



Review

Schnitzler syndrome

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Abstract

Schnitzler syndrome is characterized by monoclonal IgM gammopathy, urticaria, recurrent fever, evidence of inflammation, bone pain, and arthralgia, occasionally in combination with lymphadenopathy and/or hepatosplenomegaly. Only about 80 cases have been reported to date. Development of a hematological malignancy is the main complication. Recent reports of remissions induced by IL-1 receptor antagonist therapy shed new light on the pathophysiology of the disease.

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In 1972, the French dermatologist Liliane Schnitzler described a syndrome of monoclonal IgM gammopathy, urticaria, recurrent fever, inflammation, bone pain, and arthralgia, occasionally with lymphadenopathy and/or hepatosplenomegaly. Only about 80 cases have been reported since then [1–28]. Development of a hematological malignancy is the main complication. Recent reports that IL-1 receptor antagonists were dramatically effective shed new light on the pathophysiology of the disease [3,4,10,11].

1. Clinical features of Schnitzler syndrome

Schnitzler syndrome is slightly more common in males than in females (sex ratio, 1.45). Mean age at diagnosis is 60 years.

1.1. Urticaria

Urticaria is a consistent feature [2]. The eruption usually affects the trunk and limbs, sparing the face and neck. Individual lesions measure 0.5–3 cm in diameter but may coalesce. They clear completely within 12–24 h. New lesions

usually develop every day, although lesion-free periods of 1–2 weeks may occur. Pruritus is minimal or absent initially then develops over time in about 30% of cases. Neutrophilic urticaria is the most common histological pattern, although a few cases of leukocytoclastic vasculitis have been reported [13,18,29].

1.2. Fever

Recurrent fever of about 40 °C occurs in 90% of patients [2,30]. Chills are uncommon, and the fever spikes are usually well tolerated. The fever and urticaria are not correlated.

1.3. Lymphadenopathy and hepatosplenomegaly

Lymphadenopathy is found in 50% of patients [2,30]. The nodes measure 2–3 cm and are usually located at the axillary and inguinal sites, although the neck may be affected. Histology shows non-specific reactive hyperplasia [2,20,30]. Hepatosplenomegaly is less common (about 30% of patients).

1.4. Bone and joint manifestations

Bone pain is a feature in about 70% of patients [31]. The pelvis, femurs, and tibias are the most commonly involved sites [31], although pain may occur in the spine, clavicles,

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and forearms. Radiographs show foci of osteosclerosis, which are visible as hot spots by bone scintigraphy [2,7,11,24]. In the distal femur and proximal tibia, a periosteal reaction with increased radionuclide uptake is present [4,9,25,30,32]. On magnetic resonance imaging scans, the metaphyses generate low signal on T1 images and high signal on T2 images [25]. Bone biopsies are normal or contain non-specific infiltrates of inflammatory cells [2,24,25]. Inflammatory arthralgia and arthritis occur in 60% of patients [2]. Erosions are not a feature of Schnitzler syndrome.

1.5. Other clinical manifestations

Manifestations reported in patients with Schnitzler syndrome include peripheral neuropathy with or without anti-myelin-associated-glycoprotein antibodies [13,15,33], nodular regenerative hyperplasia of the liver [34], and arterial thrombosis with antiphospholipid antibodies [14]. These are merely chance associations.

2. Laboratory findings

2.1. Monoclonal immunoglobulin

Presence of a monoclonal immunoglobulin is a hallmark of Schnitzler syndrome. Until very recently, this monoclonal component was consistently an IgM, and the light chain was kappa in 90% of cases [2]. Two patients had two monoclonal components, an IgM kappa and either an IgG kappa [35] or an IgA lambda [36]. However, in six recent cases there was a single IgG monoclonal component; the light chain was kappa in 5 cases and lambda in 1 case [10,17,18,37]. In a single patient, no monoclonal component was identified [28].

At diagnosis, most patients meet criteria for monoclonal gammopathy of undetermined significance. The titer of the component is low, and there is no plasma cell proliferation.

2.2. Other laboratory tests

The erythrocyte sedimentation rate and C-reactive protein level are elevated. Leukocytosis is noted in 90% of cases. Thrombocytosis and inflammatory anemia are found in about 10% of patients. Low serum complement levels have been reported [15,38,39], with the most common cause being complement consumption related to cryoglobulinemia, although genetic deficiencies have been identified in a few patients [15,39].

3. Establishing the diagnosis of Schnitzler syndrome

The diagnostic criteria developed by Lipsker et al. [2] (Table 1) can help to establish the diagnosis, provided differentials are confidently ruled out. An IgG monoclonal component does not rule out Schnitzler syndrome, although Lipsker's criteria require a monoclonal IgM [10,17,18,37].

Several of the major criteria for Still disease are also found in Schnitzler syndrome, including skin lesions, fever,

Table 1

Diagnostic criteria for Schnitzler syndrome developed by Lipsker et al. [2]

Urticaria AND monoclonal IgM AND at least two of the following:

- Fever
- Arthralgia or arthritis
- Bone pain
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- High erythrocyte sedimentation rate
- Leukocytosis
- Suggestive radiographic features

arthralgia, and high neutrophil counts [40,41]. In Still disease, the skin lesions are macules or maculopapules that worsen in the afternoon, and there is no monoclonal component. Patients with Schnitzler syndrome do not have high serum ferritin levels with decreased glycosylated ferritin, a pattern characteristic of Still disease [9]. Systemic lupus erythematosus and hypocomplementemic urticarial vasculitis (McDuffie syndrome) must be ruled out. In both conditions, evidence of vasculitis is seen in skin biopsy specimens, and serum C1q is low due to the presence of anti-C1q antibodies [2]. Serological tests for the hepatitis B and C viruses should be obtained routinely to rule out viral urticarial vasculitis [2].

