

CASE REPORT

Schnitzler syndrome: Treatment failure to rituximab but response to anakinra

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Schnitzler syndrome is a rare disease characterized by a chronic urticarial rash and a monoclonal gammopathy. The exact pathogenesis is still uncertain and treatment remains a challenge. Here, we report a patient who was only recently given the diagnosis of Schnitzler syndrome although the typical symptoms had been present for about 6 years. Administration of the B-cell antibody rituximab did not exert any beneficial effect despite effective elimination of B cells and a reduction of the paraprotein. In contrast, injection of the interleukin-1-receptor antagonist anakinra caused a complete remission within a few days. (J Am Acad Dermatol 10.1016/j.jaad.2007.03.036.)

Schnitzler syndrome is characterized by a chronic urticarial rash and a monoclonal gammopathy (mainly IgM) with at least two of the following additional features: arthralgia, bone pain, intermittent fever, hepatomegaly or splenomegaly, lymphadenopathy, elevated erythrocyte sedimentation rate, leukocytosis or thrombocytosis, and abnormal findings on bone morphologic investigations.¹ Approximately 60 cases of Schnitzler syndrome have been published since its first description in 1972.² Because of the rare frequency, physicians might not be aware of this disease. Hence, the exact diagnosis may be delayed for quite a long time. In addition, Schnitzler syndrome still is a therapeutic challenge. Despite the administration of numerous regimens including azathioprine, cyclosporine, thalidomide, interferon, and psoralen plus ultraviolet A, systemic steroids in rather high doses are still the major option for long-term control or remission.

Here, we report a patient who was only recently given the diagnosis of Schnitzler syndrome although the typical symptoms had been present for about 6 years. Postulating that the paraprotein might be pathophysiologically relevant, we administered rituximab, an antibody directed against B cells,

which are the source of the paraprotein. Although B-cell counts decreased to zero accompanied with a reduction of the paraprotein, the clinical symptoms did not improve. In contrast, injection of anakinra, an interleukin (IL)-1 receptor antagonist, was highly beneficial, inducing complete remission of the dermatologic features within a few days. This indicates that anakinra may be the therapy of choice for Schnitzler syndrome and points out the essential role of IL-1 in the pathogenesis of this rare but quite often missed dermatosis.

CASE REPORT

A 54-year-old man was referred to our outpatient clinic with a history of chronic urticaria accompanied by moderate pruritus that had been present for 6 years. The urticarial lesions appeared predominantly on the trunk; individual urticae, which were only slightly elevated, persisted for approximately 48 to 72 hours. In addition, he had bone pain of the shins and arthralgia. Two years after onset of these symptoms a monoclonal gammopathy type IgM kappa was detected. Because plasmacytoma and other hematologic disorders could be ruled out, the gammopathy was classified as monoclonal gammopathy of unknown significance. Rheumatologists made the diagnosis of urticarial vasculitis; the patient was given high-dose systemic corticosteroids to which the symptoms responded only moderately. Attempting to reduce the steroid dose, azathioprine was administered in addition. However, the steroid dose could not be reduced and azathioprine was, therefore, stopped. When presenting to our department, the patient was taking 15 mg of prednisolone daily but definitely was not free of clinical symptoms.

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Fig 1. Urticarial lesions predominantly on trunk under continuous treatment with prednisolone.

Physical examination revealed a generalized urticaria predominantly affecting the trunk but no lymphadenopathy (Fig 1). In addition to bone pain, the patient had intermittent sweating attacks predominantly during the night. The histologic examination of a skin biopsy specimen was compatible with a neutrophilic and eosinophilic urticaria. Laboratory investigations showed leukocytosis ($15.8 \times 10^9/L$), an elevated erythrocyte sedimentation rate of 40 mm/h, and an increased C-reactive protein (34.1 mg/L). Immunoelectrophoresis confirmed the monoclonal gammopathy type IgM kappa (6.23 g/L). Bone marrow examination did not show any evidence of a lymphoproliferative disease. Fluorescence-activated cell sorting analysis revealed a regular distribution of the lymphocyte subpopulations. Chromosomal aberrations characteristic for hematologic systemic diseases could not be detected.

Because of the clinical appearance and laboratory findings, the diagnosis of Schnitzler syndrome was made. With the aim to reduce the systemic steroids, cyclosporine (3 mg/kg) was administered. However, it did not show any beneficial effect and, thus, was abandoned after 7 months. Postulating that the paraprotein might be pathophysiologically relevant, the anti-CD20 antibody rituximab was given with the aim to reduce or eliminate the B cells as the source of the paraprotein. Rituximab (375 mg/m² body surface) was given intravenously in first 3-weekly, then weekly, intervals. Although peripheral B-cell counts had decreased to almost 0% 5 weeks after commencement of rituximab infusions, the patient still



Fig 2. Clearance of all urticarial lesions after initiation of anakinra treatment. Hematoma on abdomen is result of subcutaneous injection of anakinra.

had urticarial lesions, fatigue, and bone pain. The decrease of B cells was accompanied by a slow but gradual reduction of IgM levels from 11.43 to 4.94 g/L (normal range 0.4-2.3). Because of this treatment failure, rituximab therapy was stopped after 4 infusions. The patient continued taking systemic steroids in a range of 15 to 25 mg daily.

