Síndrome de Sneddon: el difícil diagnóstico y el fracaso en el tratamiento con anticoagulantes orales directos

Sneddon Syndrome: the difficult diagnosis and the failure in treatment with oral direct anticoagulants

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ABSTRACT

Sneddon Syndrome (SS) is an uncommon disease characterized by cerebrovascular events and the presence of Livedo Racemosa, sometimes overlapping with other auto-immune diseases, such as antiphospholipid syndrome. It can present with positive or negative antiphospholipid antibodies. These case reports aim to increase the knowledge of the medical community about this rare condition as well as reinforce the treatment options.

Here we present two cases. The first shows a 35-year-old woman with various thrombotic events since a young age with a late diagnosis of SS. The second shows a 47-year-old woman, already with SS diagnosis, who developed a left jugular vein thrombosis, even being anticoagulated with dabigatran.

With these two cases, we can see how misunderstood and misdiagnosed this condition is, resulting in a very late diagnosis and all the sequels that come from that. Additionally, we confirmed that the oral anticoagulants may not be sufficient in preventing cerebrovascular events.

Keywords: Sneddon syndrome, livedo racemosa, oral anticoagulants, warfarin.

RESUMEN

El síndrome de Sneddon (SS) es una enfermedad poco frecuente caracterizada por episodios cerebrovasculares y la presencia de livedo racemosa, que en ocasiones se solapa con otras enfermedades autoinmunes, como el síndrome antifosfolípido. Puede presentarse con anticuerpos antifosfolípidos positivos o negativos. Estos informes de casos tienen como objetivo ampliar los conocimientos de la comunidad médica sobre esta enfermedad rara, así como reforzar las opciones terapéuticas.

Aquí presentamos dos casos. El primero corresponde a una mujer de 35 años con diversos episodios trombóticos desde una edad temprana y un diagnóstico tardío de SS. El segundo corresponde a una mujer de 47 años, que ya tenía un diagnóstico de SS, y que desarrolló una trombosis de la vena yugular izquierda, a pesar de estar en tratamiento anticoagulante con dabigatrán.

Con estos dos casos, podemos observar lo mal entendida y mal diagnosticada que está esta afección, lo que da lugar a un diagnóstico muy tardío y a todas las secuelas que ello conlleva. Además, confirmamos que los anticoagulantes orales pueden no ser suficientes para prevenir los eventos cerebrovasculares.

Palabras clave: Síndrome de Sneddon, livedo racemosa, anticoagulantes orales, warfarina.

CLINICAL CASE

We present the cases of two different patients with the same syndrome.

The first case, a 35-year-old woman was admitted to the emergency department due to anterior thoracic pain with pleuritic characteristics. Her medical history included migraines with aura, two spontaneous abortions in the first trimester, and various transient ischemic attacks (TIA) thirteen years ago.

Upon general examination, she exhibited hemodynamic stability (blood pressure of 130/70 mmHg, a heart rate of 101 bpm, and oxygen saturation of 98% with FiO2 21%). Additionally, erythematous violaceous irregular macules with a reticular pattern were observed in both lower limbs, resembling Livedo Racemosa (LR) (Figure 1).

Laboratory tests conducted in the emergency department yielded negative or normal results, but thoracic angiography revealed bilateral thromboembolism. Consequently, anticoagulation with Low Molecular Weight Heparin was initiated.

Considering the current and previous thrombotic events, additional studies were conducted to exclude thrombotic disease. All tests, except for lupus anticoagulant, returned negative results, including other antiphospholipid antibodies (APL).

Due to the patient's history of various TIAs and the LR observed during the examination, she was diagnosed with Sneddon Syndrome (SS) secondary to APS, meeting the Sapporo criteria. Anticoagulation with warfarin was initiated, and there were no other vascular complications reported after discharge.

The second case is about a 47-year-old woman, previously diagnosed with SS, having experienced prior TIAs, who underwent a routine evaluation. She also had hypertension and obesity and was an active

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smoker. She was prescribed dabigatran and spironolactone. Despite her SS diagnosis, she initiated a direct oral anticoagulant after consulting a doctor who, unaware of her medical history, switched her from warfarin to dabigatran, based on the patient's preference.

