Schnitzler syndrome associated with hairy cell leukemia presenting with chronic urticaria and arthralgias

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INTRODUCTION

Schnitzler syndrome is an underdiagnosed clinical condition characterized by 2 major criteria: chronic recurrent urticarial eruption and monoclonal IgM gammopathy, as well as at least 2 of the following minor criteria: (1) recurrent fever, (2) high C-reactive protein (CRP) levels, (3) signs of abnormal bone remodeling with or without bone pain, and (4) neutrophilic infiltrates on skin biopsy.[1] We report the case of a patient with history of hairy cell leukemia who exhibited atypical clinical presentation of chronic urticaria for 2 years before the final diagnosis of Schnitzler syndrome was established. To the best of our knowledge, this is the first reported case of Schnitzler syndrome associated with hairy cell leukemia.

Abbreviations used:

CRP: C-reactive protein
IL-1: interleukin-1

CASE REPORT

In 2013, a 50-year-old man presented with complaints of arthralgia involving knees, ankles, and fingers, which primarily manifested during the night. A few months later, he developed recurrent episodes of a nonpruritic urticarial eruption. His relevant medical history consisted of hairy cell leukemia in 2010, in remission after treatment with cladribine yet with small residual disease.

Physical examination confirmed diffuse labile erythematous macules and wheals (Fig 1). The lesions usually disappeared within 24 to 48 hours without associated angioedema. Laboratory tests found a normal blood count, increased CRP levels at 18.2 mg/L (normal, <6.0 mg/L), and an erythrocyte sedimentation rate at 32 mm/h (normal, <14 mm/h). Results were negative for antinuclear antibodies. Serum IgG, IgA, and IgM levels were within normal ranges.

Bone scintigraphy found a diffuse area of increased uptake in the distal third of both the femoral diaphysis and epiphysis. Bone marrow biopsy found a persistent population of malignant B lymphocytes but no aggressive lymphoma. Skin biopsy detected mild edema of the dermis with perivascular and interstitial infiltrates of lymphocytes, histiocytes, and numerous eosinophils.

In 2014, a diagnosis of spontaneous chronic urticaria was proposed, and the patient was initially treated with high doses of different antihistamines, such as rupatadine, cetirizine, and others, during 3 months without significant response. Oral corticotherapy was then administered for 1 month without any success. Next, treatment with subcutaneous omalizumab (2 × 150 mg/mo) for 6 months was proven inefficient. In March 2015, a new serum protein electrophoresis detected for the first time a thin band of IgM-κ monoclonal gammopathy. On additional laboratory tests, there was an increased

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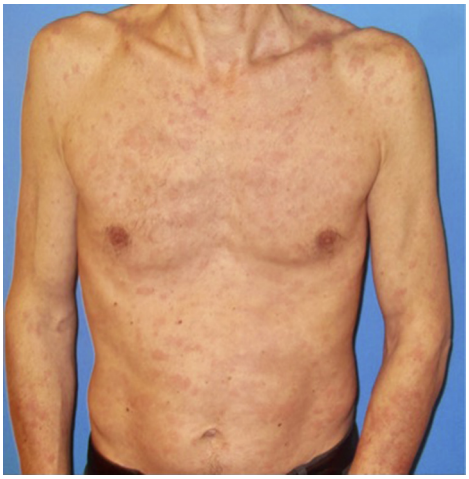

Fig 1. Schnitzler syndrome. Diffuse labile erythematous macules and wheals.

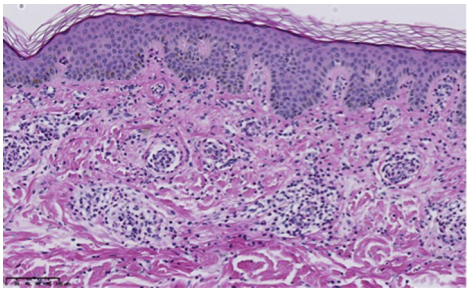

Fig 2. Skin biopsy. Perivascular and interstitial dermal infiltrate consisting of lymphocytes, histiocytes, eosinophils, and a lot of neutrophils.

CRP level at 21.0 mg/L, and serum IgM was measured at 1.92 g/L (normal range, 0.4-2.3 g/L).

A second skin biopsy found a perivascular and interstitial dermal infiltrate consisting of lymphocytes, histiocytes, eosinophils, and many neutrophils. A discrete number of leukocytoclastic foci were observed in the dermis, without sign of vasculitis (Fig 2).

Based on the clinical presentation and additional investigation results, a diagnosis of Schnitzler syndrome was proposed in April 2015. The patient exhibited the 2 obligatory criteria according to the Strasbourg diagnostic criteria for Schnitzler syndrome, namely, a chronic recurrent urticarial eruption and monoclonal IgM gammopathy, in addition to 4 minor criteria (high CRP levels, signs of abnormal bone remodeling with bone pain, and neutrophil infiltrate on the skin biopsy).[1,2]

The patient was first treated with colchicine and nonsteroidal anti-inflammatory drugs, which slightly improved his symptoms. Dapsone was later added, although not tolerated by the patient. On account of prior leukemia, administering immunosuppressive agents like cyclosporin was contraindicated. In July 2015, anakinra (Kineret; Sobi, Stockholm, Sweden), an anti—interleukin-1 (IL-1) monoclonal antibody, was injected subcutaneously at a daily dose of 100 mg (Fig 3). The symptoms significantly improved within 48 hours, with the skin rash and hand and ankle arthralgia completely disappearing, yet continued mild knee arthralgia. The inflammatory parameters were negative (CRP <1.0 mg/L), and total serum IgM decreased slightly (1.62 g/L), whereas a thin band of monoclonal IgM-κ persisted. The neutrophil count decreased after anakinra initiation (1740 cells/mm^3). In July 2016, 1 year after the first anakinra injection, the patient reported marked improvement in his quality of life, yet the skin rash systematically reappeared within 24 to 48 hours whenever therapy was discontinued.

DISCUSSION

Schnitzler syndrome is an underdiagnosed, acquired autoinflammatory syndrome that must be considered in the differential diagnosis of chronic urticaria. It is essential to continually perform complementary investigations, particularly when the urticaria appears atypical, such as associated with extracutaneous manifestations, and in the lack of response to the usual treatment. To date, more than 281 cases have been reported since its first description in 1972 by French dermatologist Liliane Schnitzler.[1] Most cases are not diagnosed before 5 years.[3] In our patient, the diagnosis was established after 2 years. The proven efficacy of new biological therapies, such as IL-1 receptor antagonist (anakinra, Kineret), has now clearly established them as treatment of choice in the Schnitzler syndrome.[1,4-8]

The originality of this case is the association between Schnitzler syndrome and hairy cell leukemia, which was never reported before. Recent studies have found that pro-inflammatory cytokine IL-1 has a crucial role in the pathogenesis of Schnitzler syndrome.[9,10] It was also recently found that a systemic overproduction of IL-1ß in the Schnitzler syndrome, caused by mutations in the inflammasome, results in a profound loss of anti-inflammatory helper T-cell 17 cell functionalities. This phenomenon can be reversed by anti—IL-1ß treatment. The role of the IgM paraprotein in the pathogenesis of the Schnitzler syndrome remains unclear. In our patient, the link between his history of leukemia and this current condition was probably due to a persistent residual disease that consists of a monoclonal population of B lymphocytes secreting a monoclonal IgM. This monoclonal IgM can be responsible for the autoactivation of