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Initial Cerebral Venous Thrombosis Revealing Extramembranous Glomerulonephritis Secondary to Primary Sjögren's Syndrome: A Rare Case Report and Literature Review

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Abstract **Case Report**

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by systemic manifestations, including neurological and renal involvement. We present the case of a 36-year-old female patient in whom cerebral venous thrombosis (CVT) revealed primary SS, associated with extramembranous glomerulonephritis (EMGN), a rare manifestation. This article highlights the importance of considering SS as an etiology of CVT and performing systematic renal screening in this context. A review of the literature emphasizes the pathophysiological complexity of extra-glandular manifestations of SS and the necessity for early diagnosis.

Keywords: Sjögren's Syndrome, Cerebral Venous Thrombosis, Extramembranous Glomerulonephritis, Autoimmunity, Anti-SSA Antibodies, Delayed Diagnosis, Systemic Manifestations.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune exocrinopathy characterized by the association of keratoconjunctivitis sicca, xerostomia, and immuno-inflammatory systemic manifestations [1]. It affects approximately 0.5 to 3% of the world's population, with a marked female predominance [2]. It is considered primary when isolated and secondary when associated with another systemic autoimmune disease [3].

Clinical renal disease is unusual in pSS, being reported in 5% of patients, but it is likely underestimated [4]. In cases of renal involvement, SS often leads to tubulointerstitial nephritis with tubular dysfunction [5], while glomerular involvement (membranoproliferative glomerulonephritis and extramembranous glomerulonephritis - EMGN) remains rare [6].

Neurological manifestations frequently affect the peripheral nervous system (PNS) [1], with an incidence between 3.7% and 16% [7]. Central nervous system (CNS) involvement ranges from mild cognitive dysfunction to transverse myelitis and paralysis [8], with a prevalence of approximately 5% [9]. The occurrence of CVT is a serious and unusual complication, the presence of which may reveal the disease [10-13].

The coexistence of CVT and EMGN as the initial presentation of SS is particularly rare and underscores the importance of a multidisciplinary diagnostic approach. We report here a clinical case of CVT as the inaugural manifestation of EMGN secondary to primary SS, highlighting the need for a thorough diagnostic investigation in the face of these unusual clinical presentations.

CASE REPORT

A 36-year-old female patient was admitted to the neurology department for the management of a second episode of CVT. The first episode occurred one year earlier, leading to an inconclusive investigation. The etiological investigation performed during this second episode revealed ocular and oral dryness evolving for several years. Biological investigations revealed positive anti-nuclear antibodies (ANA) at 1/320 with a speckled pattern, strongly positive anti-SSA antibodies, and grade 4 sialadenitis on biopsy of the minor salivary glands, confirming the diagnosis of primary SS according to the 2016 ACR/EULAR criteria with a score of 6 points. Etiological investigations for CVT (infectious workup,

thrombophilia panel, antiphospholipid antibodies, tumor markers with thoraco-abdomino-pelvic CT scan) were negative.

The patient was initially treated with low-molecular-weight heparin (LMWH) anticoagulants. However, upon discovery of proteinuria of 4.92 g/24 h associated with microscopic hematuria during systematic screening for associated renal manifestations, she was referred to our nephrology department for further evaluation. Physical examination revealed no abnormalities, apart from normal blood pressure at 120/70 mm Hg. Laboratory tests showed hypoalbuminemia at 23 g/L (N: 34-45 g/L), uremia at 0.37 g/L (N: 0.18-0.55g/L), and creatinine at 5 mg/L (N: 7-14 mg/L). Complement fractions C3 and C4 were normal. Anti-PLA2R antibodies were negative. Hepatitis B and C serologies were negative.

A renal biopsy was performed, revealing stage 2-3 EMGN. The results of the renal biopsy are illustrated in **Figures 1 and 2**.

Treatment with prednisolone and hydroxychloroquine was initiated; the evolution was marked by a progressive improvement in clinical and laboratory signs, with complete recovery at 6 months, without any clinical or radiological signs of relapse.

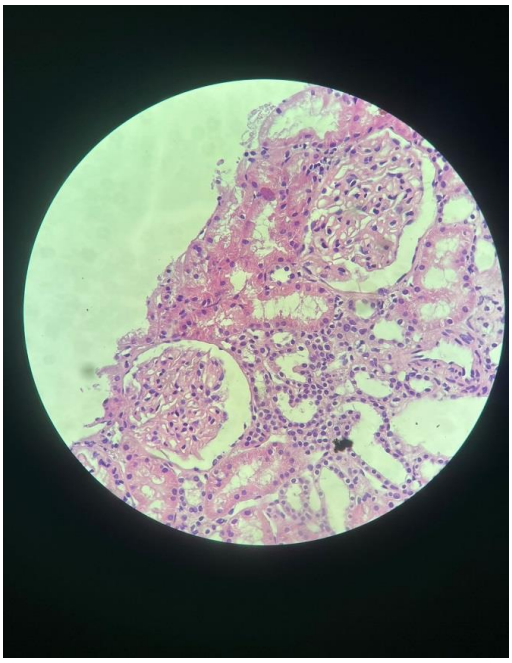

Figure 1: Renal biopsy, hematoxylin-eosin staining, 200x magnification. A glomerulus with thickening of the glomerular basement membrane is observed

