

Striking Effect of the IL-1 Receptor Antagonist Anakinra in Chronic Urticarial Rash with Polyclonal Increase in IgA and IgG

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Sir,

Schnitzler's syndrome (SS) is characterized by chronic urticarial rash, (monoclonal) gammopathy (IgM) and at least two of the following: intermittent unexplained fever, arthralgia, bone pain, lymphadenopathy, hepatosplenomegaly, elevated erythrocyte sedimentation rate (ESR), leukocytosis and abnormal findings on bone morphological investigations (1, 2).

CASE REPORT

A 58-year-old woman presented with an erythematous macular and partly urticarial rash (Fig. 1) without lymphadenopathy. She had a 13-year history of this rash, together with anaemia, fatigue, arthralgias and an elevated ESR. The symptoms were resistant to therapy with different antihistamines and non-steroidal anti-inflammatory drugs (NSAIDs), but responded in part to weekly injections of betamethasone, given for 6 months 8 years prior to consultation. Five years prior to presentation, an elevated IgA was documented, but not correlated to the rash and other symptoms. Nine months prior to presentation her condition worsened, with fever up to 38.5°C, weight loss and bone pain.

Laboratory work-up revealed the following: ESR 105 mm/h, C-reactive protein (CRP) 61 mg/dl (normal value < 0.5 mg/dl), haemoglobin 9.5 g/dl (normal 11.7–16 g/dl), mean globular volume 80.2 (normal 82–101), leukocytes $9.3 \times 10^3/\mu\text{l}$ (normal

4–9), granulocytes 86% (normal 42–75%), albumin 47.9% (normal 58–70%), α_2 -globulins 14.1% (normal 5–10%), γ -globulins 21.7% (normal 10–19%), IgG 20.1 g/l (normal 7–16 g/l), IgA 6.97 g/l (normal 0.7–4 g/l). Within the normal range were: serum values of total protein, IgM, immunofixation electrophoresis (IgG, IgA, IgM), light chains κ and λ , C1, C3, C4, cryoglobulins, serology for hepatitis C, ANA/ENA, dsDNS, rheumatoid factor, ferritin, and urinalysis for Bence Jones proteins. Histopathology showed oedema of the superficial dermis and an interstitial perivascular mononuclear and polymorphonuclear cell infiltrate (Fig. 2); direct immunofluorescence was negative. X-ray yielded no evidence of plasmacytoma. Ultrasound demonstrated mild hepatosplenomegaly. Bone marrow aspirate did not reveal lymphoplasmacytoid proliferation.

Symptoms were resistant to therapeutic attempts with oral fexofenadine, diclofenac and weekly infusions of methotrexate 15 mg. We then introduced anakinra (Kineret, Amgen GmbH, München, Germany) at a dosage of 100 μg subcutaneously once daily. Six hours after the first injection the skin lesions had already disappeared. The patient's general condition improved markedly and CRP decreased from 61 to 3.5 mg/l within 2 days. After 14 weeks on anakinra therapy the patient showed complete recovery. There were no side-effects except erythematous macules at the injection sites. The ESR (20 mm/h) and haemoglobin level (14.4 g/dl) had improved markedly, and within the normal range were leukocytes, globular volume, CRP, IgA, IgG.

DISCUSSION

As in this case, SS is frequently resistant to therapy. Previous therapeutic approaches have included glucocorticoids, NSAIDs, colchicine, dapsone, thalidomide, interferon- α , rituximab, immunoglobulins, methotrexate, cyclophosphamide, purine analogues, plasma exchange and psoralen ultraviolet A (PUVA) therapy (1, 2).

To our knowledge, this is the first report of anakinra treatment in a sine IgM variant of SS with polyclonal immunoglobulin increase (1, 3, 4). Adult-onset Still's disease was considered to be the differential diagnosis, but the patient showed no increase in serum ferritin levels, which is a major diagnostic criterion (1). There was no evidence for other autoimmune diseases.

