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# Efficacy of Anti-CD Monoclonal Antibody in SLE-Related Sneddon's Syndrome with Anti phospholipid Antibodies and Interstitial Lung Disease: A Case Report

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## Abstract

Sneddon's Syndrome (SS) is a rare condition characterized by a non-inflammatory thrombotic vasculopathy, which involves small and medium vassels. Cerebrovascular disease and livedo racemosa are the main clinical manifestations of this syndrome. The incidence of SS has been estimated of 4 cases per 1 million/year in general population with a high prevalence in young women between 20-40 years of age. Three forms of the syndrome have been described: idiopathic, without a clear causative factor, related to primary Anti-phospholipid Syndrome and related to Systemic Lupus Erythematosus (SLE) with or without anti-phospholipid antibodies. To date, there are very few indications for diagnosis and treatment. Skin biopsy and brain MRI are considered fundamental in the diagnostic process; however histologic samples could be negative or non-specific. Current treatment is based on oral anticoagulation and, in autoimmune-related SS, on immunosuppressant drugs, such as corticosteroids, cyclophosphamide, azathioprine, with unclear results. No data about the use of anti-CD20 monoclonal antibodies (Rituximab) in autoimmune-related SS are available so far. We report here, for the first time, the case of a 40 years old woman with SLE-related SS with anti-phospholipid antibodies, successfully treated with Rituximab.

Keywords: Sneddon's syndrome • Systemic lupus erythematosus • Anti-phospholipid syndrome • Interstitial lung disease • Livedo racemosa • Rituximab

## Introduction

Sneddon's Syndrome (SS) is a rare condition of unknown etiology and unclear pathogenesis. It was first described by Sneddon, a British dermatologist, in 1964 as a non-inflammatory thrombotic vasculopathy, which involves small and medium vessels, clinically manifested by Livedo Racemosa (LR) and cerebrovascular disease [1]. Although cerebral thrombotic events are predominant, rare cases of cerebral haemorrage are also described [2]. As a result of the cerebrovascular injuries, patients may develop cognitive impairment and psychiatric symptoms, such as depression and psychosis with suicide attempt. These manifestations may be the first clinical presentation of SS [3,4]. Moreover, hypertension, heart valvulopathy, decreased renal function or ophtalmologic manifestations may occur. Splenomegaly, limphadenopathy, Raynaud phenomenon, skin ulcers and fetal loss are also commonly seen in SS [5-9]. The incidence of SS has been estimated in 4 cases per 1 million/year in the general population with a high prevalence in young women between 20-40 years of age, but rare cases in young and elderly women have been reported [10].

Although the disorder usually occurs sporadically, some familial cases have been reported. In these cases SS seems to be transmitted in an autosomal dominant way with complete or incomplete penetrance, but the involved genes have not been identified yet. Three forms of SS have been described: idiopathic, without clear causative factors; primary antiphospholipid syndrome (APS)-related SS, Systemic Lupus Erythematosus (SLE)-related SS with or without anti-phospholipid antibodies [10]. Skin biopsy is crucial for an early diagnosis and may show thrombosis of arterioles and compensatory capillary dilatation with blood stagnation; other histological findings include endoarteritis obliterans from intimal endothelial proliferation and proliferation of medial smooth muscle cells. However, in some cases skin biopsies can be aspecific. Notably, these kinds of alterations have been observed also in brain tissue samples, excluding a vasculitis process [10].

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Brain magnetic resonance (MRI) is an helpful imaging method to detect brain injury. Bright small and multifocal foci on T2-weighted MRI are often localized in periventricular deep white matter or in pons, but other sites could be involved and cortical atrophy may be observed. Cerebral angiography may reveals an obliterating non-inflammatory arteriopathy with stenosis of intracranial vessels, artero-venous malformations and presence of fine collateral vessels [10,11]. Current treatment is based on oral anticoagulation in association, in autoimmune-related SS, with immunosuppressant drugs, such as corticosteroids, cyclophosphamide, azathioprine, with few results. Intravenous Immunoglobilins (IVIG) have been also used to treat the vasculopaty, while the use of prostaglandins analogues has been reported for the treatment of skin ulcers [10-13]. To our knowledge, the use of anti-CD20 (Rituximab-RTX) in autoimmune-related SS has not been reported so far. We report here for the first time, the case of a 40 years old woman with a SLE-related SS with anti-phospholipid antibodies, treated with RTX with a good response after two years of follow-up.

## Case Presentation

In October 2017, a 40-years-old woman was admitted to our Autoimmune Disease Unit because of the presence of arthralgia and diffuse paraesthesia. Her medical history reported a previous diagnosis of APS, followed by a diagnosis of undifferentiated connective tissue disease with Raynaud phenomenon and Sicca Syndrome, atrophic gastritis (presence of anti-parietal cell antibodies: 1:320), arterial hypertension and chronic liver disease of unknown etiology. She was on treatment with oral anticoagulants (with an INR of 2) and with azathioprine, 100 mg/day. On physical examination the patient showed moderate-severe neuro-cognitive impairment, with confusion, gait disturbance and apraxia, skin was interested by diffuse LR; vital signs were normal. No lymph node enlargement was found. Peripheral blood analysis showed normal blood cell count, normal CRP and ESR, while renal function was mildly altered. Auto-antibodies testing showed: ANA title of 1:160, spekled pattern, negative anti-ENA antibodies, positive anti-dsDNA antibodies, and high levels of anti-cardiolipin and anti-beta2glicoprotein I IgG and IgM antibodies. Moreover low C4 levels were found.

