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Letter to the Editor

A woman with fever, arthralgia, and chronic urticaria

Una mujer con fiebre, artralgias y urticaria crónica

Dear Editor,

Schnitzler syndrome (SS) is a systemic, autoinflammatory, very rare, and apparently acquired disease. It was first described in 1972 by the French dermatologist Liliane Schnitzler.[1] It has a late presentation, affecting mainly men in the fifth decade of life,[2] and is characterized mainly by the presence of monoclonal paraproteinemia and chronic urticaria. The pathogenic association between these 2 mandatory conditions for diagnosis is not clear.[3] We describe a case of SS with MYD88 mutation.

An 89-year-old woman from Venezuela presented to the hematology department of our hospital due to a 30-year history of intermittent pruritic maculopapular rash associated with inflammatory polyarthralgia, fatigue and fever. Her joint symptoms were attributed to previous Chikungunya infection, with previous tests that included a negative autoimmunity profile with persistently elevated inflammatory markers (erythrocyte sedimentation rate, ferritin, and C-reactive protein) and antihistamine and corticosteroid treatment failure, with adverse effects due to secondary diabetes and osteoporotic fractures. Six years earlier, she was diagnosed with low-level IgM kappa monoclonal gammopathy (0.9 g/dL) and small axillary lymphadenopathy with a negative histological result for malignancy, with loss to hematology follow-up. Three years later, for the refractory treatment of urticaria, a skin biopsy (punch) was performed on the right forearm; the results revealed perivascular and interstitial dermatitis with polymorphonuclear cells and eosinophils with negative direct immunofluorescence.

In the initial evaluation, the patient was in good general condition, emaciated, pale, and without jaundice or palpable lymphadenopathy. The cardiopulmonary and abdominal examination was unremarkable. Initial studies showed a hemoglobin concentration of 8.7 g/dL, a mean corpuscular volume of 90 fL, and a reticulocyte percentage of 0.8%, without other cytopenia and without iron and vitamin B9/B12 deficiency or a decrease in the glomerular filtration rate. Inflammatory markers remained elevated, with an erythrocyte sedimentation rate (ESR) of 110 mm. The IgM concentration was 1 g/dL with a kappa/lambda light chain ratio of 2.8. Total body tomography indicated axillary lymphadenopathy without changes in size or morphology. Bone marrow aspiration and biopsy were performed; the results indicated that the bone marrow was normocellular, with mature B lymphocyte infiltration and discrete plasmacytosis, with a nonspecific immunophenotype without light chain restriction. Molecular biology test results indicated a normal karyotype and $MYD88^{L265P}$ (Leu265Pro) mutation, without other data compatible with lymphoplasmacytic lymphoma (*Waldenström* macroglobulinemia, WM).

The patient was evaluated in conjunction with rheumatology, and it was determined that she met the criteria for SS. The patient was administered anakinra (anti-interleukin 1). She had a markedly favorable clinical response after 2 weeks of treatment, with approximately 90% resolution of the skin lesions and pruritus.

SS has some clinical and pathophysiological similarities with the autoinflammatory syndrome CAPS (*cryopyrin-associated periodic syndrome*), an autosomal dominant disorder associated with a mutation that generates gain of function of the NLRP3 gene, causing the dysregulation of inflammasomes and an increase in the production of interleukin-1 beta (IL-1B) through the activation of the nuclear factor kB (NF-kB) pathway. Antigenic stimulation generates the clonal expansion of B cells, as suggested by some reports and case series. This stimulation can facilitate the initiation of a lymphoplasmacytic clone through the interaction of IL-1 receptor complex and IL-1 receptor-associated kinase with MYD88.[3,4] SS may not be due to a mutation in inflammasome genes (NLRP3 gene) but may be the result of an increase in this pathway (NF-KB), as observed in monoclonal gammopathy of uncertain significance (MGUS) or WM.[5] Additionally, there is an increase in IL-18 produced by inflammasomes, as has been observed in rheumatoid arthritis and other autoinflammatory diseases; however, the pathophysiological role is unknown.[6]

