

# Livedo Racemosa: A Striking Dermatological Sign for the Antiphospholipid Syndrome



Hughes first described patients with clinical features associated with antiphospholipid antibodies (aPL)<sup>1</sup> in 1983. These features included a tendency to arterial and venous thrombosis, recurrent abortions, and, occasionally, thrombocytopenia. This was later named the antiphospholipid syndrome (APS)<sup>2</sup>. Since the first description of APS, a wide variety of dermatological manifestations have been reported. Livedo reticularis is the most frequently observed lesion<sup>3,4</sup>. Livedo reticularis is a striking macular violaceous netlike patterned erythema of the skin<sup>5,6</sup>. In 1907 Ehrmann distinguished 2 different patterns of livedo: the pathological livedo racemosa and the physiological livedo reticularis<sup>7</sup>. The livid rings in both forms are caused by reduced blood flow and lowered oxygen tension at the peripheries of the skin segments<sup>5,8</sup>.

Almost a century has passed since the initial description by Ehrmann and there is still no clear definition or differentiation in the literature of these 2 forms of livedo. Many textbooks and medical dictionaries still use these 2 terms synonymously. This confusion is more evident in the rheumatology literature, where livedo reticularis is the term commonly used to describe netlike cutaneous vascular patterns, whereas the term livedo racemosa is rarely used.

In the recent update of classification criteria for APS, livedo reticularis was defined as “the persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled pattern of the skin of trunk, arms or legs, consisting of regular unbroken circles (regular livedo reticularis) or irregular-broken circles (livedo racemosa).” The livedo patterns were classified, depending on the width of branching pattern ( $\leq$  or  $>$  10 mm), into 4 variants: fine livedo racemosa, large livedo racemosa, fine regular livedo reticularis, and large regular livedo reticularis<sup>9</sup>.

We will try to differentiate and classify the different forms of livedo and clarify the definition of this common dermatologic sign.

## LIVEDO RETICULARIS

Livedo reticularis may be differentiated into 4 distinct entities based on duration of the livedo pattern and its association with ambient temperature: physiologic, primary, idiopathic, and amantadine-induced livedo reticularis<sup>5,6</sup>.

Physiologic livedo reticularis, also known as cutis marmorata, mainly affects young women and most commonly

occurs on the legs on exposure to cold, with gradual resolution on rewarming. An impairment of blood flow in cutaneous vessels causes the mottling of livedo reticularis related to the vascular anatomy of normal skin. The blood supply is arranged in cones with 1–4 cm bases situated on the surface of the skin with a central arteriole supplying each area. The regular, netlike pattern of cutis marmorata results from cyanotic discoloration occurring at the anastomoses between cones, where deoxygenated blood stagnates; cutis marmorata typically resolves on rewarming of the skin<sup>5,10</sup>.

Primary livedo reticularis also has a fluctuant course, but differs from cutis marmorata in that changes in skin color are unrelated to ambient temperature<sup>6</sup>.

Idiopathic type is a persistent and unresolving form of livedo reticularis<sup>6</sup>. The diagnosis is reached when no other pathological signs except livedo reticularis are found. It may, occasionally, represent a very early stage of APS or Sneddon's syndrome.

The synthetic antiviral agent amantadine is used to treat Parkinson's disease and fatigue associated with multiple sclerosis. Amantadine-induced livedo reticularis was first described by Shealy, *et al* in 1970<sup>11</sup>, occurring in 2% to 28% of patients and more frequently in women. Skin biopsy specimens from patients with amantadine-induced livedo reticularis showed normal epidermis and corium without signs of vasculitis. The possible cause of the vascular action of amantadine is a depletion of catecholamines, through noncompetitive inhibition of the N-methyl-O-aspartic-acid-evoked release of acetylcholine.

## LIVEDO RACEMOSA

*Clinical description.* The term livedo racemosa was first introduced in 1907 by Ehrmann as a “tendrill-like bluish pattern reminiscent of forked lightning which intensified in the cold as a sign of passive hyperemia, somewhat cooler than the surrounding skin”<sup>7</sup>. Livedo racemosa is characterized by a striking violaceous netlike patterning of the skin similar to the familiar livedo reticularis, from which it differs by its location (more generalized and widespread, non-infiltrated, found not only on the limbs, but also on the trunk and/or buttocks), its shape (irregular, broken, circular segments), and its biopsy results<sup>5,8,12</sup>. Livedo racemosa is the typical sign of Sneddon's syndrome<sup>13</sup>, but also occurs in other disorders such as live-

doid vasculopathy, APS, systemic lupus erythematosus (SLE) with or without APS, essential thrombocythemia, thromboangiitis obliterans, polycythemia vera, and polyarteritis nodosa<sup>5</sup>. Although Ehrmann in his description of livedo racemosa stressed its association with a number of pathological conditions, compared to the physiologic livedo reticularis, dermatology literature still includes a number of pathologic conditions in the differential diagnosis of livedo reticularis. Hence it may be argued that although the differential diagnosis of these 2 forms of livedo may be similar and overlapping, APS has only been associated with livedo racemosa<sup>14</sup>.

