Livedoid Vasculopathy

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Livedoid vasculopathy (LV) is a thrombo-occlusive cutaneous disease of the dermal vessels with pauci-inflammatory or non-inflammatory histopathology findings (1). LV was first described by Millian in 1929 (2) under the term atrophie blanche en plaques and then better characterized by Bard & Winkelman in 1967 (3). It has been reported in the literature under various terms that make it difficult to recognize: livedoid vasculitis, PURPLE (painful purpuric ulcers with reticular pattern of the lower extremities) (1), idiopathic atrophie blanche (4), segmental hyalinizing vasculitis, and livedo reticularis with summer ulcerations (5). The current official denomination is livedoid vasculopathy (6). The term atrophie blanche (AB) should be used only to describe the typical smooth, ivory-white plaque-like area on the lower extremities surrounded by hyperpigmented border and telangiectatic blood vessels (6). However, AB may be associated with conditions other than LV (6). LV is characterized by chronic and extremely painful ulcerations of the feet and legs in relation to a vaso-occlusive phenomenon due to intraluminal thrombosis of the dermal venules. Primary ("idiopathic") and secondary forms of LV are distinguished.

Epidemiology

LV has an estimated incidence of 1/100,000 inhabitants/year. LV is typically a disease of the young. Patients are mainly aged between 15 and 50 years, and women are particularly affected, with a female to male ratio of 3:1 (1).

Clinical manifestations

The presentation of LV is quite typical, and diagnosis can be made by the dermatologist. A telangiectatic purpura leads to asymmetrical, irregular, painful, "punched-out" and recurrent ulcers of the foot, ankles and lower legs, with a slow healing and AB scarring, defined as white smooth ivory- or porcelain scars, surrounded by telangiectasia and livedoid brownish hyperpigmentation (Fig. 1a, b) (1). The lesions are usually bilateral. Active lesions are purpura, bruises, and painful ulcers, while inactive disease corresponds to scars, hyperpigmentation, and AB (Fig. 1c, d) (5). Of note, livedo racemosa (defined as a livedo with opened meches) reminiscent of Sneddon's syndrome can be seen in patients with LV (Fig. 2). This can be located on the lower or upper limbs. Finally, mononeuropathy may occur in relation to thrombosis of the vasa vasorum (1). LV is exceedingly painful and the impact on quality of life is significant (7).

Histopathology

The biopsy must include dermo-hypodermis to rule out cutaneous polyarteritis nodosa (PAN). Where possible, multiple biopsies are recommended, and they should avoid the immediate margins of the ulcers (granulation tissue, inflammation secondary to tissue repair). The main characteristics are the occlusion of dermal blood vessels by fibrin deposition

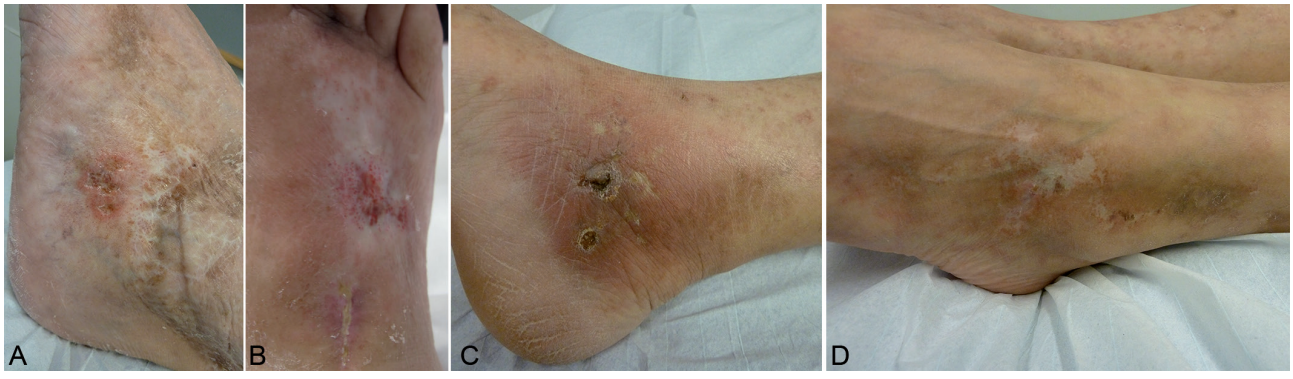

Fig. 1. (A) Active lesions of livedoid vasculopathy (LV): punched out ulcers of the external side of the ankle, inflammation and purpura. Atrophie blanche (AB) on the upper part with white ivory scars and hyperpigmentation on the border. (B) Active flare of LV on the dorsum of the foot in an 88-year-old woman with activated protein C resistance. (C) Painful ulcers in a 44-year-old woman: punched-out ulcers, inflammation, small AB scars and lack of chronic venous insufficiency. (D) AB scars on both lower legs in a 24-year-old woman with no hypercoagulable condition.