Six months after cessation of rituximab infusions, therapy with the IL-1-receptor antagonist anakinra was initiated in a daily dosage of 100-mg injections subcutaneously. Only 2 days after the first injection, the urticarial lesions had completely disappeared (Fig 2) and within a week, bone pain and arthralgia vanished. C-reactive protein and leukocyte counts decreased to normal values. As a result of the excellent response, systemic steroids could be tapered gradually to the current dose of 7.5 mg of prednisolone daily. The patient is still injecting 100 mg of anakinra daily. Complete steroid withdrawal is planned during the next weeks to months.

DISCUSSION

Although the reported patient had typical symptoms of Schnitzler syndrome, the correct diagnosis was made only 6 years after the first appearance of symptoms. Schnitzler syndrome is a rare disease, but it is also very likely that it represents an underrecognized disorder. Most cases are initially diagnosed as urticarial vasculitis. However, the diagnosis can be easily fixed upon the detection of paraproteinemia. Hence, immunoelectrophoresis and determination

of paraproteins should be added to the list of routine laboratory examinations for chronic urticaria.

A monoclonal gammopathy is mandatory for the diagnosis of Schnitzler syndrome: the majority of cases feature type IgM kappa. Only few cases presenting with an IgG gammopathy have been reported.^{3,4} It is still unclear whether the monoclonal paraprotein in Schnitzler syndrome is causative in nature or simply an epiphenomenon as a result of continuous antigenic stimulation.⁵ Direct immunofluorescence demonstrates deposition of IgM and C3 in dermal blood vessels^{5,6} and depositions of IgM in the dermis and at the dermoepidermal junction. Thus, it was proposed that the skin rash in Schnitzler syndrome could be a result of IgM-skin interactions.⁵

It is assumed that 15% of patients with Schnitzler syndrome develop a lymphoproliferative disorder within 10 to 20 years.⁷ Because of the few patients with Schnitzler syndrome reported and the relatively short follow-up period of these patients, it cannot be excluded that the number of patients who will eventually develop a lymphoproliferative disorder is probably much higher. Most commonly, patients will develop IgM myeloma or Waldenström's disease. Only recently, development of an IgM-secreting marginal zone B-cell lymphoma in a patient with Schnitzler syndrome has been described for the first time.⁸ Regular follow-ups are, therefore, necessary. Lipsker et al⁷ suggested an initial examination of bone marrow, immunoelectrophoresis of serum and urinary proteins, and determination of immunoglobulin subtypes, with biannual repetitions of the two latter parameters.

Rituximab is a chimeric monoclonal antibody directed against the B-cell marker CD20. Its primary indications are B-cell malignancies, however, it is increasingly used in rheumatoid arthritis and autoantibody-mediated autoimmune diseases.⁹ The rationale for this approach is the elimination of B cells followed by a decreased production of antibodies. Under the same premise, rituximab was administered in our patient. Although B-cell counts and the monoclonal gammopathy decreased, no significant amelioration of symptoms was noticed after an administration period of 8 weeks. Because the B-cell counts had already reached zero levels, continuation did not seem promising and, thus, treatment was stopped. To our knowledge, there is only one report of a case of Schnitzler syndrome treated with rituximab.¹⁰ As in our case, the patient did not respond.

In contrast to rituximab, administration of anakinra led to a dramatic and very rapid improvement of symptoms in our patient. Anakinra is a recombinant form of the naturally occurring IL-1-receptor

antagonist. It competitively inhibits the binding of IL-1 α and IL-1 β to the IL-1 receptor. Although it binds to the receptor, it does not induce signal transduction and, thus, acts as an antagonist. It is used successfully in rheumatoid arthritis and autoinflammatory diseases such as Muckle-Wells syndrome,¹¹ tumor necrosis factor-associated periodic syndrome, and hyper-IgD syndrome.¹² Hence, anakinra is primarily used by rheumatologists and pediatricians and is, thus, less familiar to dermatologists. So far, 4 cases of excellent response to anakinra have been reported in the literature.^{3,10} All of these patients had undergone various other treatment regimes such as azathioprine, methotrexate, immunoglobulins, phototherapy, antihistamines, interferon alfa, cyclosporin, and dapsone with little or no effect before anakinra therapy was introduced. In all of these 4 patients, improvement of symptoms could be observed within 48 hours. Patients were still in remission 6 to 18 months after initiation of anakinra treatment.

The immediate response to anakinra treatment may underline the pivotal role that IL-1 could play in the pathogenesis of Schnitzler syndrome. In a screening study of 273 sera, anti-IL-1 α -IgG-antibodies were detected in 18% of healthy individuals, the same percentage was found in all patient control groups except for patients with Schnitzler syndrome.¹³ In the sera of 6 of 9 patients with Schnitzler syndrome remarkably increased levels of anti-IL-1 α -IgG antibodies could be detected. It was postulated that these autoantibodies prolong the half-life of IL-1 α , change the tissue distribution, and, thus, enhance the systemic effects of IL-1, which is a potent proinflammatory mediator. Although this hypothesis has to be further investigated, anakinra appears to be the most promising drug for the treatment of Schnitzler syndrome at this stage. Thus, early administration is recommended.

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