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Livedo Vasculitis

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We report twenty-two patients with persistent livedo racemosa and recurrent ulcerations on the lower extremities with biopsy-proved livedoid vasculopathy. The clinical presentation, together with histopathological findings of vascular occlusion without overt vasculitis in the dermis, confirm the diagnosis of livedo vasculitis. The pathogenesis of livedo vasculitis is still unclear, but the disease is considered an occlusive thrombotic process due to a hypercoagulable state and appears on the basis of prothrombotic and procoagulant processes rather than vascular inflammation. Following the clinical evolution of the disease we resume that even discrete cutaneous finding like atrophie blanche could be a marker and first clinical sign of a thrombotic disease, which could lead to extensive skin disorders. Our cases also confirm the hypothesis that livedo vasculitis may represent a clinical sign of a sole entity or could be a clinical manifestation of heterogeneous group of diseases.

Key words: livedo vasculitis, thrombosis, atrophie blanche, histopathology.

Introduction

Livedo vasculitis (LV) is a chronic cutaneous disease characterized by painful purpuric eruptions on the legs and feet, which often ulcerate and leave atrophic, stellate, ivory to white, scarlike plaques stippled with telangiectasia and surrounded by hyperpigmentation after healing. Histologic features include hyalinizing vascular changes of the subintimal layer of dermal blood vessels, typically with minimal inflammation, endothelial proliferation, and thrombosis of the upper and middermal blood vessels.

Originally described as atrophie blanche en plaque by Milian in 1929 [10], synonyms for this disease have included "livedo reticularis with ulcerations" [4], "segmental hyalinizing vasculitis"[1], "livedo vasculitis" and "livedoid vasculitis" and more recently "PURPLE – painful purpuric ulcers with reticular pattern of the lower extremities" [12].

The pathogenesis of the disease is still not fully understood. The multifactorial nature of cutaneous ulcerations, which are the clinical sign of LV and the variable nomenclature complicate its classification. It has been described as idiopathic [13] and with immune complex–associated diseases [14]. However, there is accumulating evidence that livedoid vasculopathy is caused by increased prothrombotic and procoagulant processes rather than by vascular inflammation [8, 11]. There is still no defined therapy of

choice for this difficult-to-manage disorder may be because of its chronic or recurrent nature and its often debilitating clinical course. A lot of therapies have been attempted, including nicotinic acid, sulfapyridine, minidose heparin, aspirin and dipyridamole, and nifedipine. Recent reports have shown that warfarin therapy alone improves clinical manifestations of livedoid vasculopathy [2, 3, 9].

Herein, we report twenty-two patients with this rare diagnosis LV. The purpose of study is to further characterize the clinical features, disease associations and laboratory test result abnormalities, including coagulation markers. Based on the histopathological findings of skin efflorescence to maintain the hypothesis that LV is not a vasculitis but rather vascular coagulopathia.

Materials and Methods

We have studied the clinical, histopathological and laboratory findings in 22 patients with LV. They were 14 women and 8 men, aged between 18 and 72, mean age 46 years. We followed the evolution of clinical signs and associated symptoms (in some of the cases due to internal diseases) on the first visit, after 1 month and after 6 months. Laboratory and immunological studies, including determinations of antinuclear antibodies, antibodies to DNA, antiendothelial antibodies, antineutrophil cytoplasmic autoantibodies, anticardiolipin antibodies (ACL), lupus anticoagulant, serum complement levels (C3, C4), circulating immune complexes, cryoglobulins, cryofibrinogen and rheumatoid factor were routinely performed in all patients. ACL of IgG, IgM, IgA and beta 2-glycoprotein IgG were controlled in the beginning and at the end of the study. Biopsy specimens were obtained from active skin lesions from the edge of the livedoid vasculitis like-ulcers located on the lower portion of the legs with punch 4-mm technique. All the histological findings were studied of hematoxylin-eosin staining.