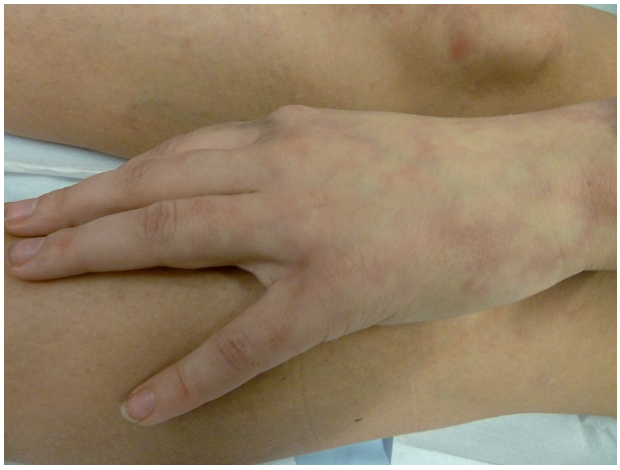

Fig. 2. Non-infiltrated permanent livedo racemosa of the hand in a patient with livedoid vasculopathy.

and intravascular thrombosis, segmental hyalinization and endothelial proliferation. There is a minimal perivascular lymphocytic infiltrate. Vasculitis features are absent (Fig. 2) (8). Direct immunofluorescence is not specific, with immunoglobulin M (IgM) deposits, fibrin and complement depositions in blood vessels (6), and care should be taken that positivity is not misdiagnosed as skin vasculitis.

Associated diseases, conditions and differential diagnoses

There are many diseases associated with LV (1, 9). One should distinguish LV associated with thrombophilia from LV associated with autoimmune diseases and other conditions. The list of diseases is summarized in Table I. It is important to stress that 50% of patients with LV have no identifiable association with a hypercoagulable condition (6). The differential diagnoses are summarized in Table II. The difficulty of differential diagnosis from cutaneous PAN should be noted (6, 10). In addition, AB lesions can be associated with conditions other than LV, such as venous insufficiency (Fig. 3).

Table I. *Conditions associated with livedoid vasculopathy (1, 9)*

Thrombophilia
Activated C protein resistance
Prothrombin gene mutation (G20210A)
Mutation of MTHFR (C677T), Hyperhomocysteinaemia
Protein C deficiency
Protein S deficiency
Factor V Leiden mutation
Antithrombin deficiency
High levels of type 1 inhibitor of tissue plasminogen activator (PAI-1)
Increased levels of lipoprotein (a)
Antiphospholipid antibodies: lupus anticoagulant and/or anticardiolipin antibody, anti-phosphatidylserine-prothrombin complex antibody
Cryoglobulinaemia
Cryofibrinogenaemia
Autoimmune and other diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Systemic scleroderma
Mixed connective tissue disease
Solid carcinoma
Haematological malignancies

Table II. *Differential diagnoses of livedoid vasculopathy (LV) (according to Criado et al. (1))*

Cutaneous vasculitis
Cutaneous polyarteritis nodosa
Antiphospholipid syndrome
Chronic venous insufficiency
Pyoderma gangrenosum
Degos disease
Dermatitis artefacta

Laboratory findings

No blood test can confirm the diagnosis of LV. However, certain tests should be performed to identify an underlying primary

