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CRYOGLOBULINEMIC VASCULITIS SECONDARY TO PRIMARY SJOGREN'S SYNDROME: A CASE REPORT

VASCULITE CRIOGLOBULINÊMICA SECUNDÁRIA À SÍNDROME DE SJOGREN PRIMÁRIA: UM RELATO DE CASO

VASCULITIS CRIOGLOBULINÉMICA SECUNDARIA AL SÍNDROME DE SJÖGREN PRIMARIO: UN CASO CLÍNICO

https://doi.org/10.56238/sevened2025.037-035

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ABSTRACT

Sjögren's syndrome is a chronic autoimmune inflammatory disease characterized by functional impairment of the lacrimal and salivary glands. Clinical manifestations are divided into extraglandular and exocrine glandular. Cryoglobulinemic vasculitis, an example of an extraglandular clinical manifestation in Sjögren's disease, develops from the deposition of immune complexes containing cryoglobulins and, when present, may be associated with higher morbidity and mortality. The association between primary Sjögren's syndrome and cryoglobulinemic vasculitis is rare, and if diagnosed and treated late, it may progress to unfavorable outcomes with a significant impact on the patient's quality of life.

Keywords: Cryoglobulinemia. Sjögren's Syndrome. Cryoglobulinemic Vasculitis.

RESUMO

A síndrome de Sjogren é uma doença inflamatória autoimune crônica, caracterizada por comprometimento funcional das glândulas lacrimais e salivares. As manifestações clínicas são divididas em extraglandulares e glandulares exócrinas. A vasculite crioglonulinêmica, um exemplo de manifestação clínica extraglandular na doença de sjogren, desenvolve-se da deposição de imunocomplexos contendo crioglobulinas e quando presente, pode apresentar maior morbidade e mortalidade. A associação entre a síndrome de Sjogren primária e a vasculite crioglobulinêmica é rara e caso diagnosticada e tratada tardiamente pode apresentar possibilidade de progressão para desfechos desfavoráveis com importante impacto na qualidade de vida do paciente.

Palavras-chave: Crioglobulinemia. Síndrome Sjogren. Vasculite Crioglobulinêmica.

RESUMEN

El síndrome de Sjögren es una enfermedad inflamatoria autoinmune crónica, caracterizada por el deterioro funcional de las glándulas lacrimales y salivales. Las manifestaciones clínicas se dividen en extraglandulares y glandulares exocrinas. La vasculitis crioglobulinémica, un

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ejemplo de manifestación clínica extraglandular en la enfermedad de Sjögren, se desarrolla a partir del depósito de inmunocomplejos que contienen crioglobulinas y, cuando está presente, puede presentar una mayor morbilidad y mortalidad. La asociación entre el síndrome de Sjögren primario y la vasculitis crioglobulinémica es poco frecuente y, si se diagnostica y trata tardíamente, puede presentar la posibilidad de progresar hacia resultados desfavorables con un impacto importante en la calidad de vida del paciente.

Palabras clave: Crioglobulinemia. Síndrome de Sjögren. Vasculitis Crioglobulinémica.

1 INTRODUCTION

Sjogren's syndrome is a chronic systemic inflammatory disease, caused by lymphocytic infiltration in the exocrine organs and characterized by lacrimal and salivary dysfunction. It can occur alone or in association with other systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis. Cryoglobulinemia results from the precipitation of immunoglobulins in the blood when cooled below 4°C and reversible when reheated. It is classified into three subtypes and can be related to neoplasms, autoimmune diseases, and viral infections. Cryoglobulinemic vasculitis is a systemic inflammatory syndrome involving small to medium-sized vessels, mediated by cryoglobulin-containing immune complexes. The association between primary Sjogren's syndrome and cryoglobulinaemic vasculitis is rare and is related to higher morbidity and risk of unfavorable outcome.

2 OBJECTIVE

This article aims to report the clinical case of a previously healthy female patient whose clinical history, laboratory and anatomopathological tests showed the presence of cryoglobulinemic vasculitis secondary to primary Sjogren's syndrome. In addition, the importance of early diagnosis and treatment for adequate symptom control and, consequently, better quality of life for the patient is emphasized.

3 METHODOLOGY

The information was obtained through the review of electronic medical records and interviews with the patient

4 CASE REPORT

A 61-year-old female patient was admitted to a tertiary referral hospital and reported that five months before hospitalization, there was the appearance of lesions similar to palpable purpura, sometimes coalescent, ulcerative, located on the arms (sparing abdomen and trunk), associated with purplish macules and paresthesia in the fingertips (distal phalanges) that worsened with exposure to cold. Three months before hospital admission, he reported disappearance of skin lesions in the upper limbs and the beginning of the same lesions in the lower limbs (below the knees to the dorsum of the feet), as well as significant worsening of paresthesia, especially in symmetrical feet (he described that he seemed to be

wearing compression stockings up to the knees). Fifteen days before hospital admission, the patient developed necrosis of the distal phalanx of the 5th left finger and necrosis of the distal phalanx of the 2nd right and left toes. In addition, she had dry eyes and had been using eye drops for 10 years, in addition, there were reports of xerostomia and weight loss (30 kilos in the last year). He denied any other complaints on several devices. He had no previous comorbidities and there was no family history of autoimmune diseases. On physical examination at hospital admission, the patient was hemodynamically stable, with normal vital signs, and pulmonary and cardiac auscultation showed no abnormalities. The patient presented necrosis of the distal phalanx of the 5th finger of the left hand and of the second toe of the right and left feet, as well as purplish macules in the distal phalanges of the hands bilaterally. On the skin, there were palpable purpura-like lesions, sometimes coalescent and ulcerative, in the lower limbs.

