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A patient with urticarial lesions, recurrent fever, and IgM-type monoclonal gammopathy

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Abstract

Schnitzler syndrome is a rare acquired autoinflammatory syndrome. It presents with an urticarial rash and a monoclonal gammopathy, usually of the IgM kappa type. In addition, patients can present with bone and/or joint pain, recurrent fever, asthenia, weight loss, myalgia, headache, lymphadenopathy, hepatomegaly, or splenomegaly. An elevation of blood inflammation markers is commonly found. Skin biopsy of the urticarial rash reveals neutrophilic infiltrate, known as neutrophilic urticarial dermatosis. To confirm the diagnosis, two sets of diagnostic criteria have been established. The syndrome shares many features with other autoinflammatory disorders, such as adult-onset Still's disease and *NLRP3*-auto-inflammatory disorders (*NLRP3*-AID, formerly known as cryopyrin-associated periodic syndromes, or CAPS). The pathogenesis of the disease is not yet fully understood; however, it is believed that interleukin (IL)-1β plays a crucial role and explains the excellent effectiveness of IL-1 blocking agents. It is a chronic disease, and some patients develop lymphoproliferative disease, and seldom AA amyloidosis.

Keywords: Schnitzler syndrome, urticarial rash, monoclonal gammopathy

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Case presentation

A 71-year-old female patient with arterial hypertension and hyperlipidemia presented to the dermatology clinic with complaints of an urticarial non-pruritic rash that resolved in 24 hours, intermittent fevers with a temperature up to 38.5 °C, and arthralgia.

She first noticed the rash 2 years prior, and it has been present almost daily since. Pain in her knees and left elbow was usually present during the night and resolved with physical activity. Fever was first observed about a year and a half after the first appearance of the dermatological signs of the disease, a few days after receiving a second dose of a COVID-19 vaccine. At that time, she was also treated for urinary tract infection at the clinic for infectious diseases. After receiving two different antibiotics, fever and elevated inflammatory markers persisted, and an infectious cause of the fever was ruled out by an infectious disease specialist. She was also examined by a rheumatology specialist for adult-onset Still's disease (AOSD). An autoimmune workup with rheumatoid factor, antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), anti-neutrophil cytoplasmic antibody (c-ANCA), anti-ENA, and complement testing was insignificant. However, elevated inflammatory markers with C-reactive protein (CRP) of 120 mg/l (< 0.5 mg/dl), erythrocyte sedimentation rate (ESR) of 55 mm/h (0–25 mm/h), and leukocytosis (12.2 × 10^9/l) were noted. The diagnosis of AOSD was not confirmed.

At the first presentation to our clinic a few months later, the patient presented with urticarial macules and papules, coalescing in plaques located mostly on the trunk and extremities (Fig. 1). The rash persisted despite antihistamine therapy. The patient did not suffer from myalgia, asthenia, or headache. No lymphadenopathy was observed. Laboratory findings revealed elevated inflammatory markers with CRP of 63 mg/l, ESR 31 mm/h, and leukocytosis (12.2 × 10^9/l). IgM kappa monoclonal gammopathy was observed (1.7). An autoimmune workup with ANA, ANCA, anti-ENA, complement levels, and cryoglobulins was negative. A punch biopsy of the skin revealed superficial, perivascular, and dermal interstitial neutrophilic infiltrate and was consistent with neutrophilic urticarial dermatosis (NUD) (Fig. 2). Direct immunofluorescence was unrevealing. Abdominal ultrasound revealed mild splenomegaly. The patient was referred to hematology for further evaluation of her monoclonal gammopathy. Evaluation by hematologists revealed monoclonal gammopathy of undetermined significance. The results of the above workup and her symptoms of chronic urticarial rash without pruritus, fevers, arthralgias with a negative rheumatologic workup, and presence of IgM kappa monoclonal gammopathy raised the suspicion of Schnitzler syndrome. The patient met the Lipsker and Strasbourg criteria for Schnitzler syndrome. The interleukin (IL)-1 receptor antagonist (anakinra) was suggested, but it has not been started yet.

