

Incomplete Schnitzler Syndrome

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ABSTRACT Schnitzler syndrome (SS) is a rare autoinflammatory disease that presents with chronic urticaria and monoclonal immunoglobulin (Ig) M or G, accompanied by fever, abnormal bone remodeling, skin biopsy with a neutrophilic dermal infiltrate, leukocytosis, or elevated C-reactive protein. It is usually refractory to antihistamines and immunosuppression. We present a case report of clinical SS without monoclonal Ig with robust response to interleukin-1 inhibitor anakinra. This suggests the possible existence of an incomplete form of SS and underlines the risk of false negative diagnosis in individuals with such "incomplete SS".

KEY WORDS: diagnosis, interleukin 1 receptor antagonist protein, Schnitzler syndrome, urticaria

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INTRODUCTION

Schnitzler Syndrome (SS) is a rare autoinflammatory disease defined by the Strasbourg criteria (1,2). According to the definition, chronic urticarial rash and monoclonal immunoglobulin (Ig) M or IgG are obligatory in combination with two of the following minor criteria: recurrent fever, objective findings of abnormal bone remodeling with or without bone pain, skin biopsy with a neutrophilic dermal infiltrate, and leukocytosis and/or elevated C-reactive protein (CRP) (1). Mean age of onset is 51 years, and the literature describes around 300 cases (1,2). Symptoms are generally refractory to antihistamine, azathioprine, methotrexate, tumor necrosis factor inhibitors, and rituximab (1,2). However, the interleukin-1 inhibitor anakinra quickly alleviates the symptoms and most likely decreases the risk of future amyloidosis, but not

Waldenström macroglobulinemia, a lymphoproliferative complication (3). Discontinued anakinra usually lead to a rapid recurrence the symptoms (2). There are reports of patients with clinical SS without monoclonal gammopathy at the time of diagnosis (4), as well as cases of delayed monoclonal gammopathy development, years after onset of symptoms (3).

CASE REPORT

A 51-year-old healthy man was referred to the dermatology department in 2016 after eight months of recurrent urticaria, fever, night sweats, joint and muscle pain, and minor weight loss (Figure 1). No one in his family had had similar symptoms. Laboratory testing indicated a normocytic, normochromic anemia with hemoglobin 129 g/L, elevated CRP 46

mg/L, leukocytosis $6.7 \times 10^9/L$, and thrombocytosis $512 \times 10^9/L$. Liver, renal, and rheumatological screening including anti-double stranded deoxyribonucleic acid antibodies, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, beta-2 microglobulin, complement factors, and extractable nuclear antigen were normal and urine and blood cultures negative. Electrophoresis showed kappa and lambda light chains of 47.2 mg/L and 28.3 mg/L, without monoclonal gammopathy. Histopathological examination revealed *subepithelial edema* and discrete interstitial and perivascular neutrophilic and eosinophilic granulocyte infiltration, indicative of urticaria, computer tomography (CT) showed sclerosis in the pelvic bone, and positron emission tomography (PET) -CT found increased *fluorodeoxyglucose (FDG) uptake* in the axillary and inguinal lymph nodes. A bone marrow biopsy indicated osteosclerosis, without evidence for malignancy. Anakinra 100 mg subcutaneously once daily was initiated for suspected SS, resulting in symptom mitigation within days, and the hemoglobin and acute phase reactants normalized. The symptoms reoccurred quickly during treatment pauses, and anakinra was discontinued due to a mild headache and nightly pruritus, and omalizumab 300 mg every four weeks was subcutaneously initiated for chronic urticaria. A few days later, the patient developed a productive cough, headache, and urticaria and upon hospitalization the blood samples revealed CRP 250 mg/L, leukocytosis $13.3 \times 10^9/L$, and hemoglobin 127 g/L. Chest X-ray, blood cultivations, and urine analysis were normal. Despite intravenous benzylpenicillin 1.2 million units four times daily and oral cetirizine ten mg daily, the symptoms were only reduced once he received prednisolone 50 mg daily. Shortly after anakinra was reinstated in the same dose as before, omalizumab was discontinued, and at clinical control two and eight months later the patient only had mild nightly pruritus and the laboratory values had normalized.

DISCUSSION

The Strasbourg criteria's sensitivity and specificity are 81% and 100%, respectively (1). This particular case underlines the risk of a false negative diagnosis when SS manifests without monoclonal gammopathy and also emphasizes the responsiveness of such "incomplete SS" to standard therapy. The laboratory findings, including anemia, elevated CRP, leukocytosis, and thrombocytosis reflect an increased inflammatory activity that together with bone marrow osteosclerosis and bone sclerosis are characteristics of SS (2,3). Increased FDG uptake and hence metabolic activity in the axillar and inguinal lymph nodules,



Figure 1. Hives on the patient's back.

described in the PET-CT, is attributed to dermal inflammation. Schnitzler syndrome has many clinical features in common with autoinflammatory cryopyrin-associated periodic syndrome (CAPS) (5). However, age of onset for CAPS is during childhood, and family members are often affected. Moreover, genetic testing for NLRP3 mutation can sometimes distinguish the two diseases. Other important differential diagnoses include chronic spontaneous and inducible urticaria, which are limited to the skin and usually have normal serum markers (5). Histological neutrophilic granulocyte infiltration is a hallmark of both SS and adult-onset Still's disease (5). They also share some laboratory findings, including leukocytosis and elevated erythrocyte sedimentation rate. However, several clinical features distinguish them from each other. Another serious differential diagnosis and potential complication is Waldenström macroglobulinemia that can be excluded with bone marrow biopsy (5). Finally, the current absence of a monoclonal gammopathy does not preclude future development of this diagnostic hallmark.

CONCLUSION

Physicians should consider "incomplete SS" despite the absence of monoclonal gammopathy if other autoinflammatory symptoms are present at

the time of diagnosis (6). Early disease recognition allows for appropriate therapeutic intervention and prompt symptom control and potentially improved long-term prognosis for the affected patient. At the end of May 2020, blood samples revealed that the patient had developed monoclonal IgM of 1.4 gram/L, confirming the diagnosis SS, almost four years after onset of symptoms.

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