# Idiopathic Livedo Racemosa Presenting With Splenomegaly and Diffuse Lymphadenopathy

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## PRACTICE **POINTS**

- The classic physical diagnostic finding of Sneddon syndrome (SS) is livedo racemosa.
- Early identification and treatment of SS can prevent serious morbidity due to stroke, myocardial infarction, and other thrombotic events.
- Preventive care in SS should include antiplatelet therapy or anticoagulants and smoking cessation along with avoidance of birth control pills.

*Sneddon syndrome (SS) is a rare condition and the diagnosis is made only when other more common disease entities have been excluded. Common manifestations in SS patients include hypertension, coronary artery disease, venous thrombosis, miscarriages, psychiatric disturbances, and arterial and venous thrombotic events. Most patients present in their early 30s with classic neurovascular and dermatologic signs. Currently, the main criteria for the diagnosis of SS include livedo racemosa, focal neurological deficits or evidence of stroke on magnetic resonance imaging, or characteristic vascular alterations seen on biopsy. We present the case of a 37-year-old woman with extensive livedo racemosa, chronic migraine headaches, splenomegaly, and lymphadenopathy. Cutaneous biopsies demonstrated a superficial perivascular lymphocytic infiltrate without the subendothelial proliferative changes or fibrosis seen in some patients with SS. The patient's medical history suggested idiopathic livedo racemosa with possible full progression to SS. This case highlights the variability in the clinical presentation of SS and that the disease often can be diagnosed before neurovascular events. Earlier diagnosis can lead to prevention of chronic occlusive neurovascular manifestations and irreversible damage such as myocardial infarction and stroke. Familiarity with the highly variable early course of SS can aid in diagnosis and reduction of morbidity and mortality that is associated with this disease.*

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Sneddon syndrome (SS) was first described in 1965 in patients with persistent livedo racemosa and neurological events.[1] Because the other manifestations of SS are nonspecific (eg, hypertension, cardiac valvulopathy, arterial and

venous occlusion), the diagnosis often is delayed. Many patients who experience prodromal neurologic symptoms such as headaches, depression, anxiety, dizziness, and neuropathy often present to a physician prior to developing ischemic brain manifestations[2] but seldom receive the correct diagnosis. Onset of cerebral occlusive events typically occurs in patients younger than 45 years and may present as a transient ischemic attack, stroke, or intracranial hemorrhage.[3] The disease is more prevalent in females than males (2:1 ratio). The exact pathogenesis of SS is still unknown, and although it has been thought of as a separate entity from systemic lupus erythematosus and other antiphospholipid disorders, it has been postulated that an immunological dysfunction damages vessel walls leading to thrombosis.

Cutaneous findings associated with SS involve small- to medium-sized dermal-subdermal arteries. Histopathology in some patients demonstrates proliferation of the endothelium and fibrin deposits with subsequent obliteration of involved arteries.[4] In many patients including our patient, histopathologic examination of involved skin fails to show specific abnormalities.[1] Zelger et al[5] reported the sequence of histopathologic skin events in a series of antiphospholipid-negative SS patients. The authors reported that only small arteries at the dermis-subcutis junction were involved and a progression of endothelial dysfunction was observed. The authors believed there were several nonspecific stages prior to fibrin occlusion of involved arteries.[5] Stage I involved loosening of endothelial cells with nonspecific perivascular lymphocytic infiltration with perivascular inflammation and lymphocytic infiltration representing the prime mover of the disease.[5,6] This stage is thought to be short lived, thus the reason why it has gone undetected for many years in SS patients. Stages II to IV progress through fibrin deposition and occlusion.[5] Histological features of stages I to II have not been reported because of late diagnosis of SS. Stage I patients typically present with an average duration of symptoms of 6 months with few neurologic symptoms, the most common being paresthesia of the legs.[5]

## Case Report

A 37-year-old woman with epigastric tenderness on the left side and splenomegaly seen on computed tomography was referred by a hematologist for evaluation of a reticular rash on the left side of the flank of 9 months' duration with a presumed diagnosis of focal melanoderma. Her medical history was remarkable for a congenital ventricular septal defect and coarctation of the aorta, as well as endometriosis, myalgia, and joint stiffness that had all developed over the last year. Her medical history also was remarkable for nephrolithiasis, irritable bowel syndrome, and chronic sinusitis, as well as psychiatric depression and anxiety disorders. She recently had been diagnosed with moderate hypertension and had experienced difficulty getting pregnant for the last several years with 3 consecutive miscarriages in the first trimester. Neurologic symptoms included neuropathy involving the feet, intermittent paresthesia of the legs, and a history of chronic migraine headaches for several months.

