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A Rare Case of Cerebral Venous Thrombosis Revealing a Primary Sjögren's Syndrome

Y. Lakrafi [a*], Barakat [a], Moudatir [a], Echchilali [a], Benzakour [a] and El Kabli [a]

[a] *Internal Medicine Department and Geriatrics Unit, CHU Ibn Rochd, Casablanca, Morocco.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Sjögren's syndrome, formerly known as Gougerot-Sjögren syndrome, is an autoimmune disease with a predilection for exocrine glands, earning it the nickname of exocrinopathy or autoimmune epithelitis of the exocrine glands. It is a rare disease that predominantly affects females, with a sex ratio of 9 women to 1 man and an incidence peak around the age of 50 years. Sjögren's syndrome can be primary when isolated, or secondary when associated with another autoimmune disease which the most common is Rheumatoid Arthritis but also Lupus Erythematosus and Scleroderma. The triad defining the disease includes dryness syndrome, pain, and fatigue [1].

Cerebral thrombophlebitis corresponds to the blockage of a vein around the brain by a blood clot, initially causing few symptoms but eventually leading to persistent headaches that worsen progressively, possibly accompanied by vomiting or epileptic seizures [2].

We report the case of a patient who presented with cerebral thrombophlebitis revealing primary Sjögren's syndrome.

**Corresponding author: E-mail: Docteurlakrafiyasser@gmail.com, Docteuryasser273@hotmail.com;*

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Keywords: Thrombosis; scleroderma; lupus erythematosus; exocrine glands; autoimmune epithelitis.

1. INTRODUCTION

Sjögren's syndrome is an autoimmune disease that predominantly affects the epithelia of exocrine glands, hence its nickname of exocrinopathy or autoimmune epithelitis. It is a rare disease with a strong female predominance (9 women to 1 man) and peaks in incidence around age 50 years. It can manifest as a primary, isolated condition, or secondary to other autoimmune diseases, most commonly Rheumatoid Arthritis, but also Systemic Lupus Erythematosus and Scleroderma. The disease is defined by a triad of symptoms: dryness syndrome, pain, and fatigue.

It is a multifactorial disease with significant genetic and environmental factors. The role of an infectious trigger (bacterial and/or viral) has long been suspected, though no specific infectious agent, known as the infamous Pathogen X, has been definitively identified. More recently, abnormal expression of endogenous retroviral sequences has been implicated in activating epithelial cells and both innate and adaptive immune systems. Genetic polymorphisms, particularly in interferon (IFN) genes, may lead to an exaggerated immune response. The IFN signature (type I or II) is present in over 50% of patients in both blood and exocrine gland tissues. This increased IFN production leads to excessive BAFF production, stimulating proliferation, maturation, and survival of B lymphocytes (B cells). This hyperactivity results in the presence of autoantibodies (anti-SSA, anti-SSB, rheumatoid factor), hypergammaglobulinemia, and lymphocytic infiltrates known as "Focus" within the salivary glands, which is a histological hallmark of Sjögren's syndrome [3,4].

Table 1. ACR-EULAR 2016 Classification Criteria: Sjögren's Syndrome if total score ≥ 4 [5]

Items:	Points:
Biopsy of accessory salivary glands (ASG) with lymphocytic sialadenitis and focus score ≥ 1	3 points
Presence of anti-SSA	3 points
Schirmer's test ≤ 5 mm/5 min in at least 1 eye	1 point
Ocular Staining Score ≥ 5 (or Van Bijsterveld score ≥ 4) in at least 1 eye	1 point
Unstimulated salivary flow rate ≤ 0.1 ml/min	1 point