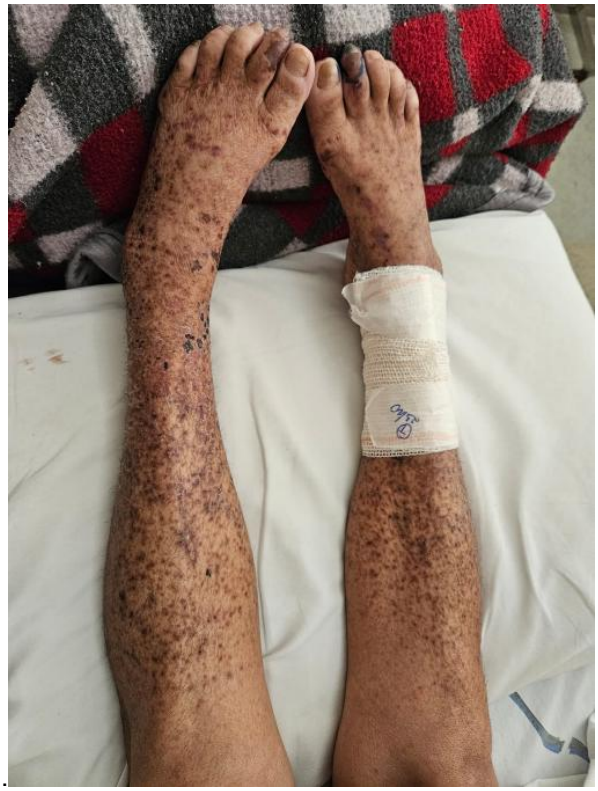
Figure 1

Necrosis of the distal phalanx of the 5th left finger and purplish macules in bilateral distal phalanges. Image captured on the day of hospital admission.

Source: own collection

Figure 2

Necrosis of the right and left 2nd toe. Palpable, coalescent, ulcerative purpura in the lower limbs. Image captured a few days after hospital admission



Source: Own collection

Laboratory tests showed the following patients: Hemoglobin: 9.6; leukocytes: 5,360; platelets: 260,000; creatinine: 0.57; urea: 20; Sodium: 140; Potassium: 4; Corrected calcium: 9.08; phosphorus: 4.4; TGO: 30; TGP: 14; Albumin: 2.4; total bilirubins: 0.38; direct bilirubin: 0.18; indirect bilirubin: 0.20; INR: 1.15; APTT: 31.5; Lactate dehydrogenase: 469; Fibrinogen: 391; Serology for HIV, HCV, Hepatitis B and syphilis: Non-reactive; Rheumatoid factor: 18; VHS: 49; Ferritin: 143; Serum iron: 33; Transferrin saturation: 16%; C3: 87; C4: 0.6; P-ANCA: Reagent 1/40; C-ANCA: Non-reactive; FAN: Heading 1/1280 with centromeric pattern – positive metaphase plate; Anti-SSA/RO: Greater than 240 (reagent); Anti-SSB/LA: less than 7 (non-reactive); SCL70 Antibody: Non-reactive; SM Antibody: Non-reactive; Antiproteinase 3 antibody: Non-reactive; Anti myeloperoxidase antibody MPO: Non-reactive; RNP Antibody: Non-reactive; Anti-DNA Antibody: Non-reactive; Cardiolipin IgG and IgM: Non-reactive; Beta-2 IgG and IgM glycoprotein: Non-reactive; Cryoglobulin dosage: 948 (reagent).

Parotid ultrasound was performed and the following were observed: Parotid glands with lobulated contours and finely heterogeneous echotexture, associated with signs of

intraglandular duct ectasia. Minor salivary gland biopsy showed periductal and periacinar inflammatory infiltrates composed of a heterogeneous mixture of lymphocytes, plasma cells, and histiocytes. These closely associated with acinar lobes with interstitial fibrosis and duct dilation. No germinal center formation is evident between the larger inflammatory foci. Conclusion: Chronic nonspecific sialoadenitis. Incisional skin biopsy on the left leg showed: superficial and middle dermis with red blood cell extravasation and perivascular inflammatory infiltrate, composed of lymphocytes, neutrophils, and eosinophils. Blood vessels show activated endothelial cells and hyaline thrombi inside. Conclusion: Micro-occlusive vascular disease. During hospitalization, the patient was evaluated by the ophthalmology team, which performed a Schirmer test with a significant reduction in tear film. (Right eye: 3mm and left eye: 4mm).