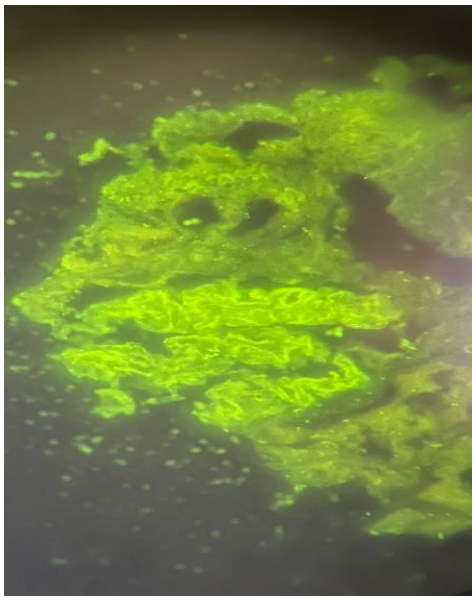

Figure 2: Immunofluorescence: granular deposits of IgG on the external aspect of the GBM, 400x magnification.

DISCUSSION

Our case reports an exceptionally rare association of CVT revealing EMGN secondary to primary SS, underscoring the diagnostic and therapeutic complexity that systemic autoimmune diseases can represent. Although each condition is individually known, their simultaneous occurrence constitutes an original clinical observation, rarely reported in the literature.

The interaction between genetic and environmental factors is considered to play a crucial role in susceptible individuals, leading to dysregulation of the immune system and the development of SS [14]. The function of specific cytokines and chemokines, and their expression by cells of the innate and adaptive immune systems, are actively involved in the pathogenesis of SS, including extraglandular involvement [15-16]:

Extra-glandular manifestations of primary SS affect approximately 70% of patients [1] and include neurological, renal, hematological, pulmonary, gastrointestinal, and cardiovascular manifestations [3-17]. They result from three types of mechanisms related to [1]:

- Extension of the lymphocytic infiltrate, which is not limited to the epithelia.
- Inflammation and immune complex deposition, explaining renal involvement.
- The pathogenic action of anti-SSA antibodies (The presence of these anti-SSA antibodies is frequently reported as often associated with systemic involvement).

The pathogenesis of EMGN in the context of SS remains partly obscure, but the involvement of circulating immune complex deposition and the action of specific autoantibodies (particularly anti-SSA) appear to play a crucial role [5]. The association of SS with EMGN is less common than tubulointerstitial involvement but constitutes a potentially severe renal manifestation of the disease [6]. Overall, among patients with SS with renal involvement, loss of renal function has only been reported in 5 to 10% and can progress to end-stage renal disease [18].

Renal involvement is generally pauci-symptomatic; requiring systematic blood and urine screening and performance of a renal biopsy in the face of any glomerular syndrome [3,19]. Our observation confirms the importance of systematic screening for renal involvement in patients with SS, even in the absence of urinary symptoms. It is essential not to overlook glomerular involvement, which may require specific therapeutic management.

CNS involvement in SS ranges from mild cognitive dysfunction to transverse myelitis and paralysis; various pathogenic mechanisms have been suggested based on histological and serological findings in patients with SS with neurological involvement. Vasculitis of the vasa nervorum has been described, with lymphocytic, macrophage, and T lymphocyte infiltration, as well as necrotizing vasculitis and anti-neuronal antibodies, depending on the type of nerve involved [20]. In addition, perineural infiltration has been observed on nerve biopsies from patients with sensorimotor neuropathy [21]. Whereas in mononeuritis multiplex, inflammation of the epineurial and perineurial blood vessels that perfuse the involved nerves leads to infarction [22].

CVT is a rare and unusual complication of SS. The incidence of CVT in the scientific literature is reported to be less than 1% [23]. Anti-SSA antibodies may also contribute to vascular involvement and neurological manifestations. The precise mechanism leading to CVT also remains poorly understood in the context of SS, although abnormalities of hemostasis, endothelial inflammation, or platelet activation have been suggested.

The etiological diagnosis of CVT is broad and includes hereditary or acquired thrombophilia disorders, central nervous system infections, head trauma, the use of oral contraceptives, and certain autoimmune diseases [24, 25]. In our patient, the initial etiological workup for CVT was negative, ruling out the most common causes. However, the recurrence of CVT led to a more thorough investigation, ultimately revealing the diagnosis of SS and EMGN, highlighting the importance of not limiting oneself to an initial negative workup in the face of CVT, especially in the presence of risk factors or persistent clinical signs.

The rarity of this neurological manifestation underscores the importance of our clinical case, which highlights the need for an etiological investigation in the face of any unexplained CVT. It is crucial to remember that an autoimmune disease such as SS can cause a variety of neurological disorders, and that it is imperative to consider it in the context of an extensive differential diagnosis.

CONCLUSION

Primary SS is a common connective tissue disease, but diagnosis is often delayed due to the insidious nature of clinical manifestations and the slow progression. Therefore, any unexplained neurological manifestation in a context of autoimmunity implies the search for SS. Renal involvement in SS should lead us to perform blood and urine tests in order not to overlook underlying nephropathy.

Conflict of Interest: The authors declare that they have no conflicts of interest related to this article.

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