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Malignant Evolution of Schnitzler Syndrome to Waldenström Macroglobulinemia: a Case Report

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ABSTRACT

Introduction: Schnitzler syndrome (SchS), first described in 1972, is a rare autoinflammatory condition characterized by chronic urticaria and monoclonal gammopathy of IgM or, exceptionally, IgG profile. Additional features include recurrent fever, evidence of abnormal bone remodeling, a neutrophilic dermal infiltrate on skin biopsy, leukocytosis or elevated C-reactive protein, according to the Strasbourg criteria. **Case Presentation:** We describe the case of a 56-year-old Caucasian male patient, who suffered from chronic urticaria, moderate-grade fever, severe generalized fatigue and arthralgias. After five years of chronic disease evolution, he was referred to the hematology department where he was found to have IgM kappa light chain monoclonal gammopathy. The constellation of symptoms, a negative rheumatologic workup, and the finding of IgM monoclonal gammopathy determined the diagnosis of Schnitzler syndrome. Bone marrow biopsy proved the association of Waldenström macroglobulinemia. **Conclusion:** The main goal of our case report was to highlight the clinical features and treatment, with emphasis on the hematological aspects, to provide a better understanding and to raise awareness of Schnitzler syndrome among healthcare professionals.

Keywords: Schnitzler syndrome, Waldenström macroglobulinemia, IgM monoclonal gammopathy, autoinflammatory disease, chronic urticaria

INTRODUCTION

Schnitzler syndrome (SchS) was first described in 1972 by a French dermatologist, Dr. Liliane Schnitzler, as an association between chronic urticarial rash and monoclonal gammopathy, accompanied by recurrent fever, elevated erythrocyte sedimentation rate (ESR), and bone pain. The mean age at onset is 52–55 years, with a male/female ratio of 1.76.[1] The first diagnostic criteria were established in 2001 by Lipsker *et al.*, later revised in 2012 and known as the Strasbourg criteria (Table 1). Because of its rarity, SchS is often underdiagnosed, and although

TABLE 1. Strasbourg diagnostic criteria

Obligate criteria
Chronic urticarial rash
Monoclonal IgM or IgG
Minor criteria
Recurrent fever[a]
Objective findings of abnormal bone remodeling with or without bone pain[b]
A neutrophilic dermal infiltrate on skin biopsy[c]
Leukocytosis and/or elevated CRP[d]
Definite diagnosis if
Two obligate criteria and at least two minor criteria if IgM and three minor criteria if IgG
Probable diagnosis if
Two obligate criteria and at least one minor criterion if IgM and two minor criteria if IgG

[a] Must be >38°C and otherwise unexplained. Occurs usually – but not obligatory – together with the skin rash
[b] As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase
[c] Corresponds usually to entity described as "neutrophilic urticarial dermatosis"; absence of fibrinoid necrosis and significant dermal edema
[d] Neutrophils >10,000/mm^3 and/or CRP >30 mg/L

its actual prevalence is not known, it is estimated that less than 300 cases have been reported worldwide. The syndrome has been most described in the dermatology literature, as urticaria is the main symptom that drives patients to seek medical care. Moreover, the exact mechanism underlying SchS remains largely unclear, but elevated levels of IL-1 proinflammatory cytokine with anti-IL-1 antibodies and elevated levels of IL-6 and IL-2 receptors suggest a cytokine pathway dysregulation.[2,3] About 15% to 20% of patients with Schnitzler syndrome will eventually progress to a hematological malignancy such as Waldenström macroglobulinemia (WM), multiple myeloma, marginal zone B-cell lymphomas, splenic marginal zone lymphoma, and in rare cases, amyloid A amyloidosis.[4] WM is defined as lymphoplasmacytic lymphoma involving the bone marrow associated with IgM monoclonal paraprotein, and it has an incidence of approximately five cases per one million persons per year, which has remained steady over time as suggested by Wang *et al*. Out of all hematologic malignancies, WM accounts for about 1–2%.[5,6] In this case report, we describe a case of Schnitzler syndrome associated with monoclonal IgM kappa gammopathy.

CASE PRESENTATION

A 56-year-old Caucasian male, with no significant comorbidities other than benign prostatic hyperplasia, initially presented to the dermatology clinic with a five-year history of chronic urticaria which involved his trunk and extremities. Approximately five years after the onset, the rash had become constant and mildly pruritic. An initial dermatologic physical examination described mul-



FIGURE 1. Urticarial rash covering the back (**A**) and lower extremities (**B**) of a patient with Schnitzler syndrome

tiple round, pale-rose papules, with distinct borders, and slightly raised pruritic plaques, located mostly on the chest, abdomen, sacral region, and proximal extremities, sparing the face, palms, and soles (Figure 1). The patient also described moderate pelvic and spine bone pain, persistent fatigue, intermittent fever accompanied by nocturnal sweating and moderate weight loss, while the clinical examination revealed palpable lymphadenopathy in the axillar and inguinal regions. There was no hepatosplenomegaly. The patient was treated symptomatically with corticosteroid and antihistamine drugs until his admission to the hematology department.

