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Review Article

Sneddon syndrome a case report and literature review

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ABSTRACT

Sneddon's syndrome (SS) is characterized by livedo racemosa (LR) or reticularis and recurrent ischemic strokes. At the skin and brain level a non-inflammatory thrombotic vasculopathy is observed. Almost 80% of cases are women around 40 years old. The most accepted etiological proposal is an autoimmune and inflammatory mechanism versus the presence of thrombophilia. Neurological manifestations occur in 3 phases: prodromal symptoms (headache, dizziness, and vertigo), recurrent strokes, and early-onset dementia. Livedo racemosa has been reported to precede strokes by more than 10 years. Treatment is mainly based on secondary prophylaxis preventing a stroke with antiplatelet and antithrombotic agents. The neuropsychiatric prognosis is relatively poor with deficits in concentration, attention, visual perception, and visuospatial skills.

Keywords: Sneddon syndrome, Livedo racemosa, Ischemic strokes, Early dementia, Antiphospholipid antibodies, Thrombophilia

INTRODUCTION

Sneddon's syndrome (SS) is a rare pathology characterized by the presence of livedo racemosa (LR) and recurrent cerebral vascular events due to vasculopathy at both levels. It was first described in 1965 by Dr. Ian Bruce Sneddon, a British dermatologist who made a detailed description of 6 cases, observing an association between LR and cerebral ischemic events; but it was not until the end of the 70's when the term SS began to be used.[1,2]

A 45-year-old woman with one-year history of arterial hypertension in addition to disseminated dermatosis to the chest, arms, thighs, and legs compatible with livedo reticularis since childhood with no clinical repercussions. She debuted with an emergency-type hypertensive crisis and an ischemic stroke with no focal data and a full recovery. Because she was out of the period for thrombolysis, she was given symptomatic treatment as well as secondary prophylaxis and was discharged. One month later, she began with symptoms compatible with a new ischemic stroke and was referred to neurology service with a magnetic resonance imaging (MRI) study which showed cortico-subcortical atrophy, gliotic and malacic lesions highly suggestive of a cerebrovascular event due to autoimmune causes or coagulopathy. In the paraclinical tests a low positive dilution of antinuclear antibodies with a nucleolar pattern stood out, with no other positive results.

Assessment by the rheumatology service was requested due to a suspected autoimmune pathology, which documented the presence of livedo reticularis in the upper and lower limbs, as well as cardiovascular involvement with sinus bradycardia, left axis deviation, and supraventricular extrasystoles with variegated conduction. Treatment with steroids and immunomodulators were

started, without obtaining clinical improvement. Among the differential diagnoses, generalized lupus erythematosus with central nervous system involvement was proposed, and sneddon's syndrome, a rare condition, was proposed as an alternative diagnosis. For this reason, a skin biopsy was obtained in which superficial and deep chronic lymphocytic dermatitis with a perivascular pattern was found, which in the clinical context was compatible with sneddon's syndrome.

Treatment with acetylsalicylic acid was started to prevent future cerebral vascular events.

The patient is currently being followed up by rheumatology, cardiology, and neurology services without presenting any new cerebral vascular event.

EPIDEMIOLOGY

Almost 80% of cases are women around 40 years.[3] In a hospital series of stroke patients, this syndrome is found between 0.25% to 0.50% of them.[4,5] LR has been reported to precede cerebrovascular accidents by up to 10 years.[2] It is reported a mortality rate of 9.5% over an observation period of 6.2 years.[4]

Most publications on this entity consist of a single case report or small case series, with a single rare report from a cohort of >50 patients from a single institute. Zelger et al estimated the incidence of SS at 4 new cases/year/1 million people, based on the diagnosis of 21 patients with SS over 10 years at Innsbruck, Austria.[3,6]

ETIOPATHOGENESIS

The most accepted etiological proposal is a vasculopathy in which autoimmunity, inflammation and thrombosis participate. It is suggested that it is a reactive inflammatory response to the obstruction of the vascular lumens. The trigger for this inflammatory response is not completely known, however it has been found that an autoimmune component, by triggering endothelial damage with inflammation, can aggravate thrombotic processes.[3]

However, patients show variability in the components that participate in the proposed pathophysiological processes and for this reason the cause of SS continues to be field of investigation.

