

Schnitzler's syndrome: no evidence for autoimmune basis in two patients

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Summary

We report two cases of Schnitzler's syndrome in which anti-interleukin-1 α autoantibodies and functional autoantibodies against the high affinity IgE receptor (Fc ϵ RI α) or against IgE were absent. One patient responded well to TL-01 phototherapy, a treatment which may be considered in patients with Schnitzler's syndrome if, as is usually the case, they are unresponsive to antihistamine therapy.

Report

Schnitzler's syndrome (SS) is a rare condition defined by the association of chronic urticaria with a monoclonal IgM gammopathy. The pathogenesis of the urticaria is unclear and treatment is difficult. It is known that approximately 30% of patients with chronic idiopathic urticaria have circulating functional anti-Fc ϵ RI α and/or anti-IgE autoantibodies. It is not known whether similar autoantibodies are present in SS. We describe two patients with SS in whom we failed to demonstrate the presence of serum histamine releasing autoantibodies. In one of them almost complete remission of the urticaria was achieved with narrow band UVB phototherapy (TL-01).

Case 1

A 59-year-old woman presented with a 5-year history of a chronic, nonpruritic urticarial eruption with no associated systemic symptoms and no apparent triggering or exacerbating factors (Fig. 1). Individual urticarial lesions lasted for 2–3 days. Previously the urticaria had been antihistamine resistant, but had shown an 85% improvement after a course of narrow band (TL-01) UVB phototherapy (20 treatments, total dose 96.21 J/cm²), with relapse shortly after cessation. Examination

revealed widespread weals involving the patient's trunk and limbs. There was no lymphadenopathy or hepatosplenomegaly.

Histology of a biopsy of a weal showed mild dermal oedema and a dermal mixed perivascular and interstitial infiltrate composed of neutrophils, lymphocytes and some eosinophils with evidence of mild leukocytoclasia. Direct immunofluorescence (DIF) was negative.

Full blood count showed moderate leukocytosis (12.9×10^9 /L with 77% neutrophils). The erythrocyte sedimentation rate (ESR) was 70 mm/h. Renal, hepatic and thyroid profiles, serological tests for hepatitis B and C virus, anti-nuclear antigen and extractable nuclear antigen were normal or negative. C4 was low (0.1 g/L; normal range, 0.20–0.50 g/L), whereas C3 levels and C1 esterase inhibitor function were normal. Cryoglobulins were absent. Immunoelectrophoresis identified a serum IgM kappa paraprotein (13 g/L). Plasma viscosity was 1.56 mPa (normal range, 1.16–1.35 mPa) and β_2 microglobulin was 2.7 mg/L (normal range, 1.2–2.4 mg/L). Urinary protein electrophoresis and bone marrow examination were normal. Serum anti-interleukin-1 α autoantibodies were absent. An X-ray skeletal survey showed no signs of osteosclerosis.

An autologous serum skin test¹ was negative and the patient's serum did not release histamine from the basophils of low or high serum IgE healthy donors indicating absence of anti-Fc ϵ RI α or anti-IgE autoantibodies.²

A further 3-month course of TL01 phototherapy (20 treatments, total dose 114.54 J/cm²) was given and

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Figure 1 Urticarial eruption on the thighs of case 1.

almost complete remission (95%) of the urticarial vasculitis was again achieved.

Case 2

A 71-year-old woman was referred with a 25-year history of chronic intermittent urticaria and arthralgia. Individual urticarial lesions lasted more than 24 h. The rash was not controlled with antihistamines, but had responded to a 1-year course of oral steroids prescribed for concurrent polymyalgia rheumatica. Examination revealed scattered urticarial lesions on the trunk and limbs. Histology of a biopsy of a weal showed mild dermal oedema and a florid upper dermal perivascular infiltrate composed of eosinophils, neutrophils and

lymphocytes with associated mild leucocytoclasia and endothelial cell swelling (Fig. 2).

Full blood count revealed thrombocytosis ($563 \times 10^9/L$). The ESR was 25 mm/h. Renal and hepatic profiles and serological tests for hepatitis B and C virus were normal or negative. There were no cryoglobulins, anti-nuclear antibodies, antimitochondrial or antithyroid cytoplasm antibodies. Rose Waaler screen was negative. C3 and C4 levels and C1 esterase inhibitor function were normal. Immunofixation identified a serum IgM kappa paraprotein (4 g/L). Urinary Bence-Jones protein was absent whilst $\beta 2$ microglobulin was raised at 2.85 mg/L. A bone marrow examination showed 3% plasma cells present compatible with a monoclonal gammopathy of uncertain significance. Serum anti-interleukin-1 α autoantibodies were absent. An X-ray skeletal survey showed no signs of osteosclerosis. Basophil histamine release assays² using the patients serum and the basophils of two healthy low- and high-serum IgE donors were negative indicating that autoantibodies against Fc ϵ RI α or IgE were not present. An autologous serum skin test and TL-01 phototherapy were refused by the patient.