Dermatologic examination revealed a slightly overweight woman with a 25×30-cm dusky, erythematous, irregular, netlike pattern on the left side of the upper and lower trunk (Figure 1). Extensive livedo racemosa was not altered by changes in temperature and had been unchanged for more than 9 months. There were no signs of pruritus or ulcerations, and areas of livedo racemosa were slightly tender to palpation.

We performed 2 sets of three 4-mm biopsies. The first set targeted areas within the violaceous pattern, while the second set targeted areas of normal tissue between the mottled areas. All 6 specimens demonstrated superficial perivascular lymphocytic infiltrate with no evidence of vasculitis or connective tissue disease. The vessels showed no microthrombi or surrounding fibrosis. No eosinophils

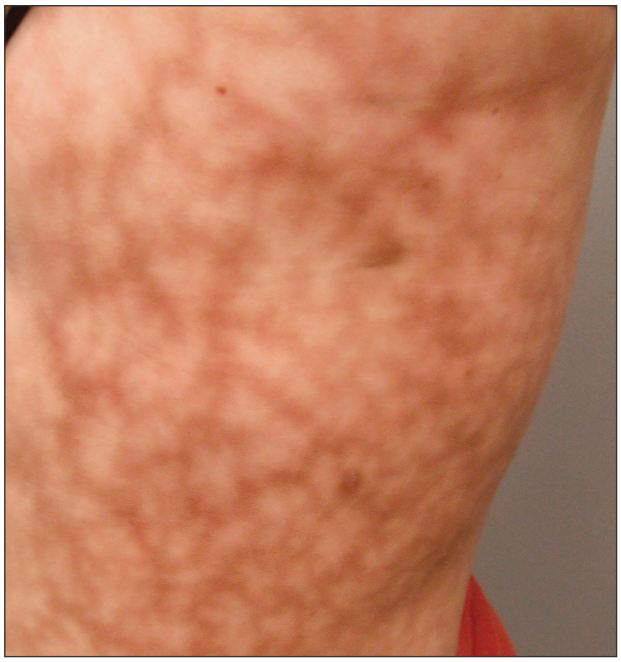

**Figure 1.** Livedo racemosa presenting as a netlike violaceous pattern on the left side of the trunk measuring 25×30 cm.

were identified within the epidermis. There was no evidence of increased dermal mucin. Both the superficial and deep vascular plexuses were unremarkable and showed no evidence of damage to the walls (Figure 2).

To rule out other possible causes of livedo racemosa, complete blood cell count, comprehensive metabolic panel, coagulation profile, lipase test, urinalysis, serologic testing, and immunologic workup were performed. Lipase was within reference range. The complete blood cell count revealed mild anemia, while the rest of the values were within reference range. An immunologic workup included Sjögren syndrome antigen A, Sjögren syndrome antigen B, anticardiolipin antibodies, and antinuclear antibody, which were all negative. Family history was remarkable for first-degree relatives with systemic lupus erythematosus and Crohn disease.

Computed tomography revealed enlargement of the spleen, as well as periaortic, portacaval, and porta hepatis lymphadenopathy. Based on the laboratory findings and clinical presentation as well as the patient's medical history, the diagnosis of exclusion was idiopathic livedo racemosa with unknown progression to full-blown SS. The patient did not meet the current diagnostic criteria for SS, and her immunologic studies failed to confirm any present antibodies, but involvement of the reticuloendothelial system pointed to production of antibodies that were not yet detectable on laboratory testing.

