CONCISE REPORT

Beneficial response to anakinra and thalidomide in Schnitzler's syndrome

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Background: 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. The cause and treatment are still unknown.

Objective: To assess treatment with thalidomide and an interleukin 1 receptor antagonist, anakinra, in Schnitzler's syndrome.

Case reports: Three patients with Schnitzler's syndrome are described, 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 6-18 months, all patients are free of symptoms.

Conclusion: Anakinra proved to be effective in three patients with Schnitzler's syndrome. This treatment is preferable to thalidomide, which induced a complete remission in one of our patients, as it has fewer side effects.

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, hepatosplenomegaly, an acute phase response, and abnormal findings on bone morphological 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 the cases of three patients with Schnitzler's syndrome, two of whom have the variant form with an IgG gammopathy instead of IgM, and our observations on treatment with thalidomide as well as with the interleukin 1 receptor antagonist (IL1Ra), anakinra. All patients were informed in detail about the nature of the treatment and possible side effects, and gave their informed consent.

CASE REPORTS

Case No 1

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 the extremities, trunk, and face. Her medical history disclosed iritis as well as hearing loss and tinnitus due to otosclerosis. For 1 year she had experienced recurrent episodes of fever (>39°C). She also complained of pain in both shins, and

arthralgia in the hands, knees, and ankles. Physical examination showed a generalised urticarial rash (fig 1A), splenomegaly, and axillary and inguinal lymphadenopathy.

Laboratory investigations showed an increased C reactive protein (CRP) (92 mg/l) and leucocytosis ($12.5 \times 10^9/l$). She has a monoclonal IgG κ component. Further examinations showed no autoimmune disease, cryoglobulinaemia or malignancy. DNA analysis showed no evidence for cryopyrin associated periodic syndrome (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 cyclo-oxygenase inhibitors, antihistamines, ciclosporin, 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: the fever and arthralgia vanished, urticarial lesions disappeared almost entirely, and the CRP level and leucocyte count normalised. Unfortunately, after 7 weeks she developed severe polyneuropathy, which was reversible when thalidomide was stopped. Soon afterwards, her symptoms relapsed. Combination therapy of corticosteroids and thalidomide 50 mg improved symptoms, but complete remission was not obtained.

We started anakinra treatment at a daily dose of 100 mg subcutaneously (SC). This caused the urticarial rash and fever to disappear within 24 hours (figs 1B and 2) with a normalisation of CRP and leucocyte 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.

Case No 2

The second patient, a 58 year old man, had a 15 year history of cold-induced urticaria and paraproteinaemia of an IgG-type κ protein. In the past year this had been accompanied by attacks of fever, myalgia, and arthritis of the ankles. These episodes of fever occurred in varying frequency from several times each week to once every 2 weeks. He had developed a weight loss of 8 kg during this year. He also had a perceptive hearing loss and bilateral distal mononeuropathy of the communal peroneal nerve.

Detailed diagnostic examination showed no signs of cryoglobulinaemia, multiple myeloma or other malignancy. A diagnosis of variant-type Schnitzler syndrome was made, and during an episode of fever, treatment of the patient with anakinra (100 mg SC daily) was started. Within 1 day, the fever subsided, the skin lesions decreased in intensity, and

Abbreviations: CAPS, cryopyrin associated periodic syndrome; CRP, C reactive protein; IL1Ra, interleukin 1 receptor antagonist; SC, subcutaneously

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).

the leucocyte count normalised. The CRP concentration dropped from 103 to 48 mg/l 48 hours after starting anakinra. The fever did not recur. Six months later the patient is still free from fever and urticaria, has gained weight, and is back at work.

Case No 3

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 (fig 1C). He complained of arthralgia of the knees and feet. He had 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 was found.

Laboratory investigations demonstrated an increased CRP (143 mg/l), leucocytosis ($13.5 \times 10^9/l$), and a monoclonal IgM κ . Examination of blood, urine, bone marrow, and radiographs showed no evidence of autoimmune disease, cryoglobulinaemia, malignancy or CAPS, and the diagnosis Schnitzler's syndrome was made. Treatment with cyclo-oxygenase inhibitors and corticosteroids improved his symptoms only partially. After starting treatment with anakinra 100 mg SC daily, complete remission was reached, which has now lasted for 1 year (fig 1D).

DISCUSSION

In this report we describe three patients with Schnitzler's syndrome who showed a remarkable clinical response to treatment with the IL1Ra, 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 with Schnitzler's syndrome reported have an 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 the variant-type syndrome do not differ from those of the typical syndrome.

Treatment of Schnitzler's syndrome remains a challenge. No consistent effectiveness was reported for non-steroidal 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 and Kolde reported 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 IL1Ra, which competitively inhibits binding of IL1 α and IL1 β to the IL1 receptor type 1. IL1 is a key proinflammatory 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

Figure 2 Temperature curves and acute phase response. Body temperature (black line) and CRP 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).

syndrome.⁴ Anakinra has also been successful in other autoinflammatory syndromes such as TNF receptor associated periodic syndrome⁸ and hyper-IgD syndrome.⁹

In our patients with Schnitzler's syndrome we observed a rapid and complete remission after starting treatment with 100 mg anakinra SC daily. After a follow up of 6–18 months, they are still in remission. Our first patient had 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 IL1 has an important role in the pathogenesis of Schnitzler's syndrome. This is corroborated by recent reports on successful treatment with interferon alfa, which induces high levels of endogenous IL1Ra.^{10–11} Saurat *et al* reported the presence of anti-IL1 α antibodies in Schnitzler's syndrome.¹² These autoantibodies are believed to prolong the half life, change tissue distribution, and enhance the systemic effects of IL1. However, these anti-IL1 α antibodies could not be detected in other patients, nor were the serum concentrations of tumour necrosis factor α , IL1 β or IL1Ra increased.^{13–15}

In conclusion, anakinra (IL1Ra) proved to be very effective in our three patients with Schnitzler's syndrome. This treatment is preferable to thalidomide, which induced a complete remission in one of our patients, as it has fewer side effects. The effect of IL1Ra underlines the important role of IL1 in the pathogenesis of the disorder.

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