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Beneficial response to anakinra and thalidomide in Schnitzler's syndrome

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Abstract

Schnitzler's syndrome is an inflammatory disorder characterised by chronic urticarial rash and monoclonal gammopathy, accompanied by periodic fever, arthralgia or arthritis and bone pain. Etiology and treatment are still enigmatic.

Objective: to assess therapy with thalidomide and interleukin-1 receptor antagonist (IL-1ra) anakinra in Schnitzler's syndrome. *Cases:* we describe three patients with Schnitzler's syndrome, one with IgM gammopathy, two with IgG type. In one patient, thalidomide induced complete remission, but was stopped because of polyneuropathy. Anakinra 100 mg daily in all three patients led to disappearance of fever and skin lesions within 24 hours. After a follow-up of six to eighteen months, all patients are free of symptoms.

Conclusion: Anakinra proved to be effective in three patients with Schnitzler's syndrome. In terms of side effects, this treatment is preferable to thalidomide, which induced a complete remission in one of our patients.

Key words: Schnitzler's syndrome, anakinra, thalidomide, interleukin-1, urticaria

Introduction

Schnitzler's syndrome is a rare disabling disorder characterised by a chronic urticarial rash and a monoclonal IgM gammopathy, accompanied by at least two of the following features: intermittent unexplained fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, an acute phase response and abnormal findings on bone morphologic investigations [1,2]. In most cases, the syndrome follows a chronic, benign course, but at least 15% will develop a lymphoproliferative disorder in the long term.¹ The pathophysiology is still unknown, although different autoantibody-mediated mechanisms have been proposed [3]. Treatment remains a challenge and to date, no spontaneous complete remissions have been reported. We report three cases of Schnitzler's syndrome, two of which suffer the variant form with an IgG gammopathy instead of IgM, and our observations on treatment with thalidomide as well as with the IL-1 receptor antagonist (IL-1ra) anakinra. All patients were informed in detail about the nature of the treatment and the possible side-effects, and gave their informed consent.

Case reports

A 55-year-old woman with a 16-year history of chronic urticaria was referred to our outpatient clinic. She experienced daily episodes of pruritic urticarial lesions on extremities, trunk and face. Her medical history revealed iritis as well as hearing loss and tinnitus due to otosclerosis. Since one year she experienced recurrent episodes of fever ($>39^{\circ}\text{C}$). She also complained of pain in both shins and arthralgia in the hands, knees and ankles. Physical examination showed a generalised urticarial rash (figure 1a), splenomegaly and axillary and inguinal lymphadenopathy. Laboratory investigations showed an increased C reactive protein (CRP) (92 mg/l) and leukocytosis ($12.5 \times 10^9/\text{l}$). She has a monoclonal IgG kappa component. Further examinations showed no evidence for auto-immune disease, cryoglobulinaemia or malignancy. DNA analysis showed no evidence for cryopyrin-associated periodic syndromes (CAPS) [4]. The combination of generalised urticaria, bone pain, arthralgia, recurrent fever and a monoclonal IgG gammopathy allowed us to make the diagnosis of variant type Schnitzler's syndrome [5,6]. Earlier, treatment with cyclooxygenase-inhibitors, antihistamines, cyclosporine, colchicine and dapsone had been ineffective. High dose corticosteroids caused only a partial remission of symptoms. Administration of 100 mg thalidomide daily strikingly improved her condition: fever and arthralgia vanished, urticarial lesions disappeared almost entirely, CRP level and leukocyte count normalised. Unfortunately, after seven weeks she developed severe polyneuropathy, which was reversible after cessation of thalidomide. Soon afterwards, her symptoms relapsed. Combination therapy of corticosteroids and thalidomide 50 mg improved symptoms, but no complete remission was obtained. We started anakinra treatment at a daily dose of 100 mg s.c. This caused the urticarial rash and fever to disappear within 24 hours (figure 1b,2) with a normalisation of CRP and leukocyte count. Interestingly, the tinnitus disappeared but the audiogram did not change. Bone pain and arthralgia slowly diminished over the next weeks until complete remission was reached, which has lasted for more than 18 months.

The second patient is a 58-year old male patient with a 15-year history of cold-induced urticaria and paraproteinemia of a IgG-type kappa protein. In the last year, this had been accompanied by attacks of fever, myalgia and arthritis of the ankles. These fever episodes occurred in varying frequency from several times each week to once every two weeks. He had developed a weight loss of 8 kg during this year. There was also a perceptible hearing loss and bilateral distal mononeuropathy of the communal peroneal nerve. Detailed diagnostic examination revealed no signs of cryoglobulinemia, multiple myeloma or other malignancy. A diagnosis of variant type Schnitzler syndrome was made, and during a fever episode the

patient was started on anakinra (100 mg s.c. daily). Within one day, fever subsided, the skin lesions decreased in intensity and leukocyte count normalised. CRP concentration dropped from 103 to 48 mg/L 48 hours after start of anakinra. The fever did not recur after start of anakinra. Six months later the patient is still free from fever and urticaria, has gained weight and is back to work.

