

Livedo Reticularis: An Enigma

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Livedo reticularis, as the name suggests, is a livedoid discoloration of the skin in a reticular pattern. In 1907 Ehrmann described two types of livedo: livedo racemosa which has an incomplete (broken) reticular lattice work pattern, and livedo reticularis where the reticular pattern comprises complete circles (unbroken) [1]. The concept was that pathological livedo was racemosa and the reticularis pattern was non-pathological. However, in clinical practice there is no clear-cut differentiation between these forms of livedo, and often “livedo reticularis” is the term used to describe all types of livedo.

Broadly speaking, livedo is divided into physiological and pathological livedo. Physiological livedo (*cutis marmorata*) is commonly seen on the legs of young healthy women in cold weather and varies according to temperature (rewarming). This lattice-like pattern is a result of livedoid discoloration due to anastomoses between vascular cones in the skin where desaturated blood stagnates [2] [Figure 1].

The classification of pathological livedo was not clear until recently. However, in the revised classification criteria for antiphospholipid syndrome (APS), pathological livedo is defined as “the persistent, non-reversible with rewarming, violaceous, red and blue, reticular or mottled pattern of the skin of trunk, arms or legs, consisting of regular unbroken circles (livedo reticularis) or irregular broken pattern (racemosa).” Here the concept was based on the extent and fixed pattern of livedo rather than the type of livedo. This was further classified according to the width of livedo (< or > 10 mm) – large and fine livedo racemosa and large and fine livedo reticularis. It is not clear whether the width of the livedo has any implications for the observed pathology in the skin [3]. The term

livedoid vasculitis is used for cutaneous ulcers with livedo and is generally of the racemosa type [4].

Certain drugs such as amantadine used in the treatment of Parkinson's disease and multiple sclerosis can induce livedo, which may occur in up to 28% of patients receiving amantadine. Skin biopsies of livedo in these patients did not show any vasculitis and it was thought to be secondary to depleted catecholamines [5].

PREVALENCE

The first description of an association between livedo reticularis and cerebrovascular accidents came from Sneddon in 1965 [6]. He described six patients, one man and five women, with cerebrovascular accidents who had livedo reticularis. All patients were negative for LE cells and had no clinical features of systemic lupus erythematosus (SLE) or polyarteritis nodosa, although none appear to have been tested for the lupus anticoagulant.

Interestingly, most of the patients were hypertensive and one patient underwent a renal biopsy which showed hypertensive changes [6]. Livedo is also observed in various autoimmune diseases such as livedoid vasculopathy, SLE with or without antiphospholipid (Hughes) syndrome (APS), thromboangiitis obliterans, primary thrombocytopenia, polyarteritis nodosa, and polycythemia vera [7]. Although livedo may present in isolation as seen in Sneddon's syndrome, there is a strong correlation between APS and livedo. In his first description of APS, Hughes included livedo as part of a syndrome associated with arterial and venous thrombosis, spontaneous abortions, neurological manifestations, thrombocytopenia and livedo [8]. Livedo is the most commonly observed cutaneous lesion in APS [9]. In their study of 200 APS patients, Frances et al. [10] found livedo in 25.5%. Livedo can be an initial manifestation in primary APS in up to 40% of patients and more frequently in up to 70% of patients with SLE and APS [11]. Similar findings were described in a cohort of 1000 patients with APS. In this cohort, livedo was observed in

Livedo reticularis is an independent marker of arterial and venous thrombosis, pregnancy morbidity, and possibly accelerated atherosclerosis

Figure 1. Livedo reticularis



20.4% of patients and was significantly more prevalent in women (26% vs. 16%) than in men [12].

There is a strong association between livedo and anticardiolipin antibodies (aCL). Weinstein and co-authors [13] found livedo in almost 50% of patients with SLE. In this cohort of 78 patients there was significant correlation between immunoglobulin G (IgG) aCL and severe to moderate livedo. On the other hand, the prevalence of the lupus anticoagulant was not significantly different between the livedo and non-livedo groups [13].