Recurrent fever and elevated ESR are prevalent in SS (93–95%), with no apparent relationship with urticaria. Additionally, there may be bone pain (68%), lymphadenopathy (47%), hepatomegaly and/or splenomegaly (34%), arthralgias/arthritis (77%), and fatigue and weight loss, among other symptoms.[2,4] There is no specific test for the diagnosis of SS; therefore, there should be a high index of suspicion based on clinical and analytical criteria, with support by histology. In addition to the 2 mandatory criteria, i.e., monoclonal gammopathy (IgM or IgG) and urticaria, there are other minor criteria (recurrent fever, leukocytosis and/or elevated CRP, neutrophilic infiltration in the dermis (skin biopsy), and alterations in bone remodeling with or without bone pain), of which at least 2 must be met for a definitive diagnosis and one for a probable diagnosis (*Strasbourg criteria*).[4,7]

Rashes are usually generalized (but it could spare head, neck, palms, and soles), macular or plaque-like, often pink, sometimes pruritic and/or burning. Angioedema and mucosal involvement are exceptional. The frequency of outbreaks is variable. The response to antihistamines is poor. Histology shows neutrophilic dermatosis that affects the periphery of the glandular areas without involvement of the hypodermis. There are cases in which vasculitis has been reported without fibrinoid necrosis, which should lead to suspicion of another diagnosis (for example, hypocomplementemic urticarial vasculitis).[2,8] Unlike SS, the presence of chronic urticaria in patients with MGUS is low compared to that in the general population.[9] Adult Still's disease can simulate SS because both present with recurrent fever, rash, persistent inflammation, and the absence of a specific test for diagnosis.[4]

Paraproteinemia does not always precede disease diagnosis and often occurs several years after the onset of cardinal symptoms. The typical form is IgM kappa (86–90%), followed by IgG kappa (7%), IgM lambda (5%), and IgG lambda (1%).[10] Unlike SS, IgM is rare in MGUS (15–20%). The progression to lymphoplasmacytic lymphoma or multiple myeloma was reported in 15–20% of cases in a 13-year follow-up of patients after the initial diagnosis, a finding that is comparable to that reported for MGUS; however, in other cases, progression was as high as 45% and as low as 8%, probably due to reference bias.[11,12]

Approximately 90% of WM cases have the somatic MYD88 L265P mutation (5), which generates gain of function and lymphoid malignancies through Toll-like receptor-dependent signaling pathways. However, MYD88 is also an adaptor protein associated with IL-1R activation. One study reported the presence of the MYD88 L265P mutation in 9 of 30 patients with SS without WM criteria.[2] Some cases can progress to amyloidosis (AA), approximately 2% in some series.[12] At the time of diagnosis, bone marrow test results are normal in most cases (80%), with other cases having nonspecific, polyclonal, lymphocytic or plasmocytic infiltrate.[2]

The response to treatment with anti-IL-1 (for example, anakinra or canakinumab) and rilonacept (anti-IL-1 Trap) is ostensible (greater than 80%), improving quality of life and ensuring adequate tolerance and safety.[2–6,8] Spontaneous remission has not been described, and relapse is generally observed when decreasing or suspending treatment (recurring at 36–48 h). Treatment with anti-IL-1 does not seem to attenuate or decrease the progression to lymphoproliferative syndromes or amyloidosis; a direct effect on clonal markers has not been reported. In addition, there seems to be no relationship between the amount of IgM and the severity of SS or its response to anti-IL-1 treatment. In some patients with mildly elevated inflammatory markers and in the absence of a significant impact on quality of life, some experts propose observation and management with colchicine, nonsteroidal anti-inflammatory drugs, and even antimalarials.[4] The follow-up should be mainly clinical and secondarily analytical, including not only inflammatory markers but also those related to the monoclonal peak.

Despite its rarity, SS is a diagnosis that should be considered in patients with chronic urticaria and persistent inflammation, in whom identifying paraproteinemia will allow for an early diagnosis. To date, the pathophysiological mechanisms underlying SS remain unclear, particularly its link with monoclonal proteins and IL-1b. MYD88 mutations are not specific to WM and can occur in a subgroup of patients with SS, with implications that are still unclear. SS can progress to WM, other lymphoproliferative disorders, or AA amyloidosis, as well as MGUS; therefore, paraprotein should be included in the follow-up. Anti-IL-1 treatment effectively reduces the symptoms related to the autoinflammatory component of SS, improving quality of life, and currently represents the best treatment option.

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Conflict of interest

The authors declare no conflict of interest.

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