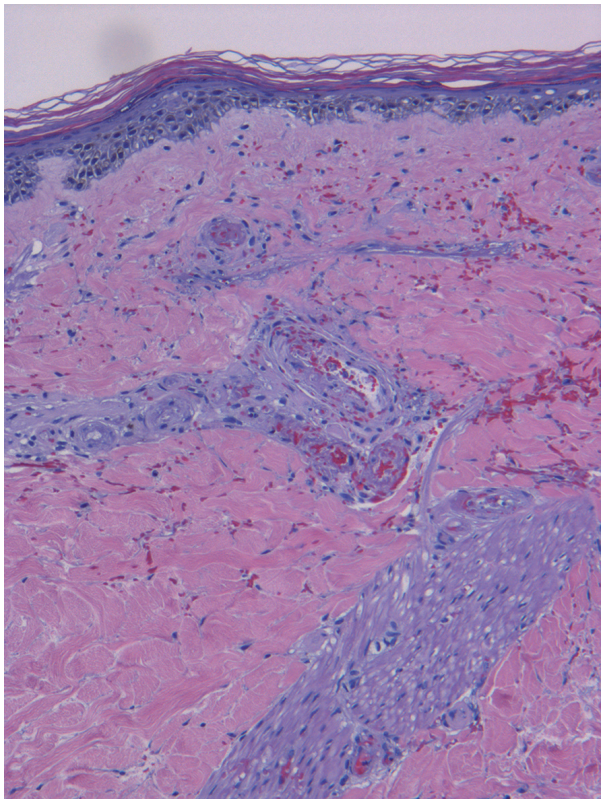

Fig. 3. Histological findings of livedoid vasculopathy: thrombosis of the skin vessels in the upper dermis with extravasation of red blood cells but lack of leukocytoclasia and inflammation (haematoxylin and eosin, ×4).

Table III. *Suggested laboratory tests in cases of livedoid vasculopathy (LV)*

Full blood count
Inherited and acquired thrombophilia investigations (cf. Table I): prothrombin time, bleeding time, activated partial thromboplastin time, ...
CRP, fibrinogen, serum protein electrophoresis
ANA, anti-DNA antibody, ANCA, RF, CH50, C3, C4
Cryoglobulinaemia
Antiphospholipid antibodies

diagnosis (Table III) (9). In addition to those tests, Doppler imaging has to be performed to rule out venous insufficiency.

Management

The management of LV is notoriously challenging and difficult. There is currently no treatment consensus (11). LV is also a self-remitting disease that can improve on its own (11). Pain management is crucial and must include the treatment of nociceptive and neuropathic pain components. Concomitant chronic venous disease will be managed by adequate compression therapy in the absence of arterial disease and adapted wound dressings (6).

Despite the lack of detection of prothrombotic abnormalities in many patients, it is likely that a thrombotic process is involved in the pathogenesis of LV, and thus it is widely accepted that the main treatment is antithrombotic. Platelet aggregation inhibitors can be used, such as acetylsalicylic acid, dipyridamole, or thienopyridine (clopidogrel, ticlopidine hydrochloride), but for some (12), treatment with antiplatelet drugs rarely results in complete remission. Anticoagulant therapies with low-molecular-weight heparin at a curative dose followed by oral vitamin K antagonists (warfarin) (12) or oral rivaroxaban, a Factor Xa inhibitor, have demonstrated efficacy (13). Corticosteroids may be used in the case of underlying connective tissue diseases (11). Other treatments are summarized in Table IV. They may be limited by their costs, such as intravenous immunoglobulins. Many patients are treated with a combination of various regimens.

Table IV. *Possible treatments for livedoid vasculopathy (LV) (1, 11)*

Platelet aggregation inhibitors: acetylsalicylic acid, dipyridamole, thienopyridine (clopidogrel, ticlopidine hydrochloride)
Anticoagulants: low-molecular-weight heparin, oral vitamin K antagonists, factor Xa inhibitors
IV methylprednisolone + pentoxifylline
Vasodilators: nifedipine, cilostazol (phosphodiesterase III inhibitor), nicotinic acid
Hemorrheologic drugs: pentoxifylline, buflomedil hydrochloride
PUVA
Low-molecular-weight dextran
Rituximab
Miscellaneous: IV immunoglobulins, cyclosporine A, hyperbaric oxygen therapy, PGI2 analogue IV, tissue plasminogen activator

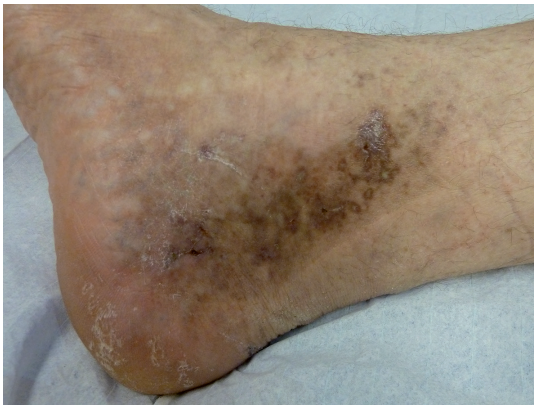

Fig. 4. Atrophie blanche (AB) and small ulcers (currently healing) in a 33-year-old patient with a known history of chronic venous insufficiency and no prothrombotic abnormalities. No biopsy was taken and the ulcers were not painful according to the patient. The diagnosis currently remains open as to whether AB is related to venous insufficiency or possible livedoid vasculopathy.

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