or skin lesions interpreted as vasculitis—is a constant challenge to the clinician; it often remains underdiagnosed or is diagnosed late. With this letter, we aimed to present this entity for those clinicians who are not aware of it, and to refresh the memory of those who are.

**Keywords**
Blood Coagulation Disorders; Leg Ulcer; Livedo Reticularis; Vasculitis

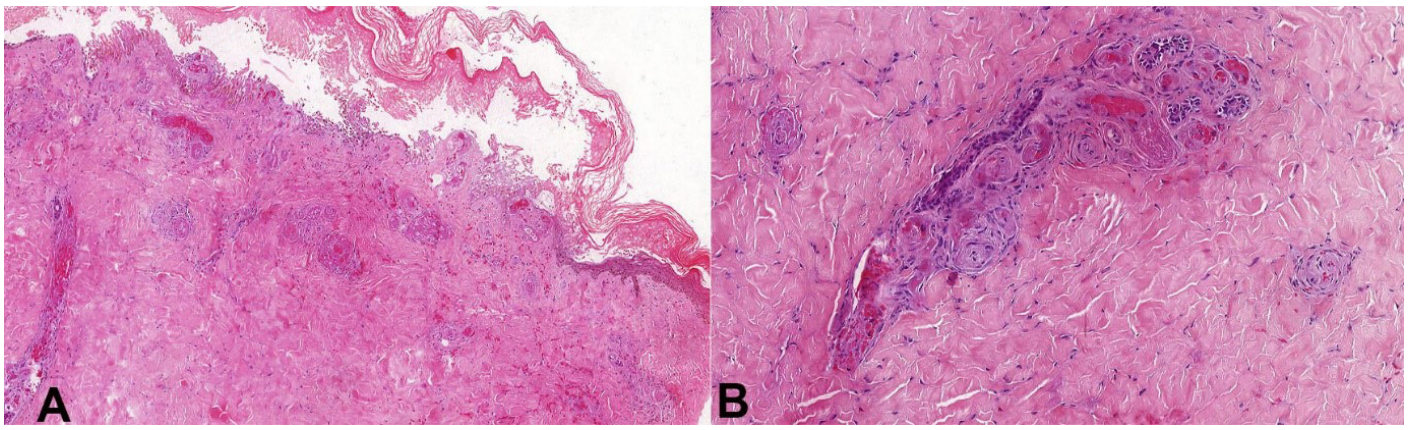


**Figure 3.** Photomicrography of the skin biopsy. **A –** Epidermal ischemic necrosis secondary to the vascular occlusion; **B –** Vascular thrombi with fibrin deposits in the lumen and in the vascular wall in the mid dermis. Note the lack of leukocytoclasia or lymphocytic infiltrate.

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**Author contributions:** Freitas TQ undertook the literature research, wrote the manuscript, and treated the patient when the disease relapsed. Halpern I was the pathologist in charge of the histological report. Criado PR treated the patient in the first presentation of the disease. All authors proofread the manuscript's final version and collectively approved it for publication.

**Conflict of interest:** None

**Financial support:** None

**Submitted on:** June 15th, 2018
**Acepted on:** July 1st ,2018

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