

The Schnitzler syndrome: Chronic urticaria and monoclonal gammopathy – an autoinflammatory syndrome?

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Summary

Schnitzler syndrome describes the simultaneous occurrence of monoclonal gammopathy and chronic urticaria with at least two additional minor symptoms (arthralgia, bone pain, fever of uncertain origin, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leukocytosis/thrombocytosis or increased bone density). Schnitzler syndrome is not well-known and very likely under-recognized. Comprehensive diagnostic examinations are necessary to rule out other diseases, especially those of hematologic origin. Close interdisciplinary collaboration is mandatory. The etiology of Schnitzler syndrome is unclear, but the rapid response to the interleukin-1 receptor inhibitor anakinra underlines the pivotal role which the proinflammatory cytokine interleukin-1 may play in the pathophysiology of this potentially autoinflammatory disorder.

Introduction

Schnitzler syndrome was first described in 1972 [1] and is characterized by the simultaneous occurrence of chronic urticaria and a monoclonal gammopathy. To a variable extent arthralgias, bone pain, fever, hepato- or splenomegaly, lymphadenopathy, increased erythrocyte sedimentation rate, leuko- and thrombocytosis as well as increased bone density occur [2]. Due to the spectrum of signs and symptoms, patients are frequently cared for by many different specialists. On average it takes 5.4 years after the appearance of the first symptoms to arrive at the diagnosis [2]. Because of the largely unknown etiology, therapy is also

a challenge. The interleukin-1 receptor antagonist anakinra (Kineret®) appears to be an efficacious and promptly acting treatment option [3–5]. The disease is presented with a view to diagnosis, differential diagnoses, pathogenesis and treatment on the basis of three patients.

Case reports

Patient 1

A 58-year-old man had been developing urticarial skin lesions with a preference for the trunk for about four years (Figure 1). Fever, fatigue, weight loss, joint and muscle pain, as well as leukocytosis and elevated CRP had been present even longer. There was no evidence for a lym-

phoma or a monoclonal gammopathy. Because of the working diagnosis of the adult form of Still disease, unsuccessful treatment attempts were made with cyclosporine, methotrexate, adalimumab, nonsteroidal antiinflammatory drugs and leflunomide. Only high-dose corticosteroids led to a moderate response. After administration of anakinra (100 mg s. c. daily), still assuming Still disease, skin lesions disappeared within 24 hours. After discontinuation of anakinra treatment, urticaria reappeared within 48 hours. The determination of immunoglobulin subclasses showed a monoclonal gammopathy of the IgM kappa type (4.87 g/l). Taking all these results together,

the diagnosis of Schnitzler syndrome was made. We recommended continuing treatment with anakinra. The patient has been lesion-free for 9 months (Figure 2), and his joint pain is milder.

Patient 2

A 54-year-old man had a six year history of chronic urticaria, predominantly on the trunk, as well as bone and joint pain. Two years after the appearance of the first symptoms a monoclonal gammopathy of the IgM kappa type was diagnosed. A plasmocytoma and other myeloproliferative diseases were excluded. The gammopathy was viewed as a

monoclonal gammopathy of undetermined significance and urticarial vasculitis was presumed to be the cause of the chronic urticaria. Systemic corticosteroid therapy (15 mg prednisolone daily) led to a moderate response; a therapeutic trial with azathioprine failed. When we first saw the patient, urticarial skin lesions were present, leukocyte count and CRP were elevated; monoclonal IgM kappa was 6.23 mg/l. The diagnosis of Schnitzler syndrome was made; neither cyclosporine nor rituximab led to improvement. Anakinra, on the other hand, produced a response within 24 hours. The patient himself has

administered 100 mg anakinra s. c. daily for 10 months. No skin lesions have appeared and corticosteroid therapy has been tapered off slowly.