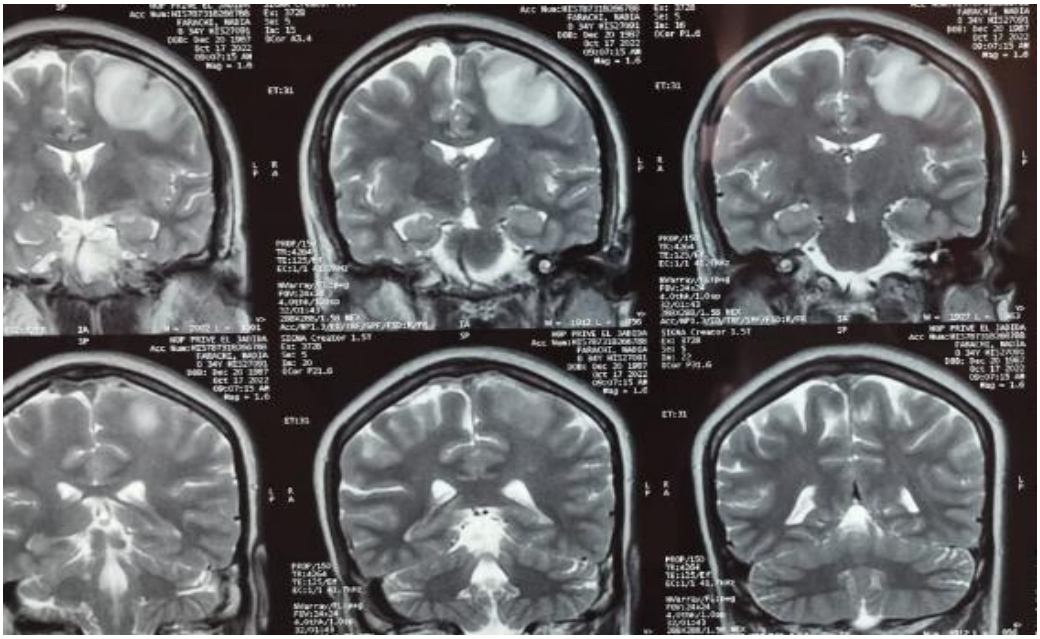

Fig. 1. Angio-MRI of the patient: cortical cerebral venous thrombosis and superior longitudinal sinus thrombosis complicated by parietal ischemic-hemorrhagic venous infarction

Cerebral Thrombophlebitis: Cerebral thrombophlebitis involves the obstruction of a brain vein by a fibrino-thrombotic clot. Initially, symptoms may be minimal, but they progress over days to persistent headaches resistant to pain medications, potentially accompanied by vomiting or epileptic seizures.

2. CASE REPORT

We present the case of a 37-year-old female patient with no significant personal medical history but a first-degree cousin with systemic lupus erythematosus. She presented intense headaches resistant to first and second-line analgesics, progressing to seizures and loss of consciousness, necessitating urgent neurology department admission. Emergency cerebral angio-MRI revealed cortical venous thrombosis of the superior longitudinal sinus complicated by ischemic-hemorrhagic infarction in the parietal lobe.

The patient was treated with sodium valproate (10mg/kg/day for 3 days then progressively going up to 30mg/kg/day for 3 months) and levetiracetam (500mg twice a day for 3 months) for seizures. Given her young age, female sex, and family history of lupus, initial suspicion centered on lupus potentially associated with antiphospholipid syndrome. However, there were no cutaneous, joint, neurologic, or psychiatric manifestations typical of lupus. Immunological investigations showed no native double-stranded DNA antibodies or anti-Sm antibodies. Hematology results were normal, with no anemia, thrombocytopenia, or lymphopenia, normal renal function, negative proteinuria, and no urinary sediment abnormalities. Despite negative results for classic antiphospholipid antibodies (lupus anticoagulant, anti-beta2 glycoprotein (IgM+IgG), and anticardiolipin antibodies), further investigation was pursued.

Immunological testing were repeated after anticoagulation cessation for 5 months which revealed positive antinuclear antibodies at 1/640 with a speckled pattern on immunofluorescence.

Along with positive anti-RO/SSA 60KDA antibodies at 98. A SAPL workup came back negative (lupus anticoagulant, anti-beta 2 glycoprotein (IgM + IgG), and anti-cardiolipin (IgM + IgG) all negative). The CBC was normal, and the JAK2 mutation test was negative. Protein S and C levels were normal, the tests for Factor V Leiden and prothrombin mutations were negative, and antithrombin levels were normal. Additionally, the patient reported a dry eye and mouth syndrome, with a clinical examination showing poor oral health without parotid gland enlargement.

