

Schnitzler's syndrome with prominent neutrophil infiltration misdiagnosed as Sweet's syndrome: a typical example of urticarial neutrophilic dermatosis

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Summary

Schnitzler's syndrome is a rare disorder of unknown aetiology characterized by a chronic urticarial eruption, intermittent fever and monoclonal gammopathy. We encountered an interesting patient with this syndrome, who had been misdiagnosed for 10 years as having Sweet's syndrome because of the histopathological picture, which was a prominent perivascular and interstitial neutrophilic infiltrate in the dermis with leucocytoclasia but without vasculitis. An urticarial eruption with this histopathological feature has recently been categorized as neutrophilic urticarial dermatosis, and it is strongly indicative of an associated systemic disease, mainly Schnitzler's syndrome and other inflammatory diseases. We therefore need to be cautious not to confuse Schnitzler's syndrome with Sweet's syndrome. Further, the serum interleukin (IL)-6 levels, but not those of other cytokines and chemokines, correlated with the disease activity in our patient, suggesting that IL-6 may be involved in some of the disease processes, including neutrophil infiltration.

Schnitzler's syndrome is a rare disorder defined by a chronic urticarial rash and monoclonal gammopathy (usually IgM) with at least two of the following features: intermittent fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, increased erythrocyte sedimentation rate (ESR), leucocytosis, and/or morphological bone abnormality. Patients are often initially considered to have lymphoma or adult-onset Still's disease.¹ The mean age at correct diagnosis is 60 ± 12 years, with a mean delay of 5.4 years, and the male : female ratio is 1.45.¹ Our patient was thought to have Sweet's syndrome because of the histopathological finding indicative of urticarial neutrophilic dermatosis.

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Report

A 49-year-old Japanese man visited us with a 10-year history of recurrent episodes of eruptions and fever of 38–39 °C. A skin biopsy had been taken at another hospital 9 years previously, and the patient had been diagnosed as having Sweet's syndrome. He was initially given colchicine without any effect.

On physical examination when he presented to us, he was found to have urticarial erythema (Fig. 1) despite being under treatment with oral betamethasone 2 mg/day. He had slight myalgia, arthralgia and tibial bone pain, but no lymphadenopathy or hepatosplenomegaly.

Laboratory investigations showed increased ESR (> 100 mm/h; normal range 0–20), increased C-reactive protein (CRP) (3.92 mg/dL; < 0.40 mg/dL) and leucocytosis ($15.89 \times 10^9/L$ with 89.7% neutrophils; $4-11 \times 10^9/L$ with 40–60% neutrophils). Tests were negative for antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, circulating immune complexes and cryoglobulins. CH50 was high



Figure 1 Urticarial eruptions on the trunk.

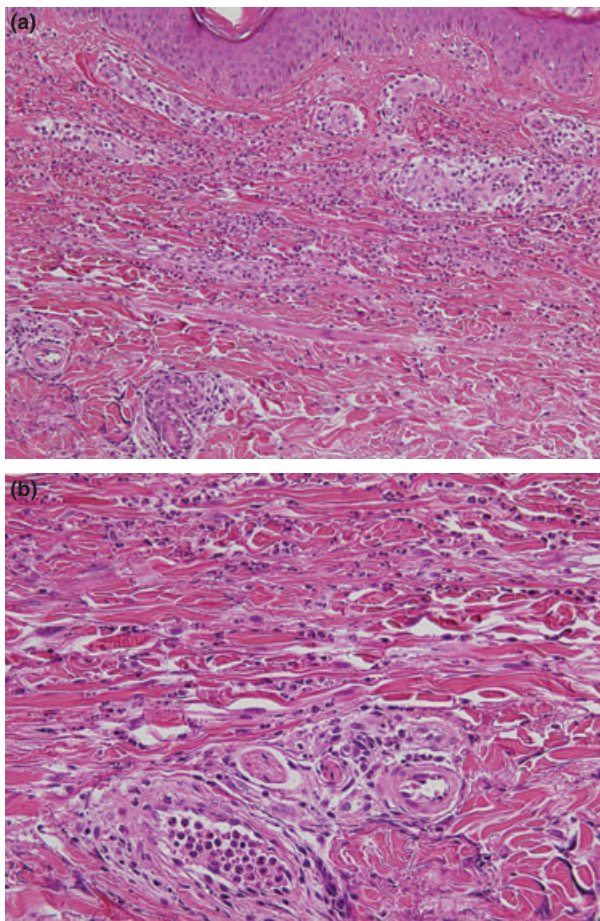


Figure 2 Histopathological picture of the eruption. (a) Dense inflammatory cell infiltration in the upper and middle dermis, mainly composed of mature neutrophils, not only around dilated capillaries but also in the dermal interstitium. Neutrophils are also seen within the capillary walls, but leucocytoclastic vasculitis is absent. (b) Neutrophil infiltration with nuclear debris. Haematoxylin and eosin, original magnification (a) $\times 100$; (b) $\times 200$.

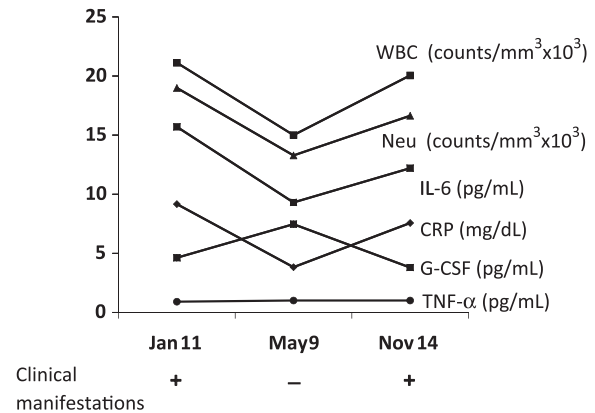


Figure 3 Measurements of cytokines and other clinical parameters at different time points. C-reactive protein levels and white blood cell counts correlated well with fluctuation of disease activity.