Patient 3

A 52-year-old woman observed urticarial skin lesions since about 1 1/2 year, often together with fever bouts and reduced general well-being. Previously existing joint pains had increased in intensity. Despite extensive diagnostics, no cause for the urticaria could be found. With 30 mg prednisolone daily the patient was lesion-free; dose reduction led to a prompt relapse of skin lesions. Therapy attempts with dapsone and antihistamines were unsuccessful. Parameters of inflammation kept rising, as joint and muscle pain increased. She lost 10 kg weight. A monoclonal gammopathy of the IgM kappa type (2.78 mg/l) was found; hemato-oncologic diseases were excluded. After dermatologic consultation, the diagnosis of Schnitzler syndrome was made. She has been treated for 5 months with 100 mg anakinra s. c. daily. Her symptoms disappeared 24 hours after the first dose.



Figure 1: Patient 1: Typical urticarial lesions of Schnitzler syndrome predominantly on the trunk with only mild pruritus.



Figure 2: Patient 1: Complete remission of urticarial lesions with 100 mg anakinra subcutaneously daily for nine months.

Definition and epidemiology

Lipsker et al. [2] require that at least two further minor criteria-in addition to the major criteria chronic urticaria and monoclonal gammopathy-must be present for the diagnosis Schnitzler syndrome (Table 1). The paraproteinemia is usually a monoclonal IgM gammopathy; in 94 % the light chain type kappa is present [3]. A monoclonal gammopathy of the IgG type is viewed as a rarer variant of Schnitzler syndrome [6–11]. Bence-Jones proteinuria occurs in 29 % of patients [3]. At the time of first manifestation of Schnitzler syndrome, a paraprotein can often not be identified. Women are more frequently affected than men (1.6: 1) [3]. Most patients documented to date are of Western European origin; only three patients of Japanese ancestry have been reported [6, 12, 13]. The low number of cases diagnosed outside of Europe may be due to a lack of familiarity with Schnitzler syndrome.

Signs and symptoms

The disease usually starts around the age of 50 years with urticarial skin lesions and characteristically with an initially

Table 1: Diagnostic criteria for Schnitzler syndrome. To fulfill the diagnostic criteria of the Schnitzler syndrome, at least two major and two minor criteria have to be fulfilled. Table adapted from Lipsker et al., 2001 [1].

Major criteria	Minor criteria
Chronic urticaria	Intermittent fever
Monoclonal gammopathy IgM (or IgG)	Arthralgia or arthritis
	Bone pain
	Lymphadenopathy
	Hepato- or splenomegaly
	Elevated ESR and/or leukocytosis
	Bone densities

mild pruritus. During the course of the disease up to 45 % of patients report intensified itching. The individual lesions last for about 12–36 hours, are only slightly elevated, small and have a predilection for the trunk. Skin lesions appear almost on a daily basis. Fever bouts are observed in about 88 % of patients and are often accompanied by flares of urticaria, reduced general well-being, fatigue and weakness [3]. The intervals between individual fever bouts vary between daily and twice yearly [2]. After months to years 80 % of patients additionally develop arthralgias, especially of the large joints [3, 14]. Bone pain, mostly of the tibia and the pelvic bones, occurs in 72 % [3].

Differential diagnoses and mandatory diagnostic approach

Table 2 lists possible differential diagnostic considerations for Schnitzler syndrome. As Schnitzler syndrome is, in principle, a diagnosis of exclusion, an extensive and careful diagnostic approach involving various medical specialties (rheumatologists, hematologists and dermatologists) is required. Monoclonal gammopathy is essential to making the diagnosis and can help exclude many other causes of chronic urticaria. A monoclonal gammopathy together with cutaneous lesions occurs for example in Waldenström macroglobulinemia, amyloidosis, plasmacytoma, scleromyxedema and necrobiotic xanthogranuloma. Cutaneous lesions in these diseases are almost never urticarial. Monoclonal gammopathy of undetermined significance (MGUS) as the most common form of monoclonal gammopathy can most easily be differentiated from Schnitzler syndrome by the diffuse lymphoid infiltration of bone marrow. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, mono-

Table 2: Differential diagnoses of Schnitzler syndrome. Adapted from de Koning et al., 2007 [2].

