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Case report

Anakinra: An effective treatment in the Schnitzler syndrome

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ABSTRACT

Schnitzler syndrome is a rare disease characterized by chronic urticarial eruption and a monoclonal gammopathy. The exact pathogenesis is still unclear and treatment remains a challenge. We report the case of a patient with a 2-year history of arthralgia, chronic urticaria rash and fever, not responding to different treatments including anti-histaminics, corticosteroids, colchicine and low dose methotrexate. A diagnostic of Schnitzler syndrome was suggested and treatment with anakinra, an interleukin-1 receptor antagonist, was started, leading to a rapid, complete and sustained remission of symptoms. Anakinra seems to constitute an efficient and safe therapeutic approach for this rare disease.

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Schnitzler syndrome is a rare disease characterized by a chronic urticarial rash, a monoclonal IgM gammopathy, and at least two of the following features: intermittent unexplained fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, elevated erythrocyte sedimentation rate, leucocytosis, radiographic signs of osteosclerosis [1]. In most cases, the syndrome follows a chronic but benign course, but 15% will develop a lymphoproliferative disorder in the long term. To date, no spontaneous complete remission has been reported [2]. The physiopathology is still unknown, although different autoantibody and/or cytokine-mediated mechanisms have been proposed [3,4]. The treatment is not codified and includes corticosteroids and/or immunosuppressive drugs with a highly variable response rate according to the rare case series published [2]. We report a patient with Schnitzler syndrome who dramatically improved under anakinra, the recombinant form of human interleukin-1 receptor antagonist (IL-1ra).

A 62-year-old man, without any personal or familial history, reported a 2-year history of chronic urticaria. Concomitantly with urticaria, he had experienced arthralgia affecting shoulders and hips, and recurrent episodes of fever. The eruption involved the whole body (Fig. 1), including the face, but the patient never presented angioedema. Clinical examination found no hepatosplenomegaly or lymphadenopathy. Laboratory investigations showed leucocytosis (19,000 per millimetre cube with 16,190 neutrophils per millimetre cube) and increased erythrocyte sedimentation rate (ESR; 40 mm/h) and C-reactive protein level (CRP; 5.0 mg/dL). Serum protein electrophoresis showed

a monoclonal IgM component with kappa light chains on immunofixation. No Bence-Jones proteinuria was detectable. The monoclonal component was estimated at 2,37 g/L; IgG, IgA, IgD, serum complement (including C1q) fractions and C1-inhibitor level were within the normal range. There were no antinuclear antibodies, rheumatoid factor or cryoglobulin. Hepatitis B, C and HIV serologies were negative. Glycosylated ferritin level was normal. Bone marrow histology was normal, especially no lymphoproliferative disorder was identified. Histological examination of a biopsy from an urticarial lesion showed edema of the upper dermis with a perivascular inflammatory infiltrate with neutrophils. Immunofluorescence studies did not show any deposit of immunoglobulins. Bone scintigraphy revealed hyperfixation of the right iliac bone (Supplementary material), with osteosclerosis on radiographs. Computer tomography (CT) scan of the thorax and the abdomen confirmed the condensing lesion on the right iliac bone (Fig. 2), but did not reveal lymph nodes or neoplasia. Magnetic resonance imaging (MRI) showed very low signal intensity on T1-weighted MR images of the right iliac bone, with high signal intensity on T2-weighted images.

Based on the combination of generalized urticaria, arthralgia, recurrent fever, and a monoclonal IgM gammopathy, a diagnosis of Schnitzler syndrome was made. Earlier, treatments with anti-histaminics, non-steroidal anti-inflammatory drugs, colchicine and methotrexate had been ineffective. High dose of oral prednisone (1 mg/kg daily) caused only partial remission of symptoms. Treatment with anakinra (100 mg SC daily) was started in January 2008; a concurrent dose of prednisone 20 mg daily was continued. Two weeks later, urticarial rash, fever and arthralgia disappeared with a normalization of CRP, ESR and leucocytes count. No adverse effect was observed, with especially no local injection-site reaction. Corticosteroids was gradually reduced and stopped 6 months

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Fig. 1. Urticarial eruption at presentation.