Laboratory investigations revealed elevated ESR of 115 mm/h (normal range: <10 mm/h), C-reactive protein at 42.11 mg/L (normal range: <5 mg/L), leukocytosis of 17,820/μL with neutrophilia (78.2%). The biochemical profile showed elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as a slightly elevated LDH at 226 U/I (normal range: 0–225 U/I). Serum protein electrophoresis and immunofixation revealed an IgM kappa monoclonal gammopathy (IgM-k) at 3,079 mg/dL (normal range: 40–230 mg/dL), while IgA and IgG levels were normal. Antinuclear antibodies (ANA) were negative. Thyroid peroxidase antibodies (TPOAb) and anti-streptolysin O (ASLO), C3 and C4 were in normal ranges. Circulating immune complexes (CICs) and the rheumatoid factor were positive. Renal and liver functions were in normal ranges, and the screening for viral hepatitis was negative. A thoracic computed tomography (CT) was performed, which, apart from bilateral axillary lymphadenopathy, found no other significant abnormalities.

Histopathological examination of an enlarged inguinal lymph node was performed, which described interfollicular hyperplasia containing small/medium-sized lymphocytes with lymphoplasmacytic differentiation. Most cells presented IgM membrane expression with kappa light chains. The cells were positive for CD20, Pax5, MUM1, CD38, CD138, and kappa, and negative for CD10, CD23, CD56, cyclin D1, and BCL6. Ki67 proliferation index was over 30%, suggestive of lymphoplasmocytic lymphoma.

A bone marrow biopsy was performed, describing 10% lymphoproliferative tissue consisting of small- and medium-sized lymphocytes. Most cells had surface IgM expression and were positive for PAX5 and MUM1, while the ones that presented plasmacytic differentiation were positive for CD138 in addition. The morphologic aspect, as well as the phenotype of tumor cells were suggestive of lymphoplasmocytic lymphoma.

According to the Strasbourg criteria (Table 1), by the presence of chronic urticarial rash, IgM monoclonal protein, recurrent fever, leukocytosis with neutrophilia, and an elevated C-reactive protein, and by the exclusion of other possible causes of systemic inflammation, the diagnosis of Schnitzler syndrome was established. The main diagnostic criteria for Waldenström macroglobulinemia were expressed by the confirmation of an IgM monoclonal protein, as well as the histological depiction of infiltration in the lymph node and bone marrow by lymphoplasmacytic cells. The patient received an initial corticosteroid treatment, which was subsequently replaced with one cycle of cyclophosphamide plus dexamethasone, and later continued with two cycles of well-tolerated chemotherapy association of rituximab, cyclophosphamide, and dexamethasone (RC-D), showing a rapid remission of both WM and SchS signs, with a significant resolution of the urticaria as well as a decrease of IgM values at 13.7 g/L.

Informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

SchS is an underdiagnosed syndrome, mainly due to nonspecific symptoms, as well as a lack of disease awareness among health care professionals, with an average delay of five years in diagnosis and treatment.[7,8] In most cases, the first symptom is urticaria, preceding the fever.[9] Although our patient expressed almost all of the classic signs and symptoms of SchS, the diagnosis was delayed by five years, as it usually happens with most patients with this syndrome.

The patient presented urticarial rash on his trunk and extremities, multiple palpable lymphadenopathies, fatigue, bone pain, and a five-year history of recurrent fever and moderate weight loss. Standard laboratory investigations revealed leukocytosis with neutrophilia, elevated ESR (>100 mm/h), and a highly elevated CRP value, due to which a suspicion of Schnitzler syndrome was raised. Serum protein electrophoresis and immunofixation revealed an IgM kappa monoclonal gammopathy, which, together with the rest of laboratory findings and the multitude of signs and symptoms presented by the patient, as well as the exclusion of other autoinflammatory diseases, established the diagnosis of SchS, according to the Strasbourg criteria. The diagnosis of WM was established based on the presence of IgM monoclonal protein associated with the finding of over 10% clonal lymphoplasmacytic cells in the bone marrow biopsy.

The pathogenesis of SchS involves IL-1, IL-6, and IL-17 activation, although the connection to monoclonal gammopathy remains unclear.[10] The treatment of choice is anakinra, an IL-1 receptor antagonist. In this case, admin-

istration of anakinra was taken into consideration; however, due to economical and availability issues, it could not be acquired. Moreover, recent studies have proven its inferiority to RC-D in the treatment of SchS associated with active moderate-to-high peak WM.[11] Our patient initially underwent corticosteroid treatment, which was later replaced by one cycle of dexamethasone and cyclophosphamide, followed by two cycles of R-CD, showing remission of both WM and SchS signs.

The prognosis of SchS is dictated by the occurrence of lymphoproliferative complications such as Waldenström macroglobulinemia, IgM myeloma or lymphoma. This emphasizes the importance of increasing physicians' awareness of this syndrome, mostly because of its potential morbidity, but also because effective treatment strategies are available, with proven safety and efficacy.[12]

CONCLUSIONS

Schnitzler syndrome is a rare autoinflammatory disease that is most often underdiagnosed, many patients having a diagnostic delay of over five years. Sign and symptoms might vary; however, the main ones are represented by chronic urticaria, recurrent fever, and the presence of monoclonal gammopathy. Awareness among physicians and an early identification of the syndrome are essential due to its possible evolution to hematological malignancies such as Waldenström macroglobulinemia.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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