Autoimmune diseases
Adult form of Still disease
Systemic Lupus erythematosus
Acquired C1-esterase inhibitor deficiency
Hematologic diseases
Monoclonal gammopathy of undetermined significance (MGUS)
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes)
Waldenström macroglobulinemia
Lymphomas
Multiple myeloma
Hereditary autoinflammatory syndromes
Cryopyrin-associated syndromes (CAPS)
Familial cold urticaria
Muckle-Wells syndrome
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)
Infectious diseases
Hepatitis B and C
Chronic meningococcemia
Other
Idiopathic chronic urticaria
Hypocomplementemic urticarial vasculitis
Delayed pressure urticaria
Cryoglobulinemia
Behçet syndrome
Mastocytosis

Abbreviations

CAPS: cryopyrin-associated syndromes

CINCA: chronic infantile neurologic cutaneous and articular syndrome

IgM: immunoglobulin M

IgG: immunoglobulin G

IL-1: interleukin-1

IL-1-RA: interleukin-1 receptor antagonist

MGUS: monoclonal gammopathy of undetermined significance

POEMS: polyneuropathy, organomegaly, Endocrinopathy, monoclonal gammopathy and skin changes

TNF: tumor necrosis factor

clonal gammopathy and skin changes) is a rare multisystem disease. The circulating monoclonal antibody classes (IgG and IgA lambda antibodies) as well as the morphology of cutaneous lesions (hyperpigmentation, limb edema, thickening of the skin, hypertrichosis and plethora) differentiate POEMS syndrome from Schnitzler syndrome [15]. Similar to Schnitzler syndrome, the adult form of Still disease presents with joint and muscle pain as well as fever bouts. Cutaneous lesions in Still disease are more maculopapular, and gammopathy does not occur. Hereditary autoinflammatory disease such as the cryopyrin-associated periodic syndrome (CAPS) and the Muckle-Wells syndrome must also be excluded. Both are accompanied by periodic fever bouts and urticarial skin lesions. Usually there is a positive family history; paraproteins cannot be identified [16].

Pathophysiology

The pathophysiology of Schnitzler syndrome is largely unclear. Histologic studies provide little information; perivascular infiltrates containing few neutrophils, eosinophils, lymphocytes and histiocytes in the superficial dermis have been described [17–18]. Deposits of monoclonal IgM at the dermoepidermal junction as well as on capillary walls [19, 20] suggest that the deposits induce a local inflammatory reaction [21]. IgM deposits can be seen in only 25 % of patients with Schnitzler syndrome and also occur in patients with Waldenström macroglobulinemia without urticaria, so that it can be assumed that the deposits more likely represent an epiphenomenon than being causative.

The discovery of IgG₃ autoantibodies towards cellular proteins and of IgG₂ antibodies specific for the α chain of IgE receptors (Fc ϵ RI) led to the presumption that autoimmune reactions mediated by helper T cells of type 1 (TH1) play a role in the pathophysiology. Elevated interleukin (IL)-6 levels were also found [12, 22]. IL-6 is the main mediator of the acute phase reaction characterized by fever, leukocytosis, increased vascular permeability and an elevation of acute phase proteins (CRP). Direct effects of IL-6 on B-cell differentiation could be the cause of the gammopathy [20].

Saurat et al. [23] were able to demonstrate IgG antibodies to the cytokine IL-1 α in

patients with Schnitzler syndrome. It was postulated that the antibodies increase the biologic half-life of IL-1 α , affect tissue distribution and thus increase systemic effects of IL-1. The antibodies also occur in 18 % of the healthy population. This observation could not be verified by others [12, 14, 24–28]. That IL-1 plays a central role in the pathophysiology of Schnitzler syndrome is shown by the excellent success of the IL-1 receptor antagonist anakinra in treatment.