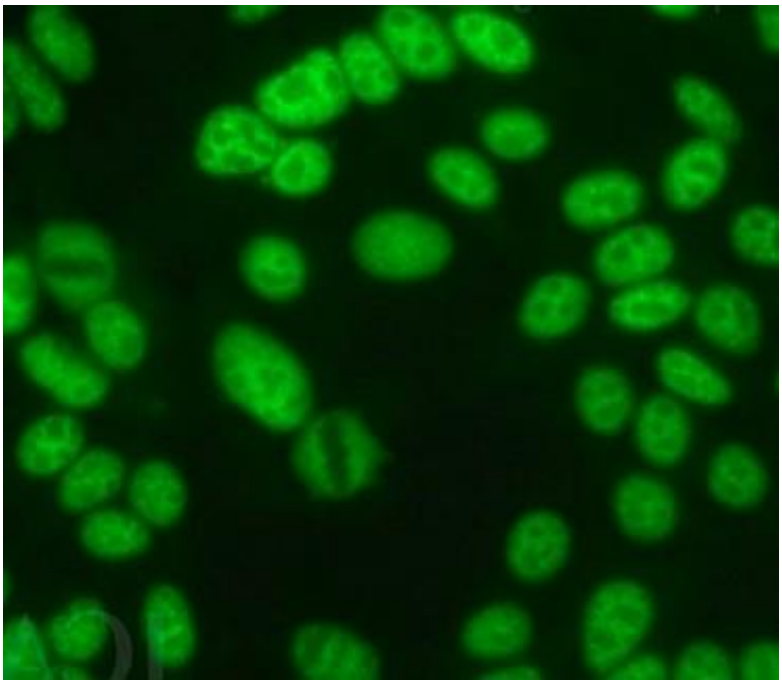

Fig. 2. Image from the media library of Bautner Laboratories illustrating antinuclear antibodies with a speckled pattern by immunofluorescence (profile found in Sjögren's disease)