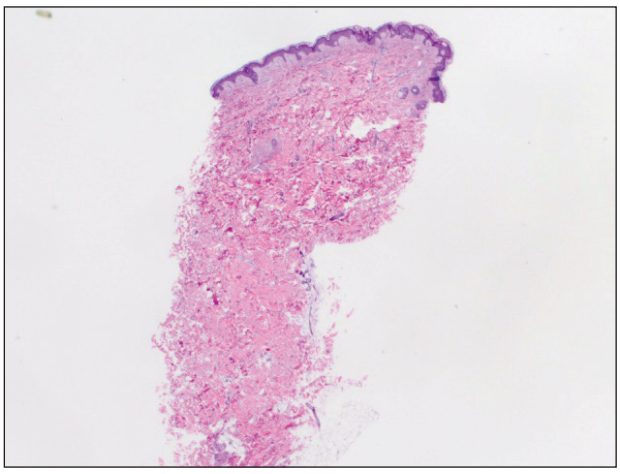

**Figure 2.** Punch biopsy from the left side of the trunk showed focal melanoderma and sparse superficial perivascular lymphocytic infiltrate with no evidence of vasculitis, microthrombi, or fibrin deposition (H&E, original magnification ×20).

## Comment

More than 50 years after the first case of SS was diagnosed, better laboratory workup is available and more information is known about the pathophysiology. Sneddon syndrome is a rare disorder, affecting only approximately 4 patients per million each year worldwide. Seronegative antiphospholipid antibody syndrome (SNAPS) describes patients with clinical presentations of antiphospholipid syndrome (APS) without detectable serological markers.[7] Antiphospholipid-negative SS, which was seen in our patient, would be categorized under SNAPS. A PubMed search of articles indexed for MEDLINE using the terms *livedo racemosa*, *Sneddon syndrome*, and *SNAPS and splenomegaly* revealed there currently are no known cases of SNAPS that have been reported with splenomegaly and lymphadenopathy. Our patient presented with the following clinical features of SS: livedo racemosa, history of miscarriage, psychiatric disturbances, and hypertension. Surprisingly, biopsies from affected skin did not show any fibrin deposition or microthrombi but did reveal perivascular lymphocytic infiltrations. Magnetic resonance imaging did not show any pathological lesions or vascular changes.

Sneddon syndrome and APS share a common pathway to occlusive arteriolopathy for which 4 stages have been described by Zelger et al.[5] Stage I involves a nonspecific Langerhans cell infiltrate with polymorphonuclear leukocytes. The tunica media and elastic lamina usually are unaltered at this early stage, while the surrounding connective tissue may appear edematous.[5] This early stage of histopathology has not been evaluated in SS patients, primarily because of delay of diagnosis. Late stages III and IV will show fibrin deposition and shrinkage of affected vessels.[7]

A PubMed search using the terms *Sneddon syndrome*, *lymphadenopathy and livedo racemosa*, and *Sneddon syndrome and lymphadenopathy* revealed that splenomegaly and lymphadenopathy have not been reported in patients with SS. In patients with antiphospholipid-negative SS, one can assume that antibodies to other phospholipids not tested must exist because of striking similarities between APS and antiphospholipid-negative SS.[8] Although our patient did not test positive for any of these antibodies, she did present with lymphadenopathy and splenic enlargement, leading us to believe that involvement of the reticuloendothelial system may be a feature of SS that has not been previously reported. Further studies are required to name specific antigens responsible for clinical manifestations in SS.

Currently, no single diagnostic test for SS exists, thus delaying both diagnosis and initiation of treatment. Histopathologic examination may be helpful, but in many cases it is nonspecific, as are serologic markers. Neuroradiological confirmation of involvement usually is the confirmatory feature in many patients with late-stage diagnosis.[2] A diagnostic schematic for SS, which was first described by Daoud et al,[2] illustrates classification of symptoms and aids in diagnosis. A working diagnosis of idiopathic livedo racemosa is made after ruling out other causes of SS in a patient with nonspecific biopsy findings and negative magnetic resonance imaging results with prodromal symptoms. The prognosis for such patients progressing to full SS is unknown with or without management using anticoagulant therapy.

## Conclusion

Early diagnosis of livedo racemosa and SS is essential, as prevention of cerebrovascular accidents, myocardial infarction, and other thromboembolic diseases can be minimized by attacking risk factors such as smoking, taking oral contraceptive pills, becoming pregnant,[9] and by initiating either antiplatelet or anticoagulation treatments. These treatments have been shown to delay the development of neurovascular damage and early-onset dementia. We present this case to demonstrate the variability of early-presenting symptoms in idiopathic livedo racemosa. Recognizing some of the early manifestations can lead to early diagnosis and initiation of treatment.

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