The involvement at the neurocutaneous level with similar histopathological findings in autopsy studies at both levels is interesting. It has been proposed by some authors that the mechanism is linked to the embryonic origin of the skin and the brain in the ectoderm.[7,8] While other authors, consider it to be a systemic dysfunction of the arterial bed.

CLASSIFICATION

Some proposals have been described to classify SS in which the presence or absence of associated autoimmune disease is considered, mainly systemic lupus erythematosus and antiphospholipid antibody syndrome. When neither of these diseases are identified, SS is recognized as idiopathic.

CLINICAL FINDINGS

The cardinal clinical manifestation is livedo reticularis, which consists of a purplish discoloration of the skin in patches, in a net form, it is the result of thrombosis of the subcutaneous arterioles and compensatory capillary dilation that causes the blood to pool, which causes a mottled discoloration (Figure 1).

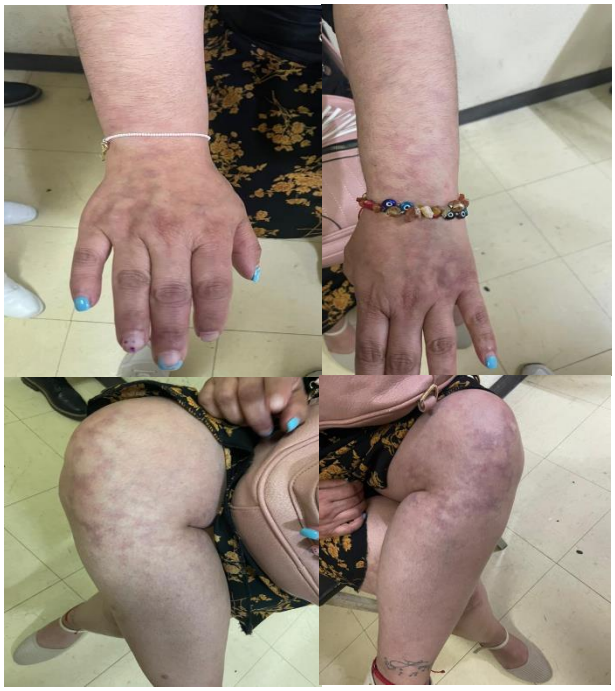

Figure 1: Livedo racemosa: localized dermatosis on the upper and lower limbs characterized by reddish-blue mottling of the skin with an irregular reticular pattern.

There is a debate in the literature about the nomenclature of racemosa versus reticularis. It is important to note that the original article by Sneddon used the term reticularis to describe the skin lesion and the distinction between these is a new concept and not distinguished in the older literature.[3]

However, livedo reticularis occurs primarily due to a transient systemic problem, such as exposure to cold, causing decreased dermal blood flow resulting in a complete circular discolored ring. On the other hand, LR develops due to a permanent focal arteriolar obstruction that produces a branching pattern in the form of a network and broken circles, characteristic of the racemosa lesion. Both have been described in the literature as a component of SS. As a dermal arteriole supplies a circular segment of the dermis, a circular pattern of low blood flow and maximum intensity hypoxia occurs along the periphery of

that circle with reactive venular dilatation, leading to the generation of a violaceous ring.[3] This skin manifestation is very important to consider because it precedes the onset of cerebral ischemia by up to 10 years.[3] However, since it is a manifestation that does not motivate the search for medical attention, it is usual for it to be documented after finding brain, cardiovascular, renal, or ophthalmic damage, as happened in the case that we present.

Neurological symptoms develop in three phases and usually are the reason for consulting.[9] The first phase consists of nonspecific symptoms such as headache, vertigo, or both. Subsequently, ischemic-type cerebrovascular events occur, especially in the territory of the middle cerebral artery, and the patients present the clinical manifestations corresponding to the affected territory.