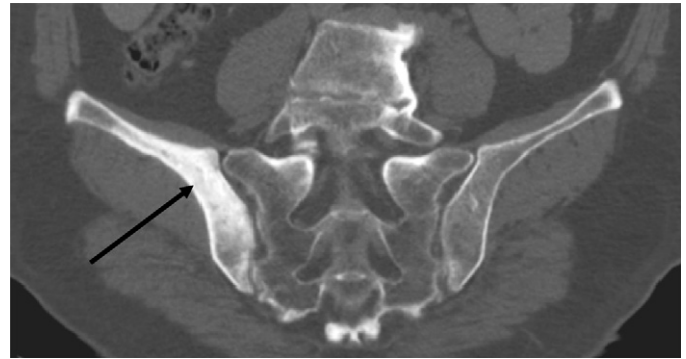


Fig. 2. Computer tomography scan indicating condensing lesion on the right iliac bone.

after starting anakinra. Six months later, the patient was still asymptomatic and laboratory findings remained completely normal, with a disappearance of the monoclonal gammopathy. We tried to stop the treatment on two occasions for three days, and indeed the patient experienced relapses with fever, arthralgias and generalized urticarial rash, with a rapid and complete resolution of symptoms after restarting anakinra. The patient is still in complete remission after 3 years of treatment; the recent explorations revealed no evidence of lymphoproliferative disorder.

Schnitzler syndrome is a rare and probably under-recognized disorder, and only about 100 cases have been reported since the first description by the French dermatologist Liliane Schnitzler in 1972 [2]. The clinical course of the disease is usually chronic, with no spontaneous remission, and treatment is difficult and often unsatisfactory. Different treatments are reported in the literature, like glucocorticoids, interferon, thalidomide, cyclophosphamide, cyclosporin and rituximab, with variable efficiency [1,2,5–7]. The physiopathology of the Schnitzler's syndrome remains unclear. There are reports suggesting activation of complement though deposition of IgM complexes, or other autoantibody-mediated mechanisms. Another hypothesis proposed a mechanism involving the uncontrolled activation of pro-inflammatory cytokines [3,4]. Schnitzler syndrome has therefore many similarities with autoimmune-inflammatory disease and adult-onset Still's disease, and it has been suggested that disturbances of the innate immune system are responsible for this syndrome. IL-1 is a key pro-inflammatory cytokine mediating cellular responses during inflammation [8] and this cytokine is probably involved in the pathophysiology of Schnitzler syndrome [4,9].

In our patient, we observed a rapid and complete remission after starting treatment with anakinra daily, and the patient is still in remission after a follow-up of 36 months. Anakinra is a recombinant form of human IL-1 receptor antagonist (IL-1ra), which competitively inhibits binding of IL-1 α and IL-1 β to the IL-1 receptor type 1. It has proved to be effective in the treatment of rheumatoid arthritis. Anakinra has also been successful in autoinflammatory syndromes such as TNF receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome and Muckle-Wells syndrome [10,11]. More recently, anakinra has been tested in a few patients with Schnitzler's syndrome, and had shown to be successful in this disorder, with very few side effects [2,6,7,12–14]. The therapeutic effect is however only suspensive requiring daily injections. We describe a new patient with Schnitzler syndrome who had complete and durable response to anakinra.

The effect of IL-1ra in Schnitzler syndrome in our patient and other cases reported in the literatures underlines the important role of IL-1 in the pathogenesis of this disorder. Anakinra seems to constitute an efficient and safe therapeutic approach for this rare disease.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data (Fig. S1) associated with this article can be found, in the online version, at [doi:10.1016/j.jbspin.2011.03.021](https://doi.org/10.1016/j.jbspin.2011.03.021).

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