

SHORT COMMUNICATION

Livedoid Vasculopathy Associated with HIV Infection in Two Patients: A Causal Relationship?

Charlotte Hurabielle¹, Gwendoline Sebillé¹, Benoît Barrou², Philippe Moguelet³, Camille Francès⁴ and Stéphane Barette¹¹Unit of Dermatology, ²Unit of Renal Transplantation, Hôpital Pitié-Salpêtrière, ³Pathology, and ⁴Dermatology Department, Hôpital Tenon, Sorbonne Universités, UPMC Paris 6, Paris, France. E-mail: stephane.barette@aphp.fr

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Livedoid vasculopathy (LV) is a rare cutaneous chronic disease characterized by recurrent, painful ulcerations of the legs and feet, following focal infiltrated purpura. Widespread LV may also occur (1). LV is commonly associated with livedo reticularis (2). Healing is slow, and leaves *atrophie blanche*, an irreversible scar (3). LV is characterized histologically by fibrin occlusion of dermal vessels without vasculitis (4). Although the pathophysiology is not fully understood, LV is classified either as idiopathic, or as a secondary form associated with hypercoagulable and/or autoimmune disorders, which justify anticoagulants or intravenous immunoglobulins (5–7). We describe here 2 patients who developed LV associated with human immunodeficiency virus (HIV)-1 infection and severe nephropathy; an association that has not been reported previously.

CASE REPORTS

Case 1. A 56-year-old Caucasian man had a 15-year history of HIV-1 infection, complicated by membranoproliferative glomerulonephritis that led to chronic renal failure and haemodialysis for 2 years. He had lipodystrophy, metabolic syndrome and hypertriglyceridaemia secondary to highly active antiretroviral therapy (HAART), but had never developed opportunistic AIDS infections. He had been treated for HIV-1 for 10 years with HAART comprising lopinavir, abacavir, and tenofovir. In 2007, he received a renal transplantation and was treated with a triple immunosuppressive regimen, including cyclosporine, prednisone, and tacrolimus. At the date of transplantation, his CD4⁺ T-cell count was 414/mm³ with undetectable HIV-1 viral load. Six months after the renal transplantation, while CD4⁺ T-cell count was 400/mm³, he developed recurrent, spontaneous, painful, necrotic ulcerations of the inner and outer faces of the right ankle and of the dorsal right foot (Fig. 1a). Purpuric lesions surrounded the successive ulcerations. Histopathological analysis performed during a flare of the disease revealed occasional intravascular thrombi and fibrinoid material in the walls of upper and

deep dermal capillaries. A lobulated capillary hyperplasia, some endothelial proliferation and slight hyaline parietal deposits were also observed. There was a scant perivascular lymphocytic infiltrate, but no vasculitis. Immunofluorescence showed C3, immunoglobulin (Ig)M and IgA positivity within the dermal vessels. Rheumatoid factor, antinuclear antibodies, anti-extractable nuclear antigens, anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies and complement were negative or within normal values. Arterial and venous Doppler ultrasounds examinations of the legs were normal. Extensive blood screening for coagulation revealed only a slight elevated hyperhomocysteinaemia. The patient also had heterozygosity for the G4/G5 promoter of the plasminogen activator inhibitor-1 (PAI-1) gene, with a normal plasmatic PAI-1 antigen level ($n < 43$ ng/ml). After 5 flares in a 4-year period, he was treated with fondaparinux (Aspen Pharma Trading Ltd, Dublin), which was stopped after 6 months due to subsequent haemorrhaging without relapse.

Case 2. A 21-year-old Caucasian woman originating from Romania was admitted to the hospital with a history of recurrent painful ulcerations. She had had HIV-1 infection since the age of 5 weeks due to an exchange transfusion with contaminated blood. She had been treated with HAART therapy since then, and had never developed any AIDS events. She had a renal biopsy-proven nephropathy at 10 years of age, with end-stage renal failure and peritoneal dialysis at the age of 19 years. At this time, she came to France for evaluation of the possibility of a renal transplantation. The HAART therapy was modified for darunavir, raltegravir and lamivudine, with CD4⁺ T-cell count of 501/mm³ and HIV-1 viral load decreasing from 2.11 log to undetectable in a few months. She started painful ulcerations one year later. Dermatological examination revealed bilateral, perimalleolar purpuric painful papules associated with livedo reticularis, and small superficial ulcers (Fig. 1b). Four flares of these lesions were notified during a period of 1.5 years, with *atrophie blanche* and ochre dermatitis in between. Skin biopsy is shown in Fig. 2. Extensive screening for autoimmune and coagulation abnormalities found antiphospholipid IgM antibodies, hyperhomocysteinaemia with heterozygous methylene tetrahydrofolate reductase gene mutation, protein S deficit (53%), heterozygous factor-V Leiden mutation, and activated protein C resistance. Venous Doppler ultrasound examinations of the legs were normal. The patient was treated with heparin, delivered only when she started haemodialysis, with good efficacy on LV, followed by complete remission of LV. She underwent renal transplantation at 25 years of age with no relapse of LV after 4 years of follow-up.