During the physical examination, she showed new swelling in her left upper limb, which had been ongoing for 15 days. The swelling was not painful, and the capillary refill time was normal. The patient denied any trauma. Due to her history of blood clotting, a CT angiography was performed, confirming the presence of a clot in the left jugular vein (Figure 2). The patient was advised to stop taking dabigatran and start taking warfarin, which resolved the venous clot. By keeping her INR within the therapeutic range, there has been no recurrence of blood clotting events.

DISCUSSION

Sneddon Syndrome is a rare medical condition characterized by the association between thrombotic cerebral events and cutaneous lesions known as LR – a generalized, irregular, violaceous, netlike-patterned erythema of the skin – predominantly affecting young women. There is limited understanding of its etiology and pathophysiology, as well as it overlaps with other autoimmune disorders. Some individuals may exhibit symptoms from an early age, but the definitive diagnosis typically occurs in adult life. That is why timely diagnosis is imperative, given the potential for serious complications arising from this undetected ailment. While thrombotic events affecting small to median arteries associated with Sneddon Syndrome are generally non-fatal, recurrent incidents may lead to functional impairment and additional comorbidities.[1]

The classification and etiology of SS remain subjects of ongoing controversy. It is acknowledged that two primary patient groups exist: those with positive APL, either in association with or independent of the antiphospholipid syndrome, now depending on the new EULAR classification, and those with negative APL, suggesting an entirely distinct entity. Despite these classifications, apparent distinctions in core physiopathological mechanisms and clinical features between APL-positive and APL-negative patients have yet to be established.[2]

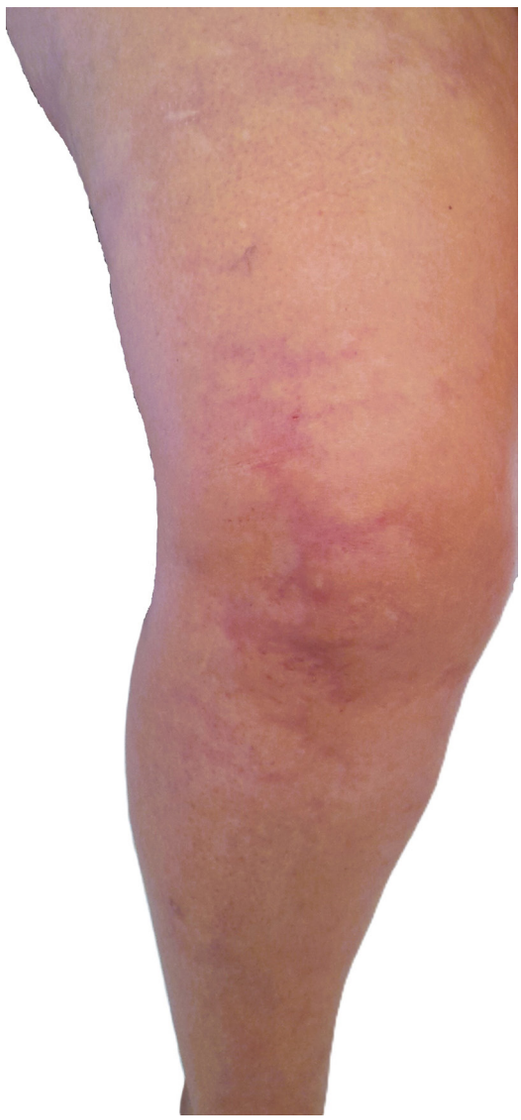
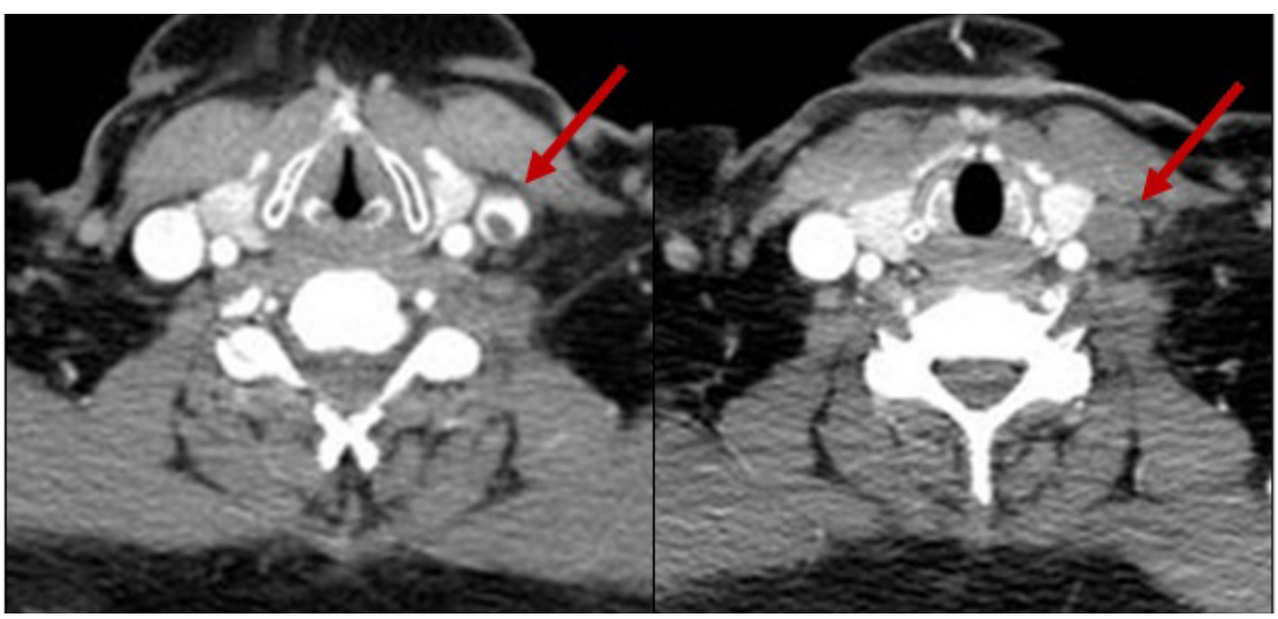