Thus, in view of the clinical picture, laboratory/anatomopathological tests, the diagnostic hypothesis of cryoglobulinaemic vasculitis secondary to primary Sjogren's syndrome was raised. Thus, the patient was evaluated by the rheumatology team, who indicated pulse therapy (in view of the presence of significant neuropathic involvement – sensory-motor polyneuropathy, length dependent and symmetrical) with methylprednisolone 500mg/day for 3 days, followed by prednisone 40mg 1x/day. A few days after pulse therapy, the patient showed clinical improvement in both polyneuropathy and skin lesions. The patient was discharged from the hospital with the use of prednisone 40mg/day, in gradual weaning, azathioprine 50mg 02 tablets/day and infusion with rituximab every 6 months. In addition, oral spray was started for the treatment of xerostomia and lubricating eye drops were maintained for the treatment of keratoconjunctivitis sicca. Currently, the patient is being followed up on an outpatient basis by a team from Rheumatology, Neuromuscular and Vascular Surgery, showing significant clinical improvement and quality of life.

5 DISCUSSION

Sjogren's syndrome is a chronic systemic inflammatory disease caused by lymphocytic infiltration in the exocrine organs. It mainly affects women between the 4th and 6th decades of life and has a prevalence of 60 cases per 100,000 inhabitants. Clinical manifestations include: xerostomia, dysphagia, increased occurrence of dental caries, xerophthalmia, keratoconjunctivitis sicca, corneal ulcers, in addition to constitutional symptoms such as: arthralgias, weight loss, asthenia, fever and myalgias. Sjogren's syndrome may be correlated with small-vessel vasculitis, Raynaud's syndrome, and peripheral neuropathy. Laboratory

tests can show the presence of anemia, ANA reagent, Anti SSA/RO/Anti SSB/LA reagents, hypocomplementemia, cryoglobulinemia reagent when associated with cryoglobulinemic vasculitis, as in the case reported. Minor salivary gland biopsy may present focal chronic sialoadenitis, but it is not necessary for diagnosis. In eye exams, the formation of tears is quantitatively measured (Schirmer's test – positive when it wets less than 5mm in 5 minutes), which can be reduced. The ACR/EULAR classification criteria for primary Sjogren's syndrome include: Salivary labial gland with focal chronic sialoadenitis: 3 points; Anti-RO/SSA positive: 3 points; Eye tinting score greater than or equal to 5:1 point; Positive Schirmer test: 1 point; Unstimulated salivary gland flow <0.1mL/min: 1 point. It is considered primary Sjogren's syndrome when the sum of the items is greater than or equal to 4. In the case reported, the sum of the items is 7 points. The treatment of Sjogren's syndrome mainly aims to reduce symptoms and includes the use of artificial saliva and lubricating eye drops, avoiding the use of anticholinergics, alcohol and smoking. In more severe cases and with extraglandular involvement, corticosteroids, immunosuppressants (azathioprine, cyclophosphamide, methotreat, mycophenolate mofetil) and rituximab can be used.

Cryoglobulinemia is characterized by the precipitation of immunoglobulins in the blood when cooled below 4°C and reversible when reheated. The estimated prevalence is approximately 1 in 100,000 population. Subtype I is composed of monoclonal immunoglobulins, typically IgG or IgM, and is related to malignant neoplasm of the B cell lineage (e.g., multiple myeloma, Waldenstrom macroglobulinemia, or chronic lymphocytic leukemia). In pathophysiology, mechanical obstruction of blood vessels occurs due to blood hyperviscosity due to excessive production of immunoglobulins. The clinical presentation may present with digital ischemia, cutaneous necrosis, Raynaud's phenomenon, peripheral neuropathy, and ischemic phenomena. Treatment is done with immunosuppressants, mainly to treat underlying hematological disorders. The Type II subtype is composed of monoclonal immunoglobulin (typically IgM) and polyclonal immunoglobulin. It is often associated with persistent viral infections (hepatitis C virus) and autoimmune diseases (mainly systemic lupus erythematosus and Sjogren's syndrome), less often associated with other infections such as hepatitis B virus (HBV) and human immunodeficiency virus (HIV). Subtype III is composed of polyclonal IgG (all isotypes) and polyclonal IgM. Like subtype II, subtype III is also often associated with autoimmune diseases and viral infections (mainly HCV). Clinical manifestations in type II and III cryoglobulinemia may present with constitutional and nonspecific symptoms, palpable purpura due to cutaneous vasculitis, and sensory alterations

or weakness due to peripheral neuropathy. Treatment of symptomatic mixed cryoglobulinemia (subtype II and III) is directed at the underlying infectious or autoimmune disorder.

6 FINAL CONSIDERATIONS

The case reported here highlights the importance of clinical and theoretical knowledge about the associations between rare syndromes, such as cryoglobulineemic vasculitis secondary to primary Sjogren's syndrome. Clinical suspicion, accurate diagnosis, and timely treatment are essential for better clinical outcomes, since these associated pathologies have higher morbidity and mortality, which may evolve unfavorably, and sometimes leave important sequelae that impact the patient's quality of life. It is noteworthy that, in the aforementioned case, the diagnosis and treatment were performed at the appropriate time, contributing to clinical improvement and therapeutic success.

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