Results

All twenty-two patients included in this study were diagnosed as LV according to their clinical and histopatholocical findings. The distribution of the cutaneous lesions was predominantly bilateral, but three of the cases were unilateral. The skin around the ankle was the most common site, followed by the leg. The dorsal surface of the foot was the least common. Most patients had efflorescence in a combination of these locations. Morphologic lesions beginning as macular purpura 1 to 2 mm in diameter, enlarging to an irregular purpuric papule 2 to 5 mm in diameter, eventuating in ulceration in the center, and a purpuric border. Fourteen patients were with painful ulcerations on the background of persistant cyanotic dyscoloration. Seventeen patients were with persistent violaceous reticulated skin pattern, called livedo reticularis that is a main clinical sign of atheromatous vascular disease and occlusive vasculopathies, such as livedo vasculitis [5,12]. Some of the lesions healed with a stellate-shaped depressed white scar with a slightly elevated border characterized by tiny telangiectatic vessels. This is so called atrophie blanche and it was seen in eight of our patients. This clinical pattern was noted to follow a painful ulcerative stage but was also seen in the absence of previous ulceration in four of our cases. Of the all patients, 15 had livedoid vasculopathy in association with other diseases, 8 of whom had antiphospholipid syndrome(APS), 4 were with rheumatoid arthritis, 2 were with associated venous insufficiency and 1 with idiopathic thrombocytopenia.

Laboratory findings, including complete blood cell count, erythrocyte sedimentation rate, antinuclear antibody, antiphospholipid antibody, cryoglobulin levels, prothrombin time, partial thromboplastin time, international normalized ratio, proteins C and S levels, were all within normal limits in the other seventh patients who we diagnosed as idiopathic LV. A deep skin biopsy specimen showed the presence of focal hyalinized regions in the mid and deep dermis with the evidence of a hyalinizing vasculitis with fibrinoid deposits around the vessels without thrombosis (Fig. 1, Fig. 2).

In eight of the patients we found elevated ACL, detected twice in 3-month period. According to clinical and laboratory criteria, they were diagnosed as having APS and histologically, skin lesions showed microvascular thromboses, which is typical for this kind of pathology, but also mild lymphocytic perivascular infiltrate and hyalinization of dermal vessels (Fig. 3). Leukocytoclastic vasculitis was not detected, although moderate perivascular infiltration of lymphocytes was seen.

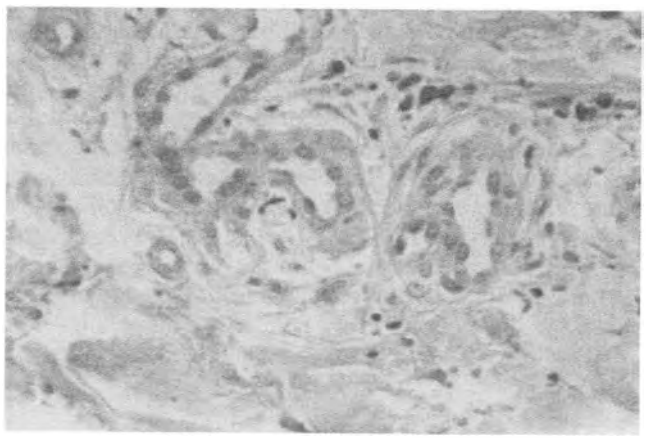

Fig. 1. Hyalinizing segmental vasculitis in the wall of dermal vessels (HE, × 20)

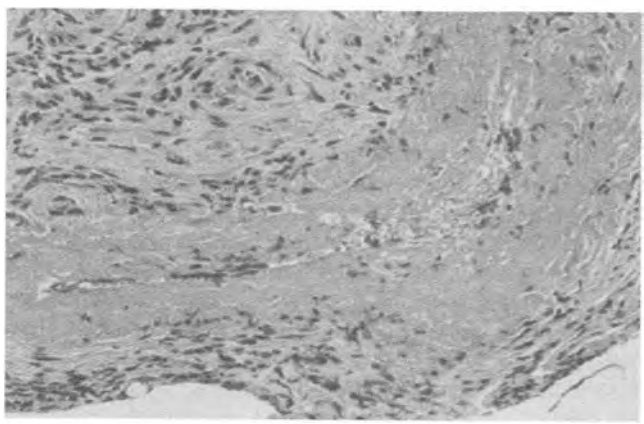

Fig. 2. Deposition of fibrin materials in the wall and lumen of a vessel in the deep dermis (HE, × 40)

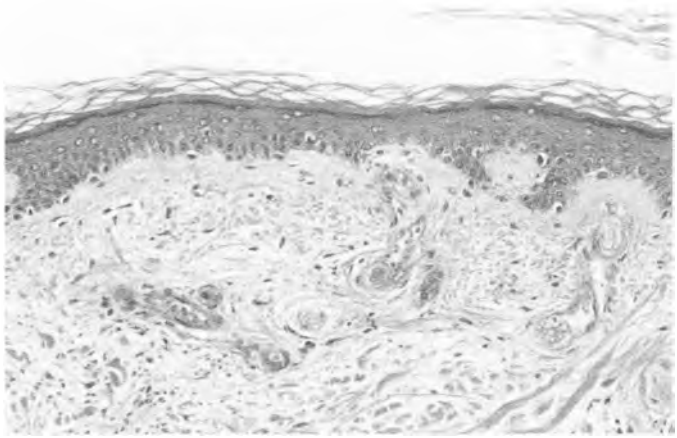

Fig. 3. Microvascular thromboses, mild lymphocytic perivascular infiltrate, and hyalinization of dermal vessels (HE, × 10)