Figure 1

Figure 2



The diagnosis primarily relies on clinical observations, particularly the correlation of dermatologic manifestations with cerebrovascular complications. The principal dermatologic manifestation is LR, resulting from arterial obstruction, most observed on the lower back and buttocks, followed by the arms and thighs, and infrequently on the face, hands, and feet. In contrast to Livedo Reticularis, this form of livedo does not respond to warming but may exacerbate during the winter period[3,4]. Additional cutaneous manifestations, though less common, include Raynaud's phenomenon.[5]

Neurologic manifestations manifest in three distinct phases. The initial phase is characterized by prodromal symptoms such as tension headaches, migraines, or dizziness. The second phase involves recurrent episodes of transient ischemic attacks and strokes. In the third and final phase, cognitive decline and early-onset dementia become evident.[6]

The therapeutic approaches for Sneddon Syndrome remain uncertain, primarily due to the limited number of documented cases upon which current knowledge is based. In this context, it seems important to differentiate between APL-positive and APL-negative cases. It is well accepted that APL-positive patients are recommended to commence anticoagulation therapy with warfarin, with an INR range between 3-4.[7]

In the case of Sneddon Syndrome with APL negativity, the evidence is unclear. Some authors suggest that APL-negative patients could be treated with antiplatelet agents rather than anticoagulation, as there appears to be no significant difference in vascular event recurrence when comparing both approaches[1]. However, our second case demonstrates the inefficacy of oral anticoagulation and, indeed, antiplatelet agents. Since the initiation of warfarin, both patients have remained without any vascular event recurrence or other complications associated with the disease. This leads us to assume that the optimal approach for both APL-positive and APL-negative cases is anticoagulation with high doses of warfarin. Nevertheless, it is essential to acknowledge that this conclusion is based on our experience, and further studies are required to validate this assertion.

In our initial case, the diagnosis was established only thirteen years after the patient's initial thrombotic event. Subsequently, secondary prophylaxis was initiated, underscoring the significant importance of discourse surrounding this ailment. Such discussions have the potential to pre-emptively mitigate a substantial burden of morbidity, psychological distress, and healthcare expenditures.

In our second case, despite having a diagnosis, the patient switched from warfarin to direct oral anticoagulation as secondary prophylaxis, culminating in the development of a significant thrombus within the jugular vein. This observation assumes particular significance due to the dearth of empirical support regarding the treatment of SS. Notably, it suggests that direct oral anticoagulants may not exhibit efficacy in preventing recurrent events in SS, thereby positioning warfarin as the sole therapeutic recourse at present.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

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This research had no funding sources.

ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

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