CLINICAL ASPECTS

• ARTERIAL AND VENOUS THROMBOSIS

Arterial and venous thrombosis was observed in patients with livedo irrespective of the presence of antiphospholipid antibodies (aPL). The relationship between livedo and stroke was first described by Sneddon [6]. Frances et al. [14] described 46 patients with livedo of whom 27 were aPL negative. They found both arterial and venous thrombosis in both groups (positive and negative aPL), and skin biopsies showed arterial occlusions in both groups [14]. Furthermore, Frances et al. reported a significant correlation between livedo and seizures, cardiac valvular defects, systemic hypertension, and Raynaud's phenomenon. Our own studies confirmed that renal artery stenosis in APS was associated with livedo [15]. In a large series of 308 patients, Toubi and colleagues [16] noted an increased prevalence of migraine, stroke and seizure disorder in patients with livedo and APS.

• PREGNANCY MORBIDITY

Pregnancy morbidity was also higher in our patients with SLE and livedo who were negative for antiphospholipid antibodies [17]. These findings further confirmed the observations of Frances et al. [14] that pregnancy loss is more common in livedo patients with and without aPL. Livedo may be independently associated with pregnancy loss in patients who are negative for aPL.

• ACCELERATED ATHEROSCLEROSIS

A preliminary controlled study in our unit found that ankle brachial pressure index (ABPI) was abnormal in patients with livedo as compared to those without livedo [18]. Taking a clue from this finding, we further investigated ABPI, pulse wave velocity (PWV) and pulse contour analysis in four groups consisting of 74 patients with APS, SLE and APS, and patients with livedo only. In this study, 41 patients had livedo and 33 did not. The PWV was significantly abnormal in the livedo group compared to the non-livedo group. In both groups there were almost equal numbers of patients with APS and SLE [19]. These results suggest that vascular dysfunction may be associated with livedo.

• LIVEDOID VASCULITIS (LV)

Livedo may present as a cutaneous ulcer (livedoid vasculopathy, LV), also known as livedo reticularis ulcerations, and atrophie blanche may be a consequence. This usually affects the legs bilaterally and is more common in summer [20-22]. It may affect all age groups but is more common in young females. Initially, it starts with a painful papular rash that develops into an ulcer. It subsequently heals, leaving a porcelain white scar that is often star-shaped: atrophie blanche [23]. LV was originally described as a clinical manifestation of vasculitis; however, the present concept is that it is a vaso-occlusive phenomenon with thrombosis of intradermal venules [24,25]. LV has been described as secondary LV when associated with a coagulation defect otherwise known as primary or idiopathic.

PATHOPHYSIOLOGY

The pathophysiology of livedo is not clearly defined. The results of skin biopsy depend on the site of the biopsy. Wohlrab and team [26] noted that biopsies from the center of the livedo lesion (white area) had better yield than other areas. Histological findings of livedo were similar in primary APS and APS associated with SLE.

Zelger et al. [27] described 15 patients with Sneddon's syndrome of whom 12 had skin biopsies. Only small to medium-sized arteries of the dermis-subcutis boundary were found to be involved. Lesions follow a distinct course. Zelger et al. described four stages. An initial phase (stage I), characterized by the attachment of lymphohistiocytic cells and detachment of endothelial cells (endothelitis), is followed by an early phase (stage II), which displays partial or complete occlusion of the lumen by a plug of lymphohistiocytic cells and fibrin. In an intermediate phase (stage III), the occluding plug is replaced by proliferating subendothelial cells accompanied by dilated capillaries in the adventitia of the occluded vessel. The late phase (stage IV) shows fibrosis and shrinkage of the affected vessels [27]. Sepp and colleagues [28] studied skin specimens of 18 patients with Sneddon's syndrome, and reported that CD3+, UCHL-1+, and HLA-DR+ cells constituted a significant proportion of the inflammatory infiltrate in the early stages, whereas in later stages, endothelial cells and leukocytes were scarce. These findings indicate the possibility of an inflammatory and/or immunological process involved in the pathogenesis of livedo. There were no significantly different histological findings of livedo on skin biopsies in primary APS and APS associated with SLE [10].