Thirdly, a 60-year-old man presented with a 3-year history of chronic urticaria. The moderately pruritic lesions were confined to his trunk and extremities and usually resolved within a few days (figure 1c). He complained of arthralgia of knees and feet. He suffered recurrent episodes of fever and bone pain affecting his pelvis and both shins. Physical examination showed urticarial lesions on his trunk and extremities. No hepatosplenomegaly or lymphadenopathy were found. Laboratory investigations demonstrated an increased CRP (143 mg/l), leukocytosis ($13.5 \times 10^9/l$) and a monoclonal IgM kappa. Examination of blood, urine, bone marrow and radiographs showed no evidence for auto-immune disease, cryoglobulinaemia, malignancy or CAPS and the diagnosis Schnitzler's syndrome was made. Treatment with cyclooxygenase-inhibitors and corticosteroids improved his symptoms only partially. After starting treatment with anakinra 100 mg s.c. daily, a complete remission was reached which lasts now for 1 year (figure 1d).

Discussion

In this report we describe three patients with Schnitzler's syndrome who showed a remarkable clinical response to treatment with the IL-1 receptor antagonist (IL-1ra) anakinra. In our first patient, thalidomide had also been effective, but treatment had to be stopped as it caused severe polyneuropathy.

Our patients fulfilled the diagnostic criteria for Schnitzler's syndrome [1]. Whereas most patients reported with Schnitzler's syndrome have a IgM paraprotein, our first two patients belong to the rare cases with a monoclonal IgG gammopathy. To date, five other patients with the IgG-variant Schnitzler's syndrome have been described [5,6]. The clinical manifestations of these variant patients do not differ from the typical syndrome.

Treatment of Schnitzler's syndrome remains a challenge. No consistent effectiveness was reported for, amongst others, nonsteroidal anti-inflammatory drugs, antihistamines, colchicine and several immunosuppressive drugs. At low doses, oral corticosteroids are usually ineffective in controlling the urticarial rash. Only high dose corticosteroids can improve the urticarial rash as well, but this regimen was not effective in our first patient and cannot be sustained for prolonged periods[1,3].

Recently, Worm reported on the efficacy of thalidomide in two patients with Schnitzler's syndrome, in whom complete resolution of urticarial skin rash and marked improvement of fever attacks and bone pain were achieved [7]. A similar remarkable response was seen in our first patient, but treatment had to be stopped because of severe polyneuropathy. Combination therapy with low dose thalidomide (50 mg) and corticosteroids subsequently induced a partial response.

In our search for a more effective treatment we tried anakinra. Anakinra is a recombinant form of human IL-1ra, which competitively inhibits binding of IL-1 α and IL-1 β to the IL-1 receptor type 1. IL-1 is a key pro-inflammatory cytokine mediating cellular responses during inflammation. Anakinra has proved to be effective in the treatment of rheumatoid arthritis and recently, it induced complete remission in the hereditary autoinflammatory disorder Muckle-Wells syndrome [4]. Anakinra has also been successful in other autoinflammatory syndromes such as TNF-receptor associated periodic syndrome (TRAPS) [8] and hyper-IgD syndrome (HIDS) [9].

In our patients with Schnitzler's syndrome we observed a rapid and complete remission after initiating treatment with 100 mg anakinra s.c. daily. With a follow-up of six to eighteen months, they are still in remission. Our first patient suffered from the commonly reported adverse effect of painful, erythematous lesions at the site of injection, but this was only during the first few weeks of treatment and no other adverse effects were noted.

The pathophysiological mechanism of Schnitzler's syndrome is still unclarified, but autoantibody-mediated mechanisms, involving the paraprotein have been proposed [3]. The remarkable responses we observed support the theory that IL-1 has an important role in the pathogenesis of Schnitzler's syndrome. This is corroborated by recent reports on successful treatment with interferon α (IFN- α), which induces high levels of endogenous IL-1ra [10,11]. Saurat et al. reported the presence of anti-IL-1 α antibodies in Schnitzler's syndrome [12]. These autoantibodies are believed to prolong the half-life, change tissue distribution and enhance systemic effects of IL-1. However, these anti-IL-1 α antibodies could not be detected in other patients, nor were the serum concentrations of TNF- α , IL-1 β or IL-1ra increased [13-15].

In conclusion, anakinra (IL-1ra) proved to be very effective in our three patients with Schnitzler's syndrome. In terms of side effects, this treatment is preferable to thalidomide, which induced a complete remission in one of our patients. The effect of IL-1ra underlines the important role of IL-1 in the pathogenesis of the disorder.

Figure legends

Figure 1: Skin manifestations in Schnitzler's syndrome. Urticarial skin rash in the first (a) and third (c) patient, and the remarkable improvement 24 hours after administration of anakinra (b,d).

Figure 2: Temperature curves and acute phase response. Body temperature (black line) and C reactive protein serum levels (dotted line) in a patient with variant Schnitzler's syndrome before and during treatment (grey areas) with thalidomide (left panel) and subsequently anakinra (right panel).

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