(61 U/mL; normal range 30–50 U/mL), and serum ferritin was low (24.2 ng/mL; 39.4–340 ng/mL). Protein electrophoresis detected a monoclonal IgM kappa band with a serum IgM concentration of 2070 mg/dL (35–220 mg/dL), raising the possibility of Schnitzler's syndrome. Serum IgA and IgG concentrations were slightly decreased. Kappa-type Bence-Jones proteinuria was detected, but bone-marrow examination did not find any evidence of lymphoproliferative disease.

Histological examination of a skin biopsy found a dense inflammatory cell infiltrate in the upper and middle dermis, mainly composed of mature neutrophils with nuclear debris, not only around capillaries but also in the dermal interstitium, with minimal oedema. Neutrophils were also found within the dilated capillaries, which displayed endothelial cell swelling, but leucocytoclastic vasculitis was absent (Fig. 2a,b). Results of direct immunofluorescence studies were negative. On skeletal survey, no osteolytic or osteosclerotic lesions were found.

The patient was put on oral potassium iodide 900 mg/day, which had no beneficial effect, but dapsone (50–75 mg/day) resulted in partial but significant improvement. There have been fewer episodes of fever and eruptions with a reduced dose of betamethasone (1.5 mg/day).

During the course of the disease, we measured serum levels of several cytokines and chemokines at three time points (Fig. 3). CRP levels, whole white blood cell counts and neutrophil counts correlated well with the fluctuation of disease activity. Serum IL-6 levels were high and also correlated with disease activity. Serum tumour necrosis factor (TNF)- α and granulocyte

colony-stimulating factor (G-CSF) levels were not increased, and IL-1 β levels were under the detectable limit.

This case highlights the need for differentiation between Schnitzler's syndrome and Sweet's syndrome. Similar to those in Schnitzler's syndrome, erythematous skin lesions and fever often occur repeatedly in Sweet's syndrome, and monoclonal gammopathy may be regarded as an associated haematological disorder. However, the typical skin lesions of Sweet's syndrome are tender erythematous papules and raised oedematous plaques, and they are thus distinct from urticarial eruptions. We believe that the main reason for the previous confusion between the two conditions was based on histopathology. Schnitzler's syndrome has heterogenous histopathological findings, such as neutrophilic urticaria, leucocytoclastic vasculitis, lymphocytic urticaria and spongiotic dermatitis. The commonest form of these is neutrophilic urticaria without leucocytoclastic vasculitis, and neutrophils are found in and around the walls of superficial dermal vessels, although eosinophils are present only rarely.² Interestingly, some cases show more neutrophils with interstitial distribution and with intense leucocytoclasia, compared with those usually seen in the neutrophilic variant of common urticaria.^{2,3} Kieffer *et al.*³ recently proposed the term 'neutrophilic urticarial dermatosis' to describe this phenomenon. They speculated that this urticarial reaction might be one of the cutaneous expressions of autoinflammation and that it might indicate an associated systemic disease, such as Schnitzler's syndrome, adult-onset Still's disease, lupus erythematosus, and the hereditary autoinflammatory fever syndromes. For diagnostic differentiation, the neutrophilic dermal infiltrate is usually much denser in Sweet's syndrome than in neutrophilic urticarial dermatosis, and dermal oedema is usually lacking in the latter.³

Several inflammatory cytokines may be involved in the aetiology of Schnitzler's syndrome. Serum levels of IL-6, a possible inducer of Ig production, are increased,^{1,4,5} and we found they correlated with fluctuation of disease activity under continuous treatment without changes in medication. IL-1 stimulates IL-6 production, and the IL-1 receptor antagonist anakinra rapidly improves disease activity.^{3,6,7} Circulating serum IL-1 levels do not seem to be increased,⁴ probably because they can be difficult to detect. Indeed, peripheral mononuclear blood cells from one patient⁶ had significant IL-1 production after stimulation, in addition to increases in IL-6 and TNF- α . Regarding neutrophil infiltration, IL-1 can induce adhesion molecule expression on endothelium and local chemokine production

for neutrophil recruitment. IL-6 causes neutrophilia either by neutrophil mobilization from the marginated pool in the circulation or by release of neutrophils from the bone marrow.⁸ The serum G-CSF level was normal in our case despite reports of its elevation in Sweet's syndrome⁹ and in one case of Schnitzler's syndrome.⁴ Serum granulocyte-macrophage colony-stimulating factor, IL-17 and plasma IL-8 levels also remained within normal limits (not shown).

Paraproteinaemia in Schnitzler's syndrome is another issue of concern with neutrophil infiltration. Paraproteins could activate complement and cause endothelial damage, leading to vasculitis and neutrophil infiltration. Vasculitis and cutaneous IgM deposits cannot be detected in many cases of Schnitzler's syndrome,¹ including ours. The observation of a similar histopathological picture in adult-onset Still disease³ also does not support a positive role for paraproteinaemia in neutrophil infiltration. On the other hand, IgA gammopathy is often associated with neutrophilic dermatoses, such as pyoderma gangrenosum and subcorneal pustular dermatosis. It needs to be elucidated whether paraproteinaemia and neutrophil infiltration are mutually linked in Schnitzler's syndrome or if they are an independent outcome of the disease process involving autoinflammation.

Finally, the partial effectiveness of dapsone may reflect its inhibition of neutrophil function. Based on our findings, not only anakinra but also tocilizumab, a monoclonal antibody against the IL-6 receptor, may be promising treatment choices⁷ and warrant further study.

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