In contrast to these findings, histopathological changes were different in patients with livedoid vasculitis (LV) and are characterized as follows:

- *Initial stage:* Occlusion of dermal vessels, intravascular fibrin deposition and thrombosis with no evidence of sig-

The underlying pathology involves prothrombotic as well as immunologic processes

nificant inflammation [24]. In this study there was a high incidence of positive aPL and low levels of tissue plasminogen activators. Indeed treatment with recombinant tissue plasminogen activator helped in resistant cutaneous ulcers that had failed to respond to conventional therapies [29]

- *Intermediate stage:* This stage is characterized by hyalinization in the dermis and sometimes endothelial proliferation. It should be noted that fibrinoid deposition is present in all stages [24]
- *Late stage:* Direct immunofluorescence usually demonstrates deposition of immunoglobulin, fibrin and complement components. In the initial stages here is deposition of fibrin on the vessel walls, and deposition of immunoglobulins and complement is detected in later stages. Schroeder et al. [30] showed that immunoglobulins and complement components (C1q, C3, and properdin) were localized in diseased vessel walls, suggesting an immune pathogenesis.

Thus, LV is a thrombo-occlusive condition with coagulation defects and/or fibrinolysis. Similarly, the description "atrophie blanche" may be attributed to conditions such as LV and other ulcerative conditions on the lower limbs [22].

In summary, there is a wide variation in the histopathological findings in livedo reticularis and LV. The spectrum includes inflammation, thrombosis, hyalinization, and immunological pathology. This probably demonstrates more than one pathogenic mechanism. In addition, as mentioned earlier, abnormal ABPI and PWV suggests accelerated atherosclerosis [18,19].

Livedo reticularis may be a marker of "seronegative" antiphospholipid (Hughes) syndrome

seronegative antiphospholipid syndrome [39], although the exact relationship of livedo with seronegative APS remains to be elucidated.

low dose aspirin, clopidogrel, dipyridamol, and vasodilators such as nifedipine and pentoxifylline, have been tried prophylactically but the benefits of these therapies are inconsistent [33]. Low molecular weight heparin and oral anticoagulants have shown promising results [34,35].

Despite these treatment options, livedoid ulcers are often resistant to therapy. Several approaches have been tried with variable success. Systemic and intradermal corticosteroids have shown little benefit [33]. Considering the low levels of tissue plasminogen activator, recombinant tissue plasminogen has been tried with some success in difficult-to-treat LV [30,36]. Therapeutic modalities such as intravenous immunoglobulins and hyperbaric oxygen have also been tried with some success [37,38].

SUMMARY

Livedo reticularis is a common cutaneous manifestation of APS and may be a prognostic marker of more severe disease. It is associated with arterial and venous thrombosis and pregnancy morbidity irrespective of the presence of antiphospholipid antibodies. Recent results suggest the possibility of an association with accelerated atherosclerosis in patients with livedo. Given the similarities between APS and livedo (aPL negative), experts in this field believe that livedo may represent the so-called

LV may present as painful cutaneous ulcers that are often difficult to treat. The underlying pathology involves prothrombotic as well as immunological processes with some overlap with APS. Treatment remains challenging and results are often variable.

DIFFERENTIAL DIAGNOSIS

There are a number of other pathological conditions that may present as livedo. Polyarteritis nodosa and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis, involving small and middle-size arteries may present as cutaneous leg ulcers associated with livedo. A skin biopsy may be confirmatory, showing true vasculitis. Other autoimmune inflammatory diseases such as cryoglobulinemic vasculitis and pyoderma gangrenosum may also manifest in a similar way [4,31,32].

TREATMENT

A variety of treatment approaches have been used and no single treatment has been found ideal. In view of the increased risks of cerebrovascular accident and arterial and venous thrombosis, patients are advised to modify traditional risk factors with measures such as weight loss, lipid-lowering therapies, blood pressure control, diabetes management, smoking cessation, and avoidance of estrogens including contraceptive pills and hormone replacement therapies. Antiplatelet agents such as

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