**Epidemiology.** Livedo reticularis may be the presenting sign of APS in 17.5% to 40% of patients<sup>3,15-17</sup> and may be seen in up to 70% of patients with SLE and APS<sup>18</sup>. In a cohort of 1000 European patients with APS<sup>19</sup>, the overall prevalence of livedo reticularis was found to be 24.1%, and was higher in patients with SLE-associated APS versus those with primary APS (36% vs 16%;  $p < 0.001$ ), and in female versus male patients (26% vs 16%;  $p < 0.005$ ). Livedo reticularis was a presenting manifestation in 20.4% of cases in that cohort. In a recent study of dermatologic manifestations of 200 consecutive patients with primary APS or SLE-related APS, livedo reticularis was the most frequent manifestation, observed in 25.5% of cases<sup>3</sup>. The presence of livedo reticularis was associated with higher levels of IgG anticardiolipin antibodies (aCL; mean 161.6 GPL units in patients with livedo reticularis vs 82.1 GPL units in patients without;  $p = 0.006$ ). In contrast, the levels of IgM aCL (mean 12.7 vs 19.7 MPL units, respectively) and prevalence of lupus anticoagulant (70.6% vs 60.8%, respectively) were similar in the presence or absence of livedo reticularis<sup>3</sup>. In the recently updated classification criteria for APS, livedo racemosa was not included in the major criteria for the disease<sup>9</sup>. Due to the high prevalence of livedo racemosa in APS, a careful reconsideration of this important dermatological sign as a major clinical feature is warranted in future revisions of these criteria.

**Histopathology.** The physiopathology of livedo racemosa is not well characterized. Skin biopsies often fail to yield diagnostic arterial lesions. Selection of the correct biopsy site (seemingly uninvolved skin at the center of a livedo racemosa area), adequate biopsy size (1 to 2 cm), and serial sections are essential for detection of relevant vascular pathology<sup>20</sup>. Wohlrab, *et al* evaluated the sensitivity of skin biopsies in Sneddon's syndrome and stressed that it is better to take more than one deep punch biopsy (4 mm) from different areas of the livedo racemosa (from both white and red areas). Sensitivity of these biopsies increased from 27% with one biopsy to 80% with 3 biopsies<sup>21</sup>. Zelger, *et al* reported that only small to medium-size arteries of the dermis-subcutis boundary were involved in a stage-specific pattern<sup>20</sup>. 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<sup>20</sup>. Sepp, *et al* 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<sup>22</sup>. These data confirmed the hypothesis that Sneddon's syndrome starts as an inflammatory and possibly immunologically mediated disorder, leading to a migration and proliferation of smooth cells of small arteries, resulting in a partial or complete narrowing of the vessel lumen<sup>22</sup>.

**Clinical associations.** Reports of a strong association between livedo reticularis and cerebrovascular accidents (CVA) in patients with SLE have appeared for more than 20 years<sup>23-26</sup>. Frances, *et al* reported a statistically significant association between the presence of livedo racemosa and cerebral or ocular ischemic arterial events, seizures, all arterial events, heart valve abnormalities detected on echocardiography, systemic hypertension (160/90 mm Hg), and Raynaud's phenomenon<sup>3</sup>. Toubi, *et al*<sup>17</sup> reported a significant association between livedo racemosa and CVA, migraines, and epilepsy in a cohort of 308 patients with APS. The strong association between stroke and livedo racemosa in patients who have persistently negative aPL tests have led us to suggest a new diagnostic entity, namely "seronegative APS"<sup>27</sup>.

Livedo racemosa is strongly associated with the arterial subset of APS. In a recent study from our unit we found that a sizeable number of APS patients with renal artery stenosis had livedo racemosa<sup>28,29</sup>. Frances, *et al* reported a statistically significant higher prevalence of livedo reticularis in APS patients with arterial thrombosis<sup>3</sup>.