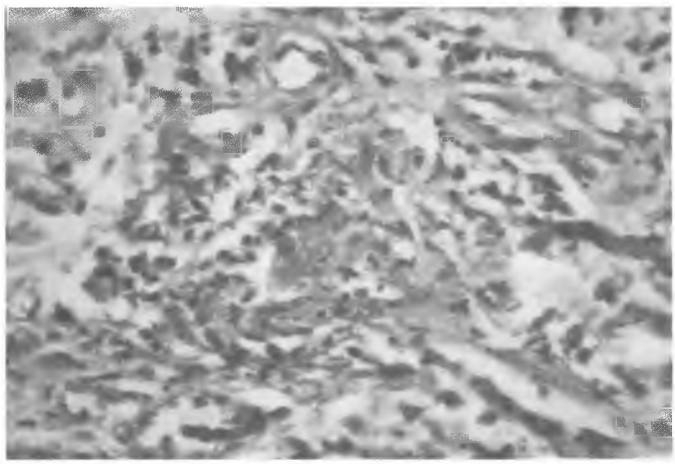

Fig. 4. Hyper and parakeratosis, acanthosis, endothelial swelling and fibriniod deposition in the lumen of dermal vessels, erythrocyte extravasation (HE, × 20)

The fourth patients with LV in association with venous insufficiency showed mild superficial and deep perivascular infiltrates of neutrophils and lymphocytes, fibrin in the vessel walls and microthromboses.

One of the patients was with idiopathic thrombocytopenia, based on the low levels of the platelets, anisocytosis with hypochromia and anti- Ro antibodies. The skin biopsy specimen showed hyper and parakeratosis, acanthosis, endothelial swelling and fibrin-iod deposition in the lumen of dermal vessels (Fig. 4).

Discussion

LV was first described in 1967 by Bard and Winkelman [1]. Livedoid vasculopathy is an uncommon skin condition that poses a diagnostic and therapeutic challenge for dermatologists and dermatopathologists.

All our patients were assessed clinically for the characteristic aspect of painful, reticulated, ulcerative lesions of the legs, which result in ivory atrophic areas, and histologically for the typical focal thrombi, segmental hyalinization, and a mild lymphocyte infiltration around the dermal vessels. No sign of fibrinoid necrosis of the dermal vessels was seen. Nuclear dust were also absent in the infiltrate.We did not detect any significant sign of leukocytoclastic vasculitis. From this point of view we support the thrombo-occlusive pathogenesis rather than a vasculitis. For some time, LV has been considered a vasculitic process and probably was misdiagnosed as vasculitis. However, it is a common observation that, at histopathologic examination, most lesions of LV lack neutrophilic infiltrate of the blood vessel walls and fibrinoid necrosis, hallmark features of true vasculitis. Many studies favoured this theory, demonstrated that in cutaneous small vessel vasculitis, the serum levels of proinflammatory cytokines are high, whereas in LV, the levels of inflammatory mediators are in the normal range [11]. Although the pathogenesis of LV is still unclear, most authors consider a hypercoagulable state as the primary pathogenic mechanism.

Livedo racemosa and livedoid vasculopathy are often associated with APS [7,12]. LV and APS are suggested to be interconnected diseases as elevated ACL in patients with LV have a predictive importance for development of thrombosis [6]. Occlusion of the smaller dermal vessels in APS may result in the clinical picture of LV. Consequently LV may represent only a clinical manifestation of APS and LV-like ulcers are considered to be very important skin feature of the disease.

In summary, we may conclude that LV arises on the basis of procoagulant and prothrombotic processes rather than a vascular inflammation. Hyalinization of the vessels must be included in the interpretation of the occlusive vasculopathy. Thrombosis is one and the same process which is seen histopathologycally both in biopsy specimens from minimal skin lesions and from life-threaten conditions as APS. Discrete cutaneous findings like atrophie blanche could be a marker and a first clinical sigh of a thrombotic disorder which may lead to extensive skin efflorescence.

Livedo vasculitis may represent a clinical manifestation of a heterogeneous group of diseases that cause an occlusive vasculopathy or that it may occur as a sole entity.

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