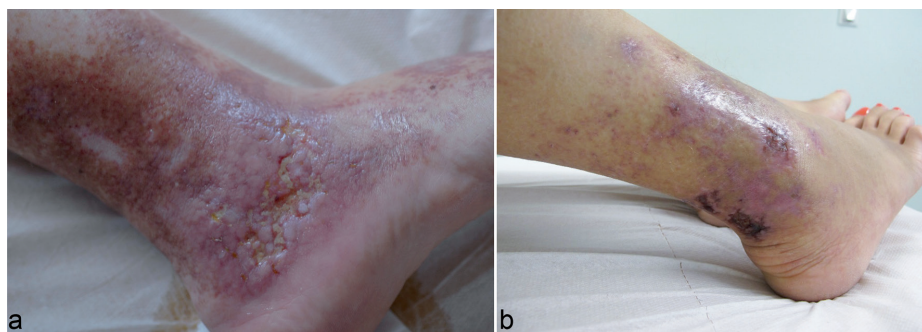


Fig. 1. (a) Ulcerated lesions and *atrophie blanche* of the ankle in patient 1. (b) Perimalleolar purpuric papules associated with livedo reticularis and small superficial ulcers in patient 2.

DISCUSSION

These 2 original cases lead us to discuss the role of the association of HIV-1 and nephropathy in the development of LV, although, a mere coincidence

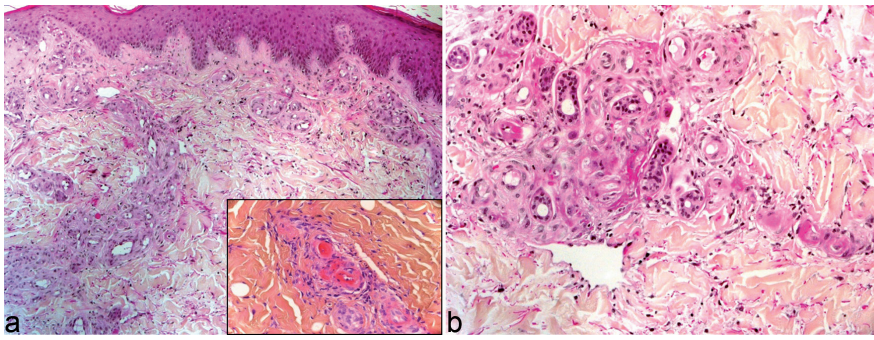


Fig. 2. (a) Lobulated capillary hyperplasia in the upper and deep dermis (haematoxylin and eosin (HE), original magnification $\times 100$) and intraluminal thrombosis, fibrinoid material and subintimal hyaline degeneration of the capillary walls seen in close-up (*inset*) (HES, original magnification $\times 400$). (b) Intravascular thrombi, endothelial proliferation and hyalinized vascular changes of the dermal capillaries with a dilated lymphatic vessel (HES, original magnification $\times 200$) (Patient 2).

cannot be excluded. France has a relatively high prevalence of the HIV-infection (253:100,000 individuals).

LV is a rare chronic dermatosis with an estimated prevalence of approximately 1:100,000 (8). This condition is frequently associated with comorbid conditions that lead to thrombosis of dermal vessels; for example, connective tissue diseases, malignancies, or venous insufficiency (4, 9). LV pathophysiology is linked to abnormalities in coagulation and/or fibrinolysis (4, 8). Associations of several factors are expected to lead to the disease, as in our 2 cases. Indeed, HIV has been shown to be an independent risk factor for thrombosis and hypercoagulable state: elevated markers of inflammation and coagulation are reported not only in patients who have AIDS, but also in HIV-infected patients on effective HAART (10, 11). In addition, HAART contributes to the development of a metabolic syndrome, characterized by lipodystrophy, dyslipidaemia and insulin resistance (12). This metabolic process contributes to the development of a proinflammatory state and subsequent chronic, subclinical vascular inflammation, which modulates and results in atherosclerotic developments (13). In addition, protease-inhibitors have been associated with higher PAI-1 levels in HIV-infected patients, which might result in a hypofibrinolytic state (14). Altogether, these elements argue for procoagulable and hypofibrinolytic states in HIV-1-infected patients; conditions that are found in LV. Moreover, these patients had nephropathy, which itself might induce coagulation abnormalities. Before transplantation, patients are frequently prone to acquire antiphospholipid antibodies and hyperhomocysteinaemia, particularly in haemodialysed patients, as observed in case 2. As the first patient had a renal transplantation before the development of LV and the second after the development of LV, renal transplantation appeared to not be directly involved in LV pathophysiology. However, renal transplantation has been associated with acquired hypercoagulable state and hypofibrinolytic state, with a multifactorial origin. Although the data are conflicting, some of these main factors are immunosuppressive drugs, especially corticosteroids and calcineurin inhibitors (15). Renal transplant recipients often develop hyperhomocysteinaemia, which contributes to an elevated risk of vascular thrombosis.

In conclusion, this report presents two patients with an original association of HIV-1 infection and LV, highlight-

ing the possible increased risk of microcirculation thrombosis associated with HIV-1 and nephropathy. However, we shall not leave out the hypothesis of a coincidence between LV and HIV-1, more than a causal relationship.

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