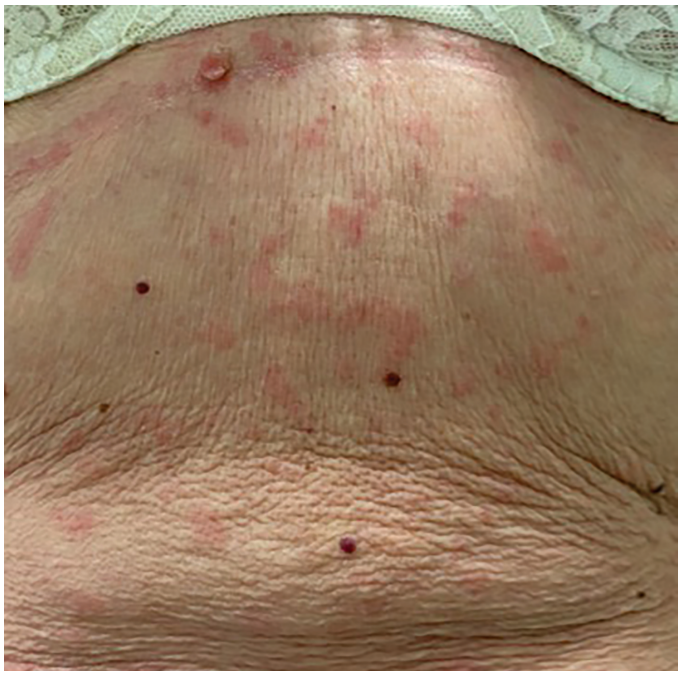

Figure 1 | Urticarial macules and papules, coalescing in plaques located mostly on the trunk and extremities.

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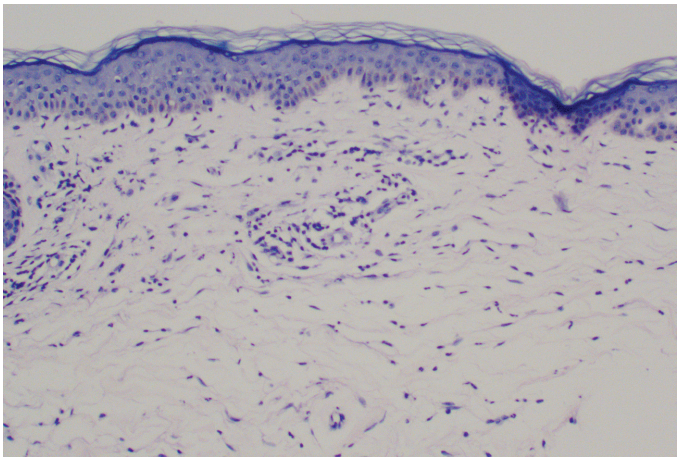

Figure 2 | A skin biopsy revealed superficial, perivascular, and dermal interstitial neutrophilic infiltrate and was consistent with neutrophilic urticarial dermatosis (courtesy of Borut Žgavec).

Discussion

Schnitzler syndrome was first described in 1972 (1). It is a rare acquired autoinflammatory syndrome. Patients typically present with urticarial rash, fever, bone and/or joint pain, and lymphadenopathy. The syndrome is associated with monoclonal gammopathy, typically of the IgM type, less common of the IgG type (2). A link between monoclonal gammopathy and the clinical signs is yet to be determined.

The pathophysiology of the disease remains unclear; however, it is believed that IL-1β plays a crucial role and explains the excellent effectiveness of IL-1 blocking agents (3). Schnitzler syndrome patients have been described all over the world in various ethnic groups. The disease affects adults, and the median age at onset is 55 years. According to the literature, no pediatric case has ever been reported (2). There is no gold standard or genetic testing for Schnitzler syndrome. Two sets of diagnostic criteria have been established and revised based on patients. In 2001, Lipsker et al. developed the first diagnostic criteria, stating that the syndrome is characterized by urticarial rash and monoclonal IgM component plus at least two of the following criteria: fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, elevated ESR, leukocytosis, or abnormal findings on bone morphologic investigations (4, 5). This was revised by an expert meeting in 2013, known as the Strasbourg criteria (Table 1) (5, 6). Revision of both criteria based on patients showed that both are reliable (7).

Urticarial rash is present in all patients, usually on the trunk and limbs. It consists of slightly itchy rose-colored or red macules or papules that can coalesce into plaques. The rash lasts less than 24 hours and generally resolves without hyperpigmentation. Dermographism and a halo of constriction can be observed in some patients. Angioedema is not common (2). Usually, recurrent fever is present concomitantly with urticarial rash and joint or bone pain (7). Bone and joint pain occur in 40% of patients. The tibia, iliac bone, and femur are typically involved, but other locations have been reported as well (8). Skeletal imaging findings are not specific. Standard radiographs usually show sclerotic lesions; however, lytic lesions can also be found. Bone scintigraphy is thought to be the examination of choice to detect bone damage, and magnetic resonance imaging (MRI) can also be performed (8). Other common clinical signs are headache, weight loss, asthenia, or myalgia. Lymphadenopathy, splenomegaly, and hepatomegaly can also be found.