Ultimately, progressive cognitive impairment occurs as a result of repeated cerebral infarcts. Cases of dementia without prior ischemic history have been described.[9-11]

An unusual but recognized neurological involvement is intraventricular hemorrhage, probably secondary to vascular dilatation and transdural anastomosis.[4,8]

Other systems that can be affected in SS are the cardiovascular system, characteristically with myocardial infarction and the presence of arterial hypertension. Heart valve thickening and/or Libman-Sacks endocarditis are the most frequent cardiac pathologies in SS. The mitral and aortic valves are the most involved, with or without stenosis and/or regurgitation. Clinical symptoms depend on the severity of the stenosis or insufficiency.[3]

Patients also commonly present with renal and retinal involvement.[8] Raynaud's phenomenon and fetal loss are also commonly seen in SS.[12,13]

DIAGNOSIS

Diagnosis requires a high index of suspicion, interviewing and complete exploration, without going through dermal lesions that are generally long-standing and asymptomatic. Within the extension studies, the importance of the histopathological study of the skin biopsy stands out because, as has been mentioned, the manifestations at this level precede the appearance of cerebral ischemia. This should be taken from the center of the lesion, where the color is predominantly pale or apparently healthy since this is where the central artery is located. Deep skin biopsies increase sensitivity from 27% with one biopsy, to 53% with two biopsies, and to 80% with three biopsies taken from white areas in most cases.[14] Multiple changes related to the course of the disease have been recognized, such as endotheliitis with perivascular inflammation, inflammatory obstruction (occlusion of the lumen by mononuclear cells, erythrocytes, and fibrin), subendothelial proliferation (subendothelial infiltration of myocytes and fibrosis) (Figures 2-4).[3]

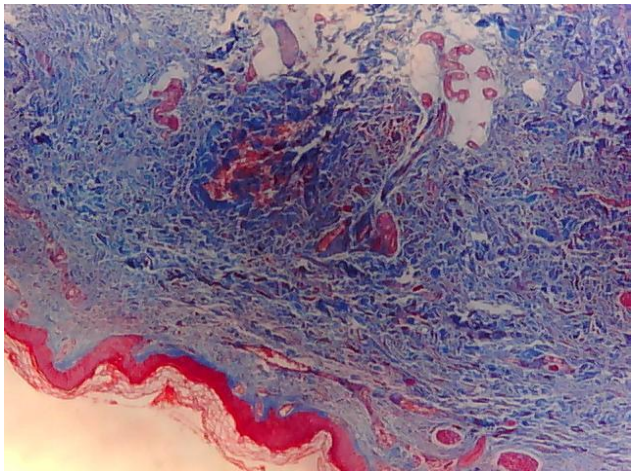

Figure 2: Skin biopsy showing epidermis with orthokeratosis, papillary and reticular dermis with predominantly perivascular lymphocytic-type inflammatory infiltrate.

When neurological manifestations are the reason for consultation, it is necessary to perform skull imaging studies such as simple and contrast computed tomography or magnetic resonance imaging. Within the resonance we will be able to identify three topographic patterns of affection have been observed; the first corresponds to a large cortico-subcortical infarction, due to the occlusion of a medium-sized artery, the second to a small cortico-subcortical infarction (Figure 4), due to the obstruction of a superficial distal perforating artery, and finally a deep infarction of white matter due to occlusion of a deep perforating artery.

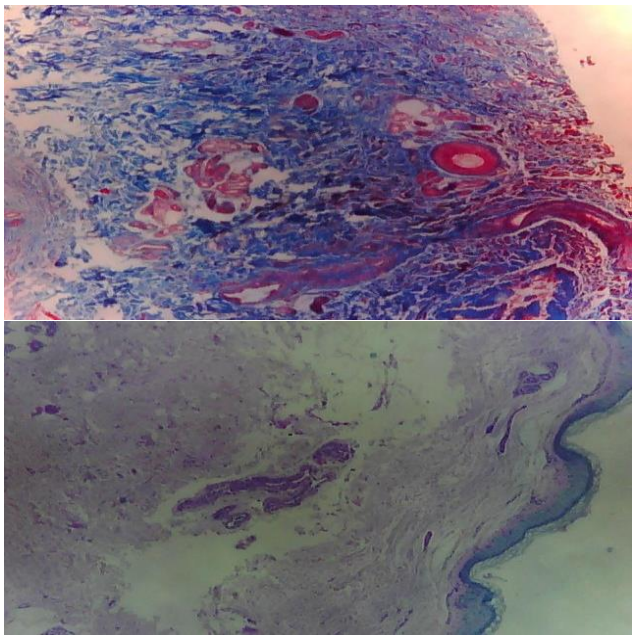

Figure 3: Skin biopsy showing medium-caliber arteries with predominantly perivascular lymphocytic-type inflammatory infiltrate and arterioles with reactive changes in the endothelium.

