Long-term follow-up of early-onset Sneddon syndrome: A case report

Stephan Forchhammer, MD, Gisela Metzler, MD, and Kamran Ghoreschi, MD
Tübingen, Germany

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INTRODUCTION

Sneddon syndrome is a rare vasculopathy of small and medium-sized arteries, characterized by the clinical occurrence of livedo racemosa together with ischemic cerebrovascular events.[1] First cases of patients with livedo racemosa and neurologic symptoms were reported in the 1950s and 1960s.[1-3] This syndrome is rare with an estimated incidence of 4 of 1 million per year and mainly affects young women with a mean onset in the third decade of life.[4,5] We present an early-onset idiopathic form of Sneddon syndrome with a long-term follow-up of 19 years in a young male.

CASE REPORT

In 1998, a 3-year-old boy presented in our department with violaceous, erythematous, irregular netlike maculae, that first appeared 3 months earlier at the face, back of the hands, lower arms, feet, and legs with slight manifestation on the trunk. The irregular netlike maculae were persisting and increased in intensity with cold temperature (Fig 1).

The boy had no other symptoms and felt healthy. Medical examination found no signs of concomitant internal or rheumatoid disease. Screening for antinuclear antibodies, antiphospholipid antibodies, cryoglobulins, or deviations in the coagulation system found no abnormalities. We performed a biopsy out of the white center of the irregular netlike maculae, which found an occluding lymphohistiocytic vasculitis of the deep dermal plexus (Fig 2).

The boy had livedo racemosa diagnosed and was followed up once a year at the rheumatology unit of our children's hospital until he was 10 years old.

Abbreviations used:

ASA: acetylsalicylic acid
IVIg: intravenous immunoglobulin

In 2013, at the age of 18 years, the patient suddenly had recurrent abdominal pain and vomiting. Gastroenterologic evaluation found an unspecific inflammatory colitis. At the same time, systemic arterial hypertension was noted. Systolic blood pressure, with episodes up to 200 mm Hg, was measured. A renal cause of the hypertension was not found. However, no antihypertensive treatment was initiated until 2015.

In February 2015, the patient woke up with palsy of the right side of his body. At the hospital, a secondary intracerebral hemorrhage after primary ischemic stroke was diagnosed. The stroke led to right-sided brachio-facial sensomotoric spastic hemiparesis, temporary aphasia, and temporary cognitive impairment. In December 2016, at the age of 21, the patient re-presented at our department of dermatology with painful sensations of the skin and joint rigidity after exposure to cold temperature. The discoloration of the skin persisted over the last 18 years but was considerably reduced. The patient had slightly violaceous irregular netlike maculae on the extremities that increased when cooling down (Fig 3).

Serologic diagnostic testing still found no signs of antinuclear antibodies, antiphospholipid antibodies, or cryoglobulines. Creatinine clearance was not impaired. Cardiac ultrasound scan found no evidence of heart valvulopathy. Meanwhile, the arterial

From the Department of Dermatology, University Medical Center, Eberhard Karls University of Tübingen.

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Correspondence to: Dr Stephan Forchhammer, Department of Dermatology, University Medical Center, Eberhard Karls University of Tübingen, Liebermeisterstr. 25, 72076 Tübingen, Germany. E-mail: stephan.forchhammer@med.uni-tuebingen.de.

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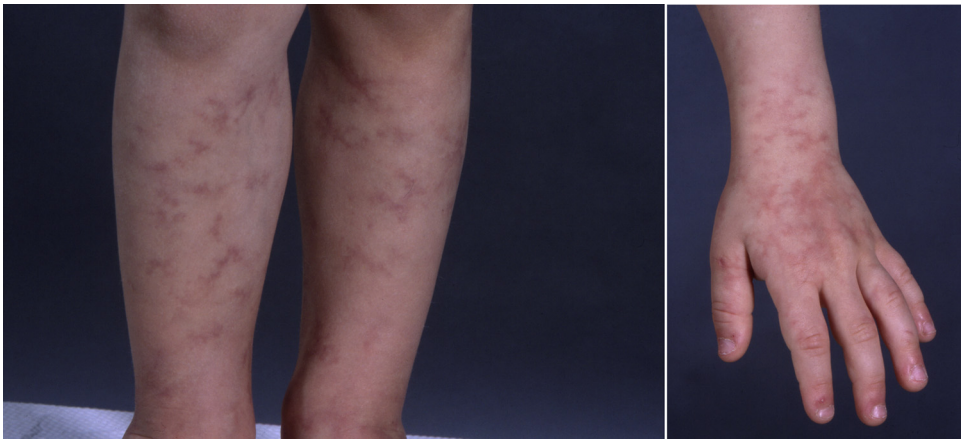

Fig 1. Livedo racemosa with marked violaceous, irregular, flash-figure–like maculae on both legs and hands. Photo documentation performed in December 1998.