Monoclonal gammopathy is present in all patients with Schnitzler syndrome. In about 88% of cases, IgM type monoclonal gammopathy is present, mainly associated with the kappa light chain. IgG type monoclonal gammopathy is infrequent and is referred to as variant Schnitzler syndrome. At diagnosis, the level of monoclonal component observed in patients is extremely variable (7). The laboratory findings also include elevated inflammatory markers such as CRP and ESR, and increased neutrophil level. Thrombocytosis and inflammatory anemia can also be detected (9). In addition, markers of abnormal bone remodeling (osteocalcin and bone-specific alkaline phosphatase) and increased vascular endothelial growth factor (VEGF) have been suggested as possible biologic markers (10). The histopathological findings are important because the Strasbourg criteria include the presence of dermal neutrophilic infiltrate as a minor criterion. Histopathology typically reveals perivascular and interstitial infiltrate of neutrophils with leukocytoclasia, with no sign of dermal edema or fibrinoid necrosis of the vessel walls, known as NUD (11). Other histopathological findings include vasculitis (12) and an appearance typical of urticaria (7).

Differential diagnosis of Schnitzler syndrome involves several diseases, especially chronic idiopathic urticaria, urticarial vasculitis, AOSD, *NLRP3*-AID, lymphoma, and Waldenström's disease. A histopathological finding of NUD is also associated with AOSD, LE, and CAPS (11).

The most successful therapies for Schnitzler syndrome are IL-1 blocking. According to the literature, anakinra, an IL-1 receptor antagonist, is especially effective (2). It was observed that clinical signs resolve within hours after the first injection (2). Furthermore, a multicentric retrospective cohort study confirmed its long-term effectiveness (13). Anakinra is delivered subcutaneously at a dose of 100 mg/day. Canakinumab, an IL-1β-specific antibody, has also been found effective (14). The efficacy of rilonacept, a recombinant fusion protein, has also been shown (15). Other treatments, such as colchicine, perfloxacine, interferon-alpha, and corticosteroids, were used to treat Schnitzler syndrome before IL-1 blocking therapies were available. However, these treatments were only moderately effective (2). IL-1 blocking therapies can achieve complete remission in 83% of patients (3). Some patients do not respond to anti IL-1. In that case, the diagnosis of Schnitzler syn-

Table 1 | **Strasbourg diagnostic criteria of Schnitzler syndrome.**

Obligate criteria	Minor criteria	Diagnosis
– Chronic urticarial rash and – Monoclonal IgM or IgG	– Recurrent fever[a] – Objective findings of abnormal bone remodeling with or without bone pain[b] – Neutrophilic dermal infiltrate on skin biopsy[c] – Leukocytosis and/or elevated C-reactive protein[d]	– Definite: two obligate criteria and at least two minor criteria if IgM, and three minor criteria if IgG – Probable: two obligate criteria and at least one minor criterion if IgM, and two minor criteria if IgG

[a]Must be › 38 °C and otherwise unexplained. Occurs usually, but not obligatory, together with skin rash.
[b]As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase.
[c]Usually corresponds to the entity described as "neutrophilic urticarial dermatosis"; absence of fibrinoid necrosis and significant dermal edema.
[d]Neutrophils › 10,000/mm³ and/or CRP › 30 mg/l.

drome should be reconsidered. If it remains certain, treatment with an IL-6 antagonist such as tocilizumab can be beneficial (16). IL-1 blocking agents are not effective on the monoclonal component, according to the literature (3). Schnitzler syndrome has a chronic evolution, with about 20% of patients developing lymphoproliferative disease, most commonly Waldenström's disease and more rarely AA amyloidosis (3).

Conclusions

Schnitzler syndrome is an acquired autoinflammatory syndrome that should be suspected in patients with monoclonal gammopathy and urticarial eruption, especially in the presence of recurrent fever. Two sets of diagnostic criteria were established to aid in the diagnosis. Remission of inflammation-linked symptoms can be completely achieved by IL-1 blocking therapy. However, it does not affect the development of hematological disorders, and therefore careful monitoring is still advised in every patient.

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