

Schnitzler's Syndrome: Monoclonal Gammopathy Associated with Chronic Urticaria

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Key Words

Monoclonal gammopathy • Skin lymphocytic infiltrate • T lymphocytes, CD4+ and CD8+ • Urticarial rash

Abstract

Schnitzler's syndrome (SS) is defined by monoclonal gammopathy and chronic urticaria combined with at least two of the following features: fever, arthralgia or arthritis, bone pain, hepato- and/or splenomegaly, palpable lymph nodes, elevated ESR, and leukocytosis. We report a 49-year-old man with monoclonal IgM gammopathy and a 4-year history of recurrent urticarial rash, unexplained fever and arthralgias. The skin biopsy from an acute lesion revealed perivascular lymphocytic infiltrates consisting of CD4+ and CD8+ T lymphocytes. To our knowledge, this is the first report of an immunophenotypic characterization of skin infiltrates in SS. A lower CD4+/CD8+ ratio of circulating T lymphocytes was also detected. SS usually has a benign course, but in 15% of patients a lymphoproliferative disorder develops.

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Introduction

Schnitzler's syndrome (SS), described for the first time in 1972 [1], is defined by the association between monoclonal immunoglobulin M (IgM) gammopathy and a recurrent urticarial rash accompanied by clinical and laboratory findings, which are considered as minor diagnostic criteria and include intermittent unexplained fever, arthralgia or arthritis, bone pain, liver and/or spleen enlargement, palpable lymph nodes, bone changes, elevated ESR, and leukocytosis. The diagnosis is based on a combination of the two major criteria, that are monoclonal IgM gammopathy and chronic urticaria, with at least two of the minor criteria [2]. Recently, the diagnosis of SS has been widened to include patients with monoclonal non-IgM gammopathy, in particular IgG, as a closely related 'variant' [3]. Since there is no specific marker of SS, the diagnosis can be made after the exclusion of other diseases such as adult-onset Still's disease, chronic idiopathic urticaria, hyper-IgD syndrome, hypocomplementemic urticarial vasculitis, and acquired C1 inhibitor deficiency [2, 3]. In the majority of cases the syndrome has a chronic benign course, but in 15% a lymphoproliferative disorder (LPD) develops in the long term. LPD consists mostly of Waldenström macroglobulinemia [3]; in addition,



Fig. 1. Erythematous macules, sometimes confluent, on the right leg.

lymphoplasmacytic lymphoma [4], multiple myeloma, and marginal zone B lymphoma [5] have been described in sporadic cases. The evolution to AA amyloidosis was reported in 3 patients [6–8].

SS is rare and little known. Ninety-four patients were included in the most recent review published on SS; among them, 89 resulted from a literature search of the PubMed and MEDLINE databases (1966–2006) and 5 were previously unreported cases [3]. The different specialists, to whom the patients are referred for the heterogeneous clinical presentation, may not be aware of this syndrome, causing a delay in diagnosis. SS has so far been better known in the dermatological literature, but it is of concern to hematologists, rheumatologists and internists as well.

Case Report

We report here a 49-year-old man, who was referred to the Hematology Department because of a serum protein electrophoresis finding, demonstrating monoclonal gammopathy. His physical examination was otherwise unremarkable except for mild hepatomegaly. The patient underwent laboratory evaluations for a recurrent nonpruritic urticarial rash over the trunk and limbs, concomitant with unexplained fever and disabling arthralgias affecting his knees, ankles, wrists, and elbows. Four years after the onset of these manifestations, no diagnosis had been established. The urticarial lesions appeared as erythematous slightly raised macules, 1 cm in diameter, sometimes confluent (fig. 1), that persisted for 4–36 h, resolved leaving normal-appearing skin, and recurred with increasing frequency (at approximately 40-day intervals, at the time of our observation). Treatments with antihis-

tamines, nonsteroidal anti-inflammatory drugs or corticosteroids (methylprednisolone at the dosage of ≤ 15 mg/day) were unsuccessful in controlling urticaria, whereas they slightly improved the fever and arthralgias.

Laboratory investigations were performed, yielding a paraprotein value of 0.9 g/dl and M isotype on immunoelectrophoresis, with a kappa light chain on immunofixation; the free light chain kappa/lambda ratio was 1.56, and Bence Jones proteinuria was undetectable. IgM were raised, being 834 mg/dl (normal: 40–230), whereas IgG and IgA were within normal ranges. Full blood cell count demonstrated WBC $9.45 \times 10^9/l$ with a normal differential count (neutrophils $7.06 \times 10^9/l$, lymphocytes $1.82 \times 10^9/l$, monocytes $0.42 \times 10^9/l$, eosinophils $0.11 \times 10^9/l$, basophils $0.049 \times 10^9/l$), Hb 15.3 g/dl, and PLT $257 \times 10^9/l$. Flow-cytometric assessment of peripheral blood lymphocytes revealed 73% CD3 expression with 36% coexpression of CD4 and 37% of CD8, resulting in a 1:1 CD4+/CD8+ ratio; CD4 and CD25 were coexpressed by 21%, CD20 only by 8%, and CD16 and CD56 by 6% of the cells. Microscopic examination of bone marrow (BM) aspirate showed 11% of lymphocytes and 2% of plasma cells. On BM biopsy, immunohistochemistry demonstrated scattered CD4- or CD8-expressing T lymphocytes, rare CD20 expression, and plasma cells reacting with anti-kappa or anti-lambda monoclonal antibodies (MAbs). ESR was increased to 40 mm in the 1st hour (normal: 1–10 mm/h) and C-reactive protein (CRP) to 2 mg/l (normal: 0–0.5 mg/l), whereas the other biochemical findings were within normal ranges. Abdominal ultrasonography demonstrated a slightly enlarged liver without focal lesions and a normal-sized spleen (longitudinal diameter 9 cm). Skeletal and chest X rays did not reveal any abnormality.