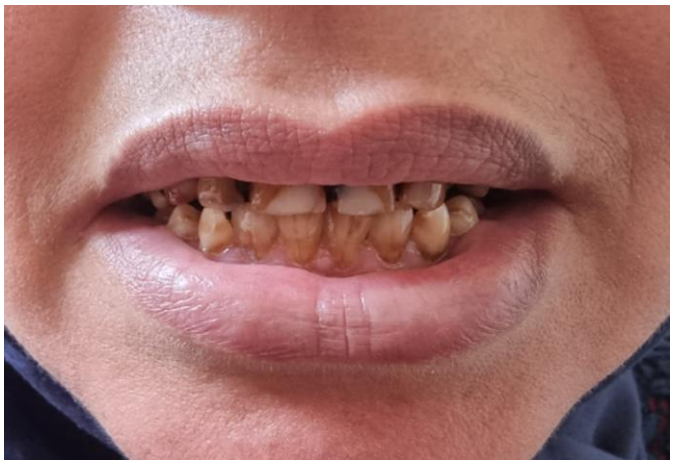

Fig. 3. Poor oral health of the patient secondary to the dry syndrome

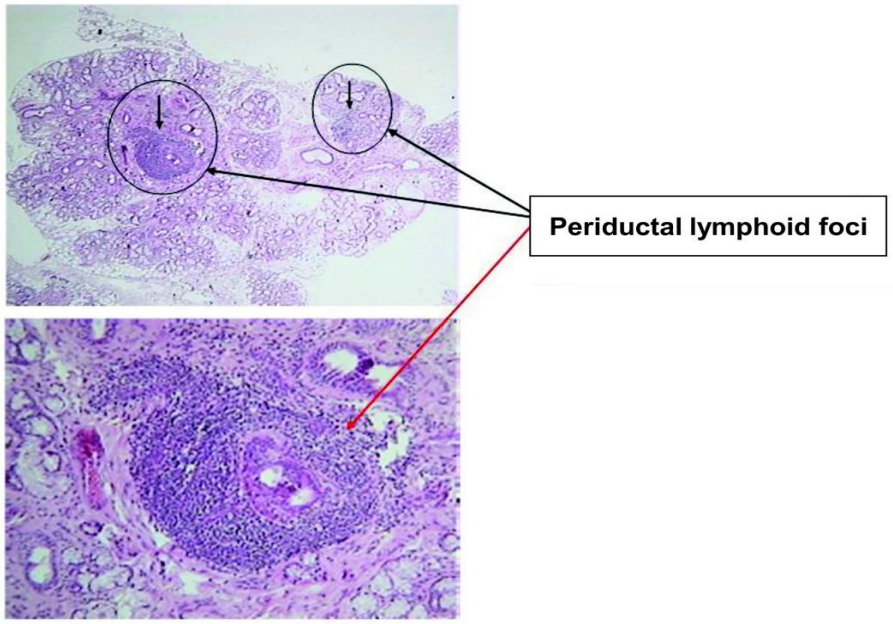

Fig. 4. Image from the team of Tincani, A., Andreoli, L., Cavazzana, I. et al. Published in Novel aspects of Sjögren's syndrome in 2012. BMC Med 11, 93 (2013), illustrating a minor salivary gland biopsy with the presence of foci indicative of Sjögren's Syndrome

A thorough evaluation confirmed primary Sjögren's syndrome, supported by subjective dry syndrome, salivary gland biopsy showing Grade IV Chisholm sialadenitis with 3 Focus, and positive anti-SSA antibodies, consistent with ACR/EULAR 2016 criteria.

3. DISCUSSION

Our observation concerns a patient with a family history of Systemic Lupus Erythematosus in a paternal first-degree cousin, admitted to CHU Ibn Rochd of Casablanca for cerebral thrombophlebitis. Considering her young age, female sex, and family history of lupus, we initially suspected lupus potentially associated with antiphospholipid syndrome. However, the patient showed no cutaneous, mucosal, articular, neurological, or psychological manifestations indicative of lupus. Immunological tests revealed no anti-double-stranded DNA or anti-Sm antibodies, and her blood count showed no anemia, thrombocytopenia, or lymphopenia. Renal function was preserved with negative proteinuria and no urinary sediment abnormalities. Antiphospholipid antibodies were

tested twice and came back negative. However, atypical antiphospholipids like IgA or anti-annexin were not tested. Given her relatively young age, we considered constitutional thrombophilias. Tests for protein S and C were normal, the factor V Leiden and prothrombin mutations were negative, and antithrombin levels were normal. Despite the absence of hemogram anomalies suggestive of a myeloproliferative syndrome, we also tested for the Jak2 mutation, which was negative. An HIV serology was performed due to her sexual activity and came back negative. Only after excluding common causes of thrombosis did we consider Sjögren's Syndrome, indicated by the subjective dry syndrome, a salivary gland biopsy showing 03 foci, and positive anti-SSA antibodies. We found studies from various medical teams establishing a direct causal link between Sjögren's Syndrome and thrombotic episodes, particularly cerebral thrombophlebitis, though the exact pathophysiological mechanism remains unclear.

Two cases of cerebral thrombophlebitis revealing Sjögren's Syndrome were reported in collaboration by the Italian team from the Department of Neurology and Psychiatric Diseases and the Department of Physical Medicine and Rehabilitation of the University of Rome in October 2012 [6]. One case was reported by the Chinese team from the Department of Neurology and Neuroscience at the First Hospital of Jilin in 2020 [7]. Another case was reported by the Indian team from the Department of Internal Medicine at Mysore Medical College in 2022 [8], and another by the Chinese team from the Department of Nuclear Medicine at the Second Hospital of Jilin in 2023 [9]. The Taiwanese team conducted a study in 2014 on 8,920 patients, evaluating the thromboembolic risk in patients with primary Sjögren's Syndrome compared to the general population, finding a 1.83 to 3.29 times higher risk [10].

4. CONCLUSION

Sjögren's syndrome is a nonspecific autoimmune disease affecting exocrine glands, most commonly salivary and lacrimal glands. It can present as primary Sjögren's syndrome or in association with other autoimmune diseases. While relatively rare, Sjögren's syndrome is associated with an increased thromboembolic risk, especially when coexisting with other autoimmune conditions. Despite established causality, the thrombotic mechanism remains unclear and warrants further investigation.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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