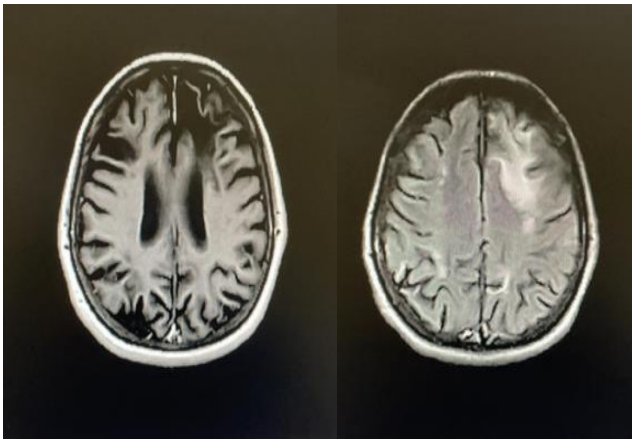

Figure 4: Magnetic resonance imaging in T2 Flair sequence showing cortico-subcortical atrophy with multiple areas of cerebral vascular event.

Once a vascular or autoimmune etiology is suspected, it will be necessary to complete the study of the patient with blood studies that guide towards these causes, as illustrated in the reported case.

TREATMENT

The treatment of patients with SS remains an unresolved issue and controlled trials have not yet been performed. It has been reported that nifedipine can reduce skin symptoms but does not prevent cerebrovascular complications.[4]

The suspension of the use of contraceptives, smoking, control of diabetes, hypertension and dyslipidemia is suggested. Platelet antiaggregant and anticoagulants are used at therapeutic doses, with which a decrease in thrombotic events has been observed.[2] Corticosteroids, cyclophosphamide, and azathioprine are ineffective treating SS. However, discrete changes towards improvement have been described in early stages or in isolated patients.[15] Due to the small number of patients with this syndrome, more studies are needed to address improvements in treatment and evaluate its impact on prognosis.

DISCUSSION

The case presented has classic characteristics of SS, with the appearance of long-standing skin lesions, and preceding the neurological manifestations.[3] She debuted with a hypertensive emergency with target organ damage in the brain with multiple cerebral infarcts demonstrated in imaging study. This was the main reason for consulting that, as has been described in other trials on this disease, the severity and sequelae of these problems motivate the patient to seek medical attention and not so the skin manifestations.[9] Later she was classified with a diagnosis of systemic arterial hypertension. In addition, signs of heart disease were documented by electrocardiogram with ischemia in the lower face. No data on renal or ophthalmic diseases were found.

Although the histopathological result of the skin biopsy was not characteristic with findings commonly described in the literature, it can be assumed this was result of taking in the initial phase of the disease, by having only one sample, as previously mentioned, the performance of this test increases if more than one sample is taken.[14]

The SS is a rare disease of unknown etiology with striking dermatological manifestation and recurrent strokes.[1] Recent research suggests that the prognosis of stroke recurrence might be better compared to the historical data due to the increasing use of antiplatelet/antithrombotic agents for secondary stroke prophylaxis. However, long-term data are needed to see an improvement in the cognitive profile with decreasing stroke recurrence. As several manifestations can precede strokes by several years in SS, an awareness of those features and the adoption of a primary prevention approach such as aggressive control of hypertension and avoiding hormonal contraceptives may be helpful.[6] Further research to explore genetic susceptibility including ADA2 deficiency, the cause of predomi- nance in young women and the role of novel biological therapy such as anticytokine therapy is needed.[3]

There are few bibliographic references about this disease due to its low prevalence and perhaps due to underdiagnosis as it is not part of the main diagnostic suspicions.

In comparison with other studies, agreement is found with the classic description of SS and its evolution.

CONCLUSION

SS is a rare entity but with a very unfavourable evolution for affected patients. A high index of suspicion is required in patients with skin manifestations such as livedo reticularis or racemosa, even if they are asymptomatic.

On the other hand, the approach to a young patient with a cerebrovascular event with or without hypertension should be comprehensive, without omitting vasculopathy as a possible etiology. A careful examination is required as this may have a great relevance for the diagnosis, treatment, and prognosis of these patients. Thus, dermatological manifestations may be the key to the diagnosis of systemic diseases such as SS and therefore should not be omitted in any patient.

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