Further investigations, performed to exclude allergic, autoimmune and infectious causes, yielded the following results: a normal eosinophil count and total IgE level; slightly increased anti-thyroperoxidase antibodies (Abs) to 43.09 IU/ml (normal: 1–16 IU/ml) and anti-thyreoglobulin Abs to 211.5 IU/ml (normal: 5–100 IU/ml), normal levels of complement fractions and rheumatoid factor, absence of cold agglutinins and cryoglobulins. The search for antinuclear Abs was negative, as also for p- and c-anti-neutrophil cytoplasmic Abs. Extensive cultures and serological evaluations for acute viral or streptococcal infections were negative as well.

A skin biopsy was performed of an active lesion which was about 10 h old. On histological examination, the specimen revealed dermal lymphocytic infiltrates with a perivascular distribution, also found around the piliferous follicles. The vessels were intact, and there was no evidence of blood red extravasation, nuclear dust or fibrinoid necrosis; eosinophils were seen only rarely. Immunohistochemistry revealed CD3 expression by the infiltrating lymphocytes, which also reacted positively with anti-CD4 or anti-CD8 MAbs, whereas no cells reacted with anti-CD20 MAbs. Outside the lymphocytic infiltrate, scattered macrophages reacting with anti-CD68 MAbs (clone PG-M1) were observed.

Discussion

In the wide spectrum of cutaneous manifestations, characterized by the association with monoclonal gammopathy and classifiable on the basis of their pathoge-

netic mechanisms, SS has been related to the biologic activity of paraprotein [9].

The search for paraprotein was obviously essential to establish the diagnosis in our patient, whose clinical presentation itself was suggestive of SS. In particular, the monoclonal Ig resulted in M isotype mounting a kappa light chain, as is most commonly observed in SS [3]. The urticaria was unrelated to the intake of alcohol, spicy foods or to stress. It appeared distinctive of SS in terms of both lesion type and distribution, the face, palms and soles usually being unaffected by the eruption. Typically, pruritus that affects only few patients, usually 3 or 4 years after the urticaria onset, was absent [2]. Moreover, the unresponsiveness of urticaria to antihistamines, together with the absence of pruritus, supported a histamine-independent etiology. The high fever accompanying the urticarial rash appeared to be of unknown origin, the aching joints did not show any abnormal radiographic signs, and ESR and CRP levels were continuously elevated throughout the disease course. In addition, a nonspecific hepatomegaly as well as increased levels of anti-thyroid autoantibodies are common findings among SS patients [2, 10], while the negative results of other investigations made it possible to rule out those diseases mainly requiring differential diagnosis from SS [2, 3].

The macrophages observed in the skin biopsy from our patient have never previously been reported whereas the coexistent dermal lymphocytic infiltrates are included in the spectrum of the heterogeneous histopathological changes described in the SS literature, ranging from mild perivascular inflammation to leukocytoclastic vasculitis. In particular, in a histopathological review of 15 cases of SS, the majority of patients (9/15) disclosed dermal neutrophilic infiltrates with a predominantly perivascular distribution (neutrophilic urticaria); among the others, 5/15 showed lymphocytic infiltrates (lymphocytic urticaria) and 1/15 exhibited leukocytoclastic vasculitis [11]. Bearing in mind a possible dynamic evolution of the infiltrates, the predominance of a different cell type within them may be related to the timing of the biopsy [12]. Therefore, in our patient the finding of lymphocytic infiltrates may be related to the age of the lesion; an earlier biopsy might have shown a neutrophilic infiltrate evolving to a lymphocytic type over time. Finally, vasculitis is fairly rare in SS, as supported by the frequently negative results of immunofluorescence studies and the infrequent findings of vascular damage, fibrin deposition, red blood cell extravasation, and significant leukocytoclasia [11].

To our knowledge, this is the first report of an immunophenotypic characterization of SS skin infiltrates, in our case involving of CD4+ and CD8+ T lymphocytes, in the absence of CD20+ cells. Furthermore, immunophenotyping of peripheral blood lymphocytes revealed a lower CD4+/CD8+ ratio. Abnormalities of circulating T cell subsets have previously been reported, and polyclonal lymphocytic or plasma cell infiltrates were described in 20% of BM biopsies [13]. These data support a role of T lymphocytes in the pathogenesis of SS cutaneous lesions, whose mechanisms are still unclear. In particular, an uncontrolled activation of interleukin-1 α (IL-1 α) and paraprotein/skin interactions leading to the activation of the complement cascade have been proposed [3, 14, 15].

Since our patient missed work periodically because of his systemic symptoms, he underwent treatment with the above-mentioned standard agents, yielding the known unsatisfactory results. Until recently, only long-term courses of high-dose corticosteroids showed a transient effectiveness in controlling urticaria [16]. At present, the most promising therapeutic options are novel agents, such as thalidomide and anakinra [17]. Particularly anakinra, a synthetic analog of the endogenous IL-1 receptor antagonist, is considered the treatment of choice in patients with severe manifestations [2, 16, 18, 19]. The risk of SS evolution to LPD after a latency period was of concern in our patient and underlined the need for periodic long-term monitoring. During the year following the diagnosis, the disease remained stable as regards monoclonal gammopathy and clinical manifestations.

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