Therapy

Therapy of Schnitzler syndrome was considered difficult for a long time. Antihistamines have no effect on the urticarial cutaneous lesions, analgetics and antipyretic agents can only limitedly alleviate joint and bone pain and fever bouts. Although high-dose corticosteroids led to a significant response in 39 % of patients [2], they are unsuitable for long-term therapy. Treatment successes with interferon- α [2, 5, 11, 29–30] and thalidomide have been reported [7, 31–32]. A retrospective analysis showed that many patients responded only slightly or not at all to these two substances [3]. In a recent article a response to the gyrase inhibitor pefloxacin in 11 patients was reported [33]. Pefloxacin especially improved urticaria, but osteoarthritic complaints continued. Therapy had to be discontinued in three patients due to side effects, while one patient did not respond. The mechanism of action was explained by a possible effect of fluoroquinolones on the regulation of messenger RNA for cytokines as well as their receptors [34].

Rituximab is a monoclonal chimeric CD20 antibody that selectively binds on CD20-positive B lymphocytes and induces destruction of the B cells. Under the assumption that B-cell destruction is accompanied by a decline in monoclonal gamma globulins, we administered rituximab to patient 2. The number of peripheral B lymphocytes declined drastically, the level of monoclonal gamma globulins, however, decreased only slightly, and symptoms persisted [4]. A further treatment attempt with rituximab was also unsuccessful [5]. The persistence of symptoms despite reduction of paraproteins supports the assumption that paraproteins are not of primary relevance for the pathophysiology of Schnitzler syndrome [4].

In all three cases we treated, there was an excellent response to anakinra. Anakinra is the recombinant form of the human IL-1 receptor antagonist (IL-1-RA). It binds to the IL-1 receptor but does not induce signal transduction and thus competitively inhibits the binding of IL-1 α and IL-1 β to the IL-1 receptor. It is successfully employed for rheumatoid arthritis and other autoinflammatory diseases such as Muckle-Wells syndrome, TRAPS and hyperimmunoglobulinemia D syndrome [35–37]. All patients report a cessation of urticarial cutaneous lesions within 24 hours of the first subcutaneous administration of 100 mg anakinra. Accompanying symptoms such as bone and joint pain were significantly reduced subsequently, parameters of inflammation returned to the normal range. Paraproteins were still present. De Koning et al. [3] report a complete remission in all eight patients treated with anakinra. The longest follow-up in the meantime is three years with still continuing good efficacy. The only side effect observed is redness at the injection site [3, 4].

Outlooks

The mortality of patients with Schnitzler syndrome with a survival rate of 94 % after 15 years is comparable with the survival rate of the average population of the same age group in the Netherlands [3], but they have an increased risk of lymphoproliferative diseases. In the cohort studies by de Koning et al. [3] 15 % of the cases developed a Waldenström macroglobulinemia 10 years after the initial manifestation of symptoms. One patient developed a lymphoplasmacytic B-cell lymphoma [38], another myeloma [39], and a third a marginal zone B-cell lymphoma [32]. Up to now no cases of lymphoproliferative diseases have been reported in the patient collective with IgG paraproteinemia. A long-term follow-up of all patients with Schnitzler syndrome including regular blood and bone marrow tests is therefore indicated. Routine neurologic exams should be conducted, as monoclonal gammopathies are associated with peripheral neuropathy in 7–10 % [40].

The rapid and long-lasting therapy success with anakinra supports the assumption that Schnitzler syndrome is primarily an autoinflammatory disease. In

patients with Schnitzler syndrome, a treatment trial with anakinra is highly recommended as it can currently be considered the therapy of first choice. To this date no randomised and controlled study can prove this assumption and can also not be expected for the future due to the low frequency of the disease. <<<

Conflict of interest

None.

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