Similarities exist between Schnitzler syndrome and several autoinflammatory syndromes, including cryopyrin-associated periodic syndromes (CAPS) and hyper-IgD syndrome (related to mutations in the mevalonate kinase gene) [42]. Disorders in the CAPS group include, from the least to the most severe, familial cold urticaria, Muckle–Wells syndrome, and chronic infantile neurologic cutaneous articular (CINCA) syndrome. Fever and rash are features shared by all these disorders. CAPS is related to a mutation in the *CIAS1* gene for cryopyrin, which regulates caspase activation and the NF- κ B pathway. A rash is also a feature of hyper-IgD syndrome. The adulthood onset of Schnitzler syndrome and negative family history for similar manifestations militate against an autoinflammatory syndrome. One patient with Schnitzler syndrome underwent testing for *CIAS1* mutation, which proved negative [10].

4. Pathophysiology

4.1. The monoclonal immunoglobulin

Monoclonal IgM deposits are found along the basement membrane of the skin or within the capillaries in 30% of cases [30]. Using immunoelectron microscopy studies and immunoblotting, Lipsker et al. identified IgM-kappa antiskin autoantibodies at the dermal-epidermal junction [43]. The presence of antiskin autoantibodies having the same isotype as the circulating monoclonal component suggests deposition of the monoclonal component in the skin [43]. It seems unlikely, however, that IgM deposits cause the eruption, as some patients lack IgM deposits. In addition, antiskin IgM autoantibodies have been identified in individuals who did

not have Schnitzler syndrome [30]. Finally, the monoclonal component is an IgG in a minority of patients with Schnitzler syndrome.

4.2. Proinflammatory cytokines

IL-1 is probably involved in the pathophysiology of Schnitzler syndrome. As early as 1991, Saurat et al. reported that 6 of 9 patients with Schnitzler syndrome had IgG autoantibodies to IL-1 [44] and suggested that these autoantibodies might increase the half-life of IL-1, thus causing the clinical manifestations. Another group found no evidence of autoantibodies in 2 patients [26]. However, interferon alpha, which increases the expression of IL-1 receptor antagonist (IL1RA), has been found to improve the clinical manifestations, supporting a pathophysiological role for IL-1 [20]. Even more importantly, IL1RA was dramatically effective in 6 patients who had Schnitzler syndrome refractory to numerous treatments [3,4,10,11]. IL-1 is involved in Still disease and in CAPS, which share many clinical and laboratory features with Schnitzler syndrome [45]. Studies are needed to confirm the pathophysiological role for IL-1, to determine the mechanisms leading to IL-1 elevation, and to identify the link between IL-1 and the monoclonal component.

5. Outcomes of Schnitzler syndrome

A hematological malignancy develops eventually in about 15% of patients. However, this proportion may be an underestimation, the malignancy may occur after many years, and follow-up was short in most reports of Schnitzler syndrome. In the first case, described by L. Schnitzler, Waldenström macroglobulinemia was diagnosed after 23 years [35]. Waldenström macroglobulinemia and IgM myeloma are the most common hematological malignancies in patients with Schnitzler syndrome [22].

6. Treatment

Although the treatment of Schnitzler syndrome is not standardized, IL1RA (anakinra) may be the treatment of choice in patients with highly active disease.

6.1. Conventional drugs

6.1.1. Skin lesions

Ibuprofen therapy may improve the skin lesions, although the effect is usually short-lived [2]. Antihistamines are not effective and should not be used, since there is no pruritus. Glucocorticoids are not effective when used in low dosages; high dosages may induce improvements but only at the cost of adverse effects that preclude long-term therapy [2,30]. Leukocyte migration inhibitors (colchicine and dapsone) have produced variable results [2,30]. Neither plasma exchange nor intravenous immunoglobulin therapy is effective [2,9,30]. PUVA therapy may lessen the rash [2,24,26].

Immunosuppressants are usually unhelpful, although cyclophosphamide or cyclosporin induced responses in a few patients [9,14,18].

6.1.2. Bone and joint manifestations

The bone pain and arthralgia usually respond to non-steroidal antiinflammatory drugs. Pamidronate therapy may alleviate the bone pain [2,30].

6.2. New drugs

– *Rituximab*. Only three patients with Schnitzler syndrome have been treated with rituximab. Dramatic improvements occurred in 1 patient, whose follow-up was 1 year. A fleeting improvement in the skin lesions was the only effect in another patient. No benefits were recorded in the third patient [3,5,6].

– *Thalidomide*. Thalidomide inhibits the production of proinflammatory cytokines. Marked improvements in the skin, joint, and systemic manifestations were recorded in 3 patients [16,10], including 2 who were followed up for more than 1 year. Severe neuropathy required rapid withdrawal of the drug in the remaining patient [10].

– *Anakinra*, or recombinant IL1RA, competes with IL-1 α and IL-1 β for IL-1 receptor type 1. Anakinra may be the treatment of choice in patients with Schnitzler syndrome. The two most striking cases were reported by Martinez-Tobaoda et al. and Eiling et al. [3,11]. Previous failed treatments were celecoxib, azathioprine, pamidronate, cyclosporin, interferon, infliximab plus methotrexate, intravenous immunoglobulins, and phototherapy in one patient [11]; and glucocorticoids, azathioprine, cyclosporin, and rituximab in the other patient [3]. With anakinra therapy, both patients achieved a remission within 1 week, which was sustained after 10 months. In the four other reported cases, similarly dramatic improvements were noted; follow-up was 18 months in one of these cases [4,10].

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