Brain MRI showed bright small and multifocal foci on T2-weighted sequences and encephalomalacia, revealing a severe brain involvement (Figure 1), although she was on oral anticoagulation and on azathioprine. Pulmonary angio-CT scan and lung scintigraphy excluded a chronic thromboembolism. High resolution CT of the chest showed the presence of nonspecific interstitial

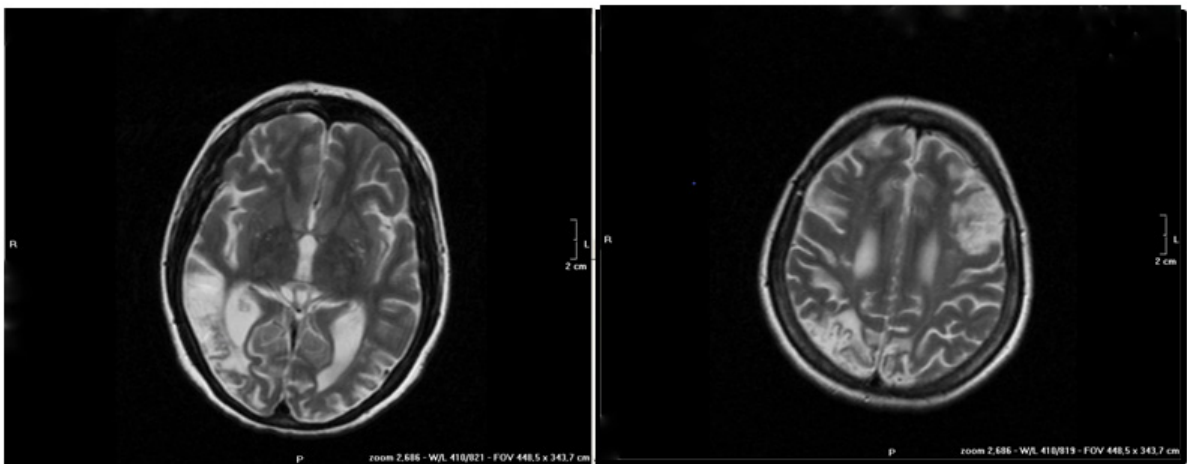

**Figure 1.** T2-wighted Brain MRI shows presence of brigth mulftifocal foci and encephalomalacia areas in right parietal-occipital lobe (A) and left parietal lobe (B).

lung disease. Head and neck ultrasound and oftalmologic evaluation resulted normal. According to these findings a diagnosis of "SLE-related Sneddon's Syndrome with presence of anti-phospholipid antibodies and with Interstitial Lung disease" was performed. We increased oral anticoagulation treatment, maintaining INR between 3-4, and introduced ASA and Metilprednisolone at a dose of 4 mg/die. Considering the progression of the disease, the lung involvement and the presence of high levels of autoantibodies, we decided to treat the patient with RTX and two cycles were carried out six months apart. After two years of follow up, no ischemic events have been documented. Patient is continuing oral anticoagulation and neuro-cognitive rehabilitation, with a good clinical response.

## Discussion

Sneddon's Syndrome (SS) is a rare condition of unknown etiology and unclear pathogenesis characterized by a non-inflammatory thrombotic vasculopathy, which involves small and medium vassels, clinically manifested by LR and cerebrovascular disease. Several other organs may be involved. Our patient presented LR of the skin and a vascular brain injury, as showed by brain MRI. She also presented high blood pressure, decreased renal function and a positive history of liver disease. Furthermore we found an interstitial lung involvement. Considering the presence of arthralgias, Raynaud phenomenon, central nervous system involvement, positive ANA, Anti-dsDNA and aPL antibodies and low C4 levels we performed the diagnosis of Systemic Lupus Erythematosus, according to SLICC criteria [14]. Furthermore, the combination of brain MRI alterations and of LR was highly suggestive for a SS.

## Conclusion

We can speculate on whether interstitial lung involvement may be considered associated or not with SS, since no other cases have been described in the literature to date. Our opinion is that ILD was a possible manifestation of SLE. There are no reports on the use of RTX in the treatment of SS; our experience shows a good clinical response after one year of treatment, without relapses of disease in the following year of observation. To date, very little is known on Sneddon's Syndrome and its pathogenesis and further studies are needed. The diagnosis may be a challenge for several specialists (Cardiologist, Dermatologist, Ophthalmologist, Neurologist, Rheumatologist and Internist). This case report underlines the importance of the diagnosis of a rare disease and the good response of this rare disease to a short treatment with RTX.

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