

LETTER

Urticarial skin rash, fever, and arthralgia: a rare case of Schnitzler's syndrome

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Schnitzler's syndrome (SS) was first described in 1972 by Liliane Schnitzler (1). It is a rare acquired autoinflammatory disease of unknown origin and represents a diagnostic challenge for most clinicians. It is associated with non-specific clinical and biological signs of inflammation and hence the time from the onset of symptoms to diagnosis has been estimated to be more than 5 years (2).

A 66-year-old man with a history of diabetes mellitus type II presented with recurrent episodes of a non-pruritic urticarial rash of 9 months. It started on the chest and then spread to the arms and thighs. It was associated with fever, generalized mild arthralgia, and weight loss of 20 pounds. His medications were metformin and sitagliptin. Later sitagliptin was discontinued, but no improvement was noted. The skin rash resolved initially with topical and oral steroids but recurred a few weeks later despite continued use of the steroids. Subsequently, the patient was referred to the Division of Infectious Diseases. Examination revealed an urticarial erythematous rash on the arms, chest, abdomen, and upper thighs (Figure 1). A skin biopsy was consistent with

neutrophilic urticaria. Laboratory studies revealed a white blood cell count of $16.4 \times 10^3/\mu\text{L}$, an erythrocyte sediment rate (ESR) of 32 mm/h, and a C-reactive protein (CRP) level of 10.3 mg/dL (normal < 1.0 mg/dL). Tests were negative for HIV and viral hepatitis. There was no evidence for connective tissue diseases. Serum electrophoresis revealed a monoclonal immunoglobulin (Ig)M-kappa component and a bone marrow aspiration and biopsy was consistent with monoclonal gammopathy of undetermined significance.

Based on the recurrent urticarial skin rash, fever, arthralgia, elevated ESR and CRP, and the presence of monoclonal IgM-kappa, the diagnosis of SS was made. The patient was started on an interleukin (IL)-1 antagonist and his skin rash resolved after the first dose of anakinra therapy. After 15 weeks of continuous therapy the patient has remained symptom free.

SS is a rare acquired autoinflammatory disease and should be suspected in adult patients, usually aged ≥ 40 years, with a recurrent urticarial rash, intermittent fever, musculoskeletal pain, and lymphadenopathy (3). The urticarial rash is typically the first clinical manifestation. In the beginning it is non-pruritic and can occur on any part of the body. Patients can have daily flares of urticarial rash for months or years, or may go into remission for days to weeks (4, 5). Recurrent fever, bone pain, and arthralgia are characteristic findings but only rarely do patients developed arthritis (5). Lymphadenopathy has been seen in about 45% of reported cases and hepato- or splenomegaly occurs in about a third of the patients (6, 7). Although the pathogenesis of SS is unknown, a role for uncontrolled activation of IL-1 and dysfunction of inflammasome have been suggested (5, 6, 8).

The histopathological findings on skin biopsy mostly show neutrophilic urticaria and interstitial inflammation similar to that found in adult-onset Still's disease, lupus erythematosus, and cryopyrinopathies (4, 9). Overall, the prognosis for SS is about



Figure 1. Right and left forearms and arms showing classic urticarial skin rash.

90% survival rate at 15 years' follow-up (7). When associated with amyloidosis and lymphoproliferative malignancies, the prognosis is poor (5, 7, 10).

The differential diagnosis includes autoimmune diseases, a wide variety of infections, cryopyrin-associated periodic syndrome, acquired C1 inhibitor deficiency, and hyper IgD syndrome (5, 7). There is no specific test for SS; however, Lipsker et al have proposed the following scheme (6): the diagnosis can be made if a patient has an urticarial skin rash and a monoclonal IgM gammopathy plus at least two of the following minor criteria: (a) recurrent fever, (b) arthralgia or arthritis, (c) bone pain, (d) lymphadenopathy, (e) hepato- or splenomegaly, (f) elevated ESR and/or leucocytosis, and (g) abnormal findings on bone imaging.

The treatment of SS is mainly symptomatic. Patients with no impairment in quality of life and without persistent elevation of inflammatory markers need no therapy. The skin rash is usually resolved with an IL-1 receptor antagonist such as anakinra (3, 5). The long-term efficacy of anakinra and the potential for secondary treatment failure are unknown.

Our patient's symptoms resolved with the first dose of anakinra therapy. At the time of writing the patient had completed 15 weeks of therapy and remained symptom free. The plan was to continue with the anakinra for 1 year and follow for late complications, in addition to determining whether there was a sustained response to anakinra.

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