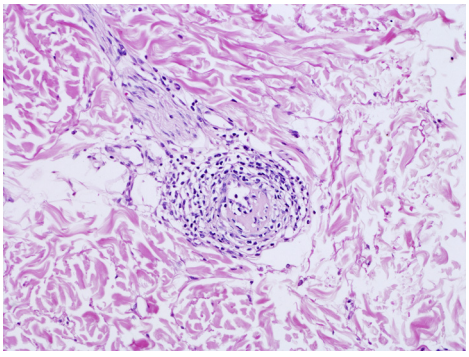

Fig 2. Small-sized vessel in the deep dermal plexus, on the boarder of dermis and subcutis with loosening of endothelial cells and a lymphohistiocytic inflammatory infiltrate. The lumen is occluded by hyalinic material. Histologic sample taken out of the center of livedo racemosa on the right thigh in 1999.

hypertension was treated with amlodipine and enalapril and was well controlled.

We initiated antiplatelet therapy with acetylsalicylic acid (ASA), 100 mg once daily, to prevent further cerebrovascular complications. Because of the persisting skin pain, we started treatment with intravenous immunoglobulin (IVIg) 2 g/kg body weight, administered over 5 days.

After 1 cycle, the patient stated distinct reduced pain as well as reduced joint rigidity. Because skin pain increased 10 month after initial treatment, a second and third cycle of IVIg were performed with renewed improvement of symptoms.

DISCUSSION

The pathophysiologic correlate of Sneddon syndrome is a vasculopathy leading to livedo racemosa on the skin and ischemic cerebrovascular events.

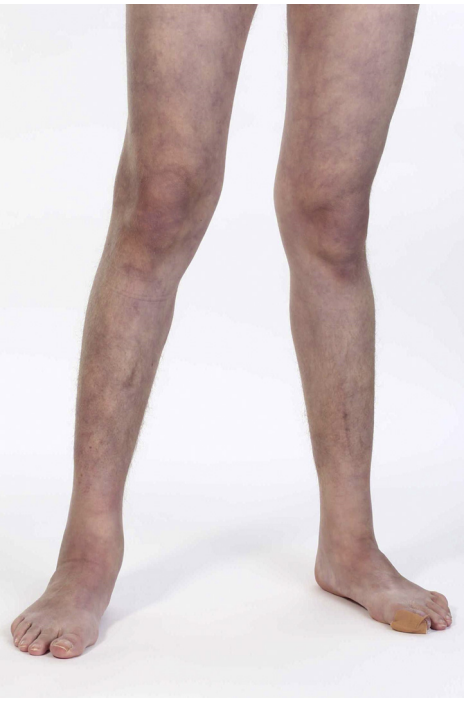

Fig 3. Livedo racemosa with discretely violaceous, faint netlike maculae particularly on the left thigh. Spastic paresis of the right leg. Photo documentation performed in January 2017.

Histologic analyses, taken from the white skin at the center of livedo racemosa, showed inflammation, occlusion, and fibrosis of small and medium-sized arteries in the deep dermal plexus. A stepwise process of inflammation and secondary tissue reorganization is proposed in the pathogenesis of Sneddon syndrome.[6] Starting with detachment of endothelial cells, edema of the surrounding tissue, and a lymphohistiocytic inflammatory infiltrate in the initial phase, followed by lumen occlusion by

mononuclear cells, fibrin, and red blood cells. The third step involves subendothelial proliferation of smooth muscle cells leading to occlusion of the vessel. The late phase is then characterized by fibrosis and atrophy of the affected artery.[6] In our case, the histologic changes can be classified as initial-to-early phase (Fig 2).

Besides the syndrome defining cutaneous and neurologic symptoms, systemic hypertension, and valvular and ischemic heart disease, renal disease, retinopathy, Raynaud phenomenon, and fetal loss are also commonly seen in Sneddon Syndrome.[4] Our patient had systemic hypertension diagnosed in 2013. There were no signs of cardiac, renal, or ophthalmic disease.

Sneddon syndrome can be classified as idiopathic with no causative factor identified, primary antiphospholipid syndrome associated, and systemic lupus erythematosus related.[4] In this case, Sneddon syndrome was classified as idiopathic.

Therapy of patients with Sneddon syndrome is yet an unresolved problem, as there are no controlled trials available because of the rare incidence of the disease. The main goal is to prevent further cerebrovascular events and to lessen skin symptoms. The use of corticosteroids and immunosupressants seems to be detrimental.[4,7] Antiplatelet therapy and anticoagulation both decrease the risk of secondary ischemic events. In patients with antiphospholipid syndrome or coagulation disorder, anticoagulation with high-dose warfarin (international normalized ratio, <3) seems to be more effective than ASA treatment, whereas in antiphospholipid-negative patients, antiplatelet therapy with ASA seems to be equally effective as anticoagulation treatment.[4,8] In our patient, the diagnosis of Sneddon syndrome was not made until the cerebrovascular event appeared, so antiplatelet therapy was regrettably not started at the age of 3 years. Because our patient is at higher risk of hemorrhage after suffering hemorrhagic stroke, is negative for antinuclear or antiphospholipid antibodies and cryoglobulines, we initiated antiplatelet treatment in consultation with our neurologic department.

Because the antiplatelet therapy did not reduce skin and joint pain in our patient, we decided to additionally initiate IVIg treatment in analogy to patients suffering from livedo vasculopathy.[9,10] As reported, IVIg significantly reduces erythema, ulceration, and particularly pain in patients with livedo vasculopathy, possibly via anti-inflammatory and anticoagulatory effects.[9,10]

Because our patient experienced distinct pain relief after the first cycle of IVIg (2 g/kg body weight), we propose IVIg as an additional treatment option for patients with Sneddon syndrome.

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