Anakinra is an interleukin-1 α and -1 β antagonist (IL1Ra) that competitively blocks the action of this cytokine at the receptor level. The efficacy of anakinra in SS was reported for the first time in a patient who became asymptomatic within one week on 100 μg /day of anakinra plus methotrexate (5 mg/week) (5). Another study described the resolution of the rash and fever in three patients with the classical variant of SS (with monoclonal IgM or IgG) within one day on monotherapy with anakinra at 100 g/day (6).



Fig. 1. Erythematous macular and partly urticarial lesions on the patient's arm in July 2006. The rash disappeared within 6h of the first application of the interleukin-1 antagonist, anakinra.

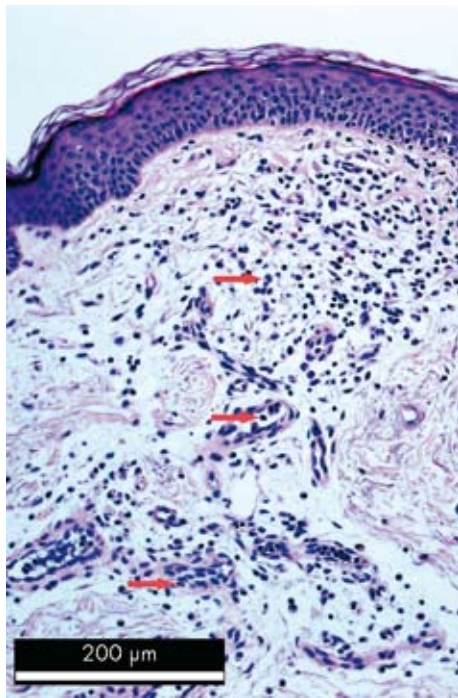


Fig. 2. Histopathology (haematoxylin-eosin staining) revealed oedema of the superficial dermis and an interstitial mixed perivascular mononuclear and polymorphonuclear cell infiltrate with many neutrophils (arrows).

IL-1 has been suggested to be pathogenetically important in SS, and an IgG auto-antibody mediated prolongation of the half-life of IL-1 has been suggested to account for symptoms of the disease (7). As IL-1 may limit the availability of iron for erythrocytes, our patient's anaemia was attributed to the chronic inflammatory process (8).

The successful treatment of SS with anakinra, including a clear improvement in anaemia, supports the theory that IL-1 has an important role in the pathogenesis of this disease.

REFERENCES

1. Lipsker D, Imrie K, Simon A, Sullivan K. Hot and hobbling with hives: Schnitzler syndrome. *Clin Immunol* 2006; 119: 131–134.
2. Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine* 2001; 80: 37–44.
3. Husak R, Nestoris S, Goerdts S, Orfanos CE. Severe course of chronic urticaria, arthralgia fever and elevation of erythrocyte sedimentation rate. Schnitzler's syndrome without monoclonal gammopathy? *Br J Dermatol* 2000; 142: 581–582.
4. Varella TC, Nishimura MY, Machado MC, de Moraes-Vasconcelos D, Rivitti EA. Schnitzler's syndrome without monoclonal gammopathy. *Acta Derm Venereol* 2005; 85: 272–273.
5. Martinez-Taboada VM, Fontalba A, Blanco R, Fernandez-Luna JL. Successful treatment of refractory Schnitzler syndrome with anakinra: comment on the article by Hawkins et al. *Arthr Rheumat* 2005; 52: 2226–2228.
6. de Koning HD, Bodar EJ, Simon A, van der Hilst JC, Netea MG, van der Meer JW. Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. *Ann Rheumat Dis* 2006; 65: 542–544.
7. Saurat JH, Schifferli J, Steiger G, Dayer JM, Didierjean L. Anti-interleukin-1 alpha autoantibodies in humans: characterization, isotype distribution, and receptor-binding inhibition – higher frequency in Schnitzler's syndrome (urticaria and macroglobulinemia). *J Allergy Clin Immunol* 1991; 88: 244–256.
8. Weiss G, Godnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011–1023.