In 1974, Schnitzler described a patient with chronic nonpruritic urticaria with underlying leucocytoclastic vasculitis, bone pain with hyperostosis, intermittent fever and a monoclonal IgM gammopathy.³ Today, 'Schnitzler's Syndrome' is recognized as a specific entity that falls within the spectrum of cutaneous manifestations associated with the monoclonal gammopathies. The clinical and histopathological features of the 36 cases reported to date, however, are not homogeneous and beside typical cases fitting the original description,

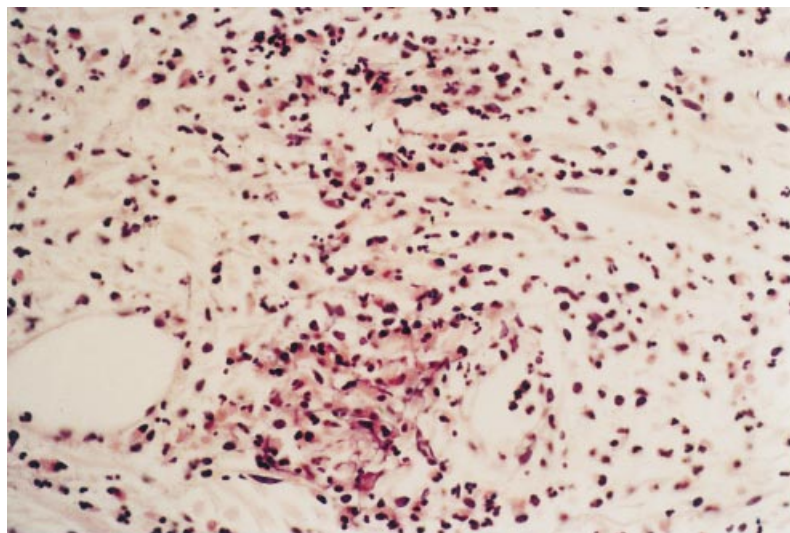


Figure 2 Photomicrograph ($\times 100$) of a biopsy taken from case 2, showing mild leucocytoclasia and an infiltrate of neutrophils, eosinophils and lymphocytes.

there are patients from whom some of the cardinal features, such as bone pain or fever, are absent.⁴ Additionally, sporadic association with other conditions such as peripheral neuropathy⁵ or pseudoxanthoma elasticum⁶ have been described.

The monoclonal gammopathy is generally of the IgM kappa type, although a patient with features of SS and an IgG monoclonal gammopathy has also been reported.⁷ Usually, SS dysproteinaemia has a benign evolution. However, seven of the 36 patients reported developed a lymphoproliferative malignancy in the course of time⁸ and careful followup is necessary.

In order of frequency, other associated biochemical abnormalities include: an elevated ESR rate, leukocytosis, a positive urine Bence–Jones protein, anaemia and thrombocytosis, hypocomplementemia, positive antinuclear antibodies, positive rheumatoid factor, cryoglobulinemia.⁴ All these findings, as well as the raised $\beta 2$ microglobulin and plasma viscosity of our patients, may also occur in patients with an isolated monoclonal gammopathy.

In two cases of SS a genetic deficit of C4 was described.⁹ Our first patient had a low C4, but normal C1 esterase inhibitor. The C4 phenotype was not investigated and we have no information on C4 levels in other family members, although none gave a history of angioedema/urticaria.

The histological changes of skin biopsies of patients with SS are not uniform, possibly depending on the age and dynamic evolution of the urticarial lesions. They range from mild perivascular chronic inflammation without fibrinoid changes and negative DIF, to frank leukocytoclastic vasculitis and positive DIF with C₃ and/or IgM deposits in the dermal vessels. According to a recent histopathological review of 15 cases of SS, clearcut features of leukocytoclastic vasculitis are generally absent and the most common finding is that of a dermal neutrophilic infiltrate in a predominantly superficial perivascular distribution.¹⁰

The pathogenesis of the urticaria in SS is unclear. Immune complex deposition may play a major role in those SS patients who have clear histological features of leukocytoclastic vasculitis and positive DIF.

Anti-interleukin-1 α autoantibodies have been found in the serum of seven patients and credited with a pathogenetic role.^{5–11} However, such autoantibodies have also been demonstrated in healthy subjects and have not been found in all patients with SS,⁴ including the two reported here.

de Castro and colleagues observed that the histopathological features found in nine out of 15 cases of SS are reminiscent of those described by Grattan *et al.* in

the autologous serum skin test response of patients with chronic idiopathic urticaria with serum histamine-releasing antiFc ϵ RI α or anti-IgE autoantibodies.^{10,12} Recently such autoantibodies have been identified in approximately one-third of patients with chronic idiopathic urticaria.¹³ We have found functional autoantibodies in the serum of three patients with biopsy-proven urticarial vasculitis (unpublished data), although the frequency overall in patients with urticarial vasculitis is not known. Additionally, it is not known whether these autoantibodies are present in patients with SS. We investigated both patients in this report for the presence of such autoantibodies, using the autologous serum skin test *in vivo*¹ and basophil histamine release assays *in vitro*.² All tests were negative. Whilst we cannot exclude the presence of nonhistamine-releasing autoantibodies or low levels of functional autoantibodies, it seems unlikely that they were playing an important role in the pathogenesis of the urticaria in these two patients.

Therapy of the urticaria in SS is difficult. Antihistamines are ineffective. Nonsteroidal anti-inflammatory drugs, dapsone, chloroquine, colchicine and immunosuppressive treatments, including cyclosporin and intravenous immunoglobulins have been tried in different patients with contradictory and often disappointing results. Systemic corticosteroids, alone or in combination, are sometimes helpful but high doses and long-term treatment are generally necessary.⁴

In one previously reported case, PUVA therapy induced a rapid regression of the urticaria and allowed a significant reduction of the dose of oral steroids.¹⁴ The almost complete remission of the urticaria induced by narrow band UVB phototherapy (TL-01) in one of our patients would support the use of ultraviolet light therapy in SS.

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