This interesting relationship between livedo racemosa and arterial thrombosis suggests a possible role for the endothelial cells (EC). The vasoconstriction of livedo racemosa may be induced by an interaction of aPL with EC or other cellular elements of vessels in a way that alters their function<sup>28,30</sup>. It is now recognized that many autoantibodies associated with APS are directed against phospholipid-protein complexes expressed on or bound to the surface of vascular EC, platelets, or other cells, in addition to phospholipid-binding plasma proteins. Autoantibodies against these cell-bound proteins may alter the properties of bound EC from antithrombotic to prothrombotic, leading to the production of procoagulant substances such as tissue factor (TF), plasminogen activator inhibitor 1, and endothelin 1<sup>31</sup>. In a recent study investigating intracellular signals induced by aPL that mediate TF activation in monocytes from patients with APS, we found that aPL induces TF expression in monocytes by activating, simultaneously and independently, the phosphorylation of MEK-1/ERK proteins, and the p38 mitogen-activated protein kinase-

dependent nuclear translocation and activation of nuclear factor-B/Rel proteins<sup>32</sup>. Increased TF expression on EC and monocytes induced by aPL could be responsible, in part, for hypercoagulability and might explain the thrombosis in both arterial and venous circulation that characterizes these patients.

Pregnancy morbidity has also been frequently observed in patients with livedo racemosa. In a more recent study from our unit we observed a 63% pregnancy related morbidity in 52 patients with widespread livedo racemosa who were persistently negative for aPL, suggesting that pregnancy loss may also be independently associated with widespread livedo racemosa in patients who are aPL-negative<sup>13</sup>. Therefore, livedo racemosa constitutes an independent additive thrombotic risk factor in some patients with primary and SLE associated APS, possibly including some patients with seronegative APS<sup>27,33,34</sup>.

*Livedo racemosa and Sneddon's syndrome.* Many studies on livedo racemosa have been carried out in patients with Sneddon's syndrome, a rare but potentially severe condition, characterized by the association of an ischemic CVA and widespread livedo racemosa<sup>35,36</sup>. It typically affects women before or during middle age, with the first CVA typically occurring before age 45 years<sup>37,38</sup>. Livedo racemosa may precede the onset of stroke by years and may be located on limbs, trunk, buttocks, face, hands, or feet. The trunk and/or buttocks are involved in nearly all patients. Livedo was noted before cerebrovascular events in more than half of patients<sup>5,39</sup>. The relationship between APS and Sneddon's syndrome is not clear. It was first documented by Hughes<sup>2</sup> and later confirmed by others<sup>40,41</sup>. The prevalence of aPL in Sneddon's syndrome has ranged from 0% to 85% depending upon the series<sup>12</sup>. Most authors suggest that 40%–50% of patients with Sneddon's syndrome are aPL-positive<sup>5</sup>. Frances, *et al*<sup>12</sup> compared 46 patients with Sneddon's syndrome according to the presence or absence of aPL (Group I: aPL-negative, n = 27, and Group II: aPL-positive, n = 19). All patients except one in the aPL-positive group had livedo racemosa. Large livedo racemosa was more frequently observed in Group I (89%) than in Group II (21%; p < 0.001). On skin biopsy, arteriolar obstruction was detected in only 8 patients (4 in each group). Seizures, mitral regurgitation on echocardiogram, and thrombocytopenia < 150,000/ $\mu$ l were more frequently observed in Group II<sup>12</sup>. Arterial hypertension has been reported in both Sneddon's syndrome and APS, in the latter often due to renal artery stenosis<sup>28</sup>. However, the frequency of renal artery stenosis in patients with Sneddon's syndrome with hypertension has not been determined.

*Treatment.* No treatment has proven to be effective for livedo racemosa, which may extend or appear despite anticoagulant or antiplatelet therapy. In view of the higher tendency for CVA and arterial thrombosis in patients with livedo racemosa, it is important to reduce or remove other risk factors for thrombosis or arterial wall lesions. Patients are advised to stop smok-

ing and women are counselled against the use of estrogen-containing oral contraceptive pills. Low-dose aspirin is frequently prescribed for prevention of strokes, but its effectiveness is doubtful. The potential benefit of clopidogrel, statins, or angiotensin-converting enzyme inhibitors in these patients needs to be determined<sup>42</sup>.

## CONCLUSION

The skin appears to be an important target organ for aPL and in many cases APS may present with skin lesions. Livedo racemosa is the most common dermatologic manifestation of APS, frequently associated with cerebrovascular events, arterial thrombosis, and pregnancy morbidity, and considered an independent, additive, thrombotic risk factor. Since the initial description of APS, the term livedo reticularis has been used indiscriminately. It is important to differentiate and distinguish clinically between the 2 patterns of livedo. A more uniform terminology and careful description of this striking violaceous netlike patterned erythema of the skin in future studies or reports in the rheumatology literature will gradually help distinguish aPL-associated livedo racemosa from livedo reticularis.

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