

Prompt response of refractory Schnitzler syndrome to treatment with anakinra

To the Editor: Schnitzler syndrome (SS), first reported by a French dermatologist in 1972,¹ is an extremely rare and probably underrecognized disorder. It is defined as chronic urticarial rash with a monoclonal IgM gammopathy (seldom IgG type).²⁻⁴ After 10 to 20 years, 15% of patients with SS develop lymphoproliferative disorders.^{3,5} Further cardinal features are intermittent fever of unknown origin, disabling bone pain, hyperostosis, and increased erythrocyte sedimentation rate. Even though it is a rare disease, SS should be considered in case of dramatic bone pain, mainly located in the distal femur and proximal tibia, and a minimally itchy chronic urticaria. Treatment is difficult, and so far there exists no treatment of choice for SS.^{2,3,5} The exact pathogenesis of SS is unclear.^{2,6-8} Some hypothesize that the deposition of the IgM paraprotein, leading to the formation of immune complexes and the activation of the complement cascade, is responsible for the cutaneous manifestations.⁶⁻⁸ Another proposed mechanism involves the uncontrolled activation of interleukin 1 α (IL-1 α). IL-1 α is a known mediator of inflammation, and its injection into the skin causes persistent erythema.⁶ In 1991, Saurat et al⁹ found that the serum from 6 out of

9 patients with SS contained anti-IL-1 α IgG autoantibodies. These antibodies have been shown to prolong the half-life of IL-1 α , to change its tissue distribution, and might enhance its effects. Therefore, this increase in IL-1 α activity could account for the symptoms of urticaria and fever found in SS. However, other reports could not reproduce these findings.⁸

A 59-year-old male had a 4-year-history of widespread urticaria (Fig 1, A), disabling bone pain, and intermittent high spiking fever. Laboratory investigations revealed anemia, an IgM kappa gammopathy, and elevated acute-phase reactants (Table I). A three-phase bone scintigraphic study showed an abnormal enhanced isotope uptake in the proximal right tibia and bilateral distal femur (Fig 1, B). Bone marrow examination and a computer tomography-guided bone biopsy of the femur did not provide further information but could exclude a hematoproliferative disease. Therefore, all clinical and serologic findings were in line with SS. Therapies including a combination of antihistamines (fexofenadine, promethazine, levocetirizine, and clemastine), oral methotrexate (25 mg/wk), pentoxifylline (3 $\times$ 400 mg/d) in combination with hydroxychloroquine (400 mg/d) and colchicine (4 $\times$ 0.5 mg/d) and in combination with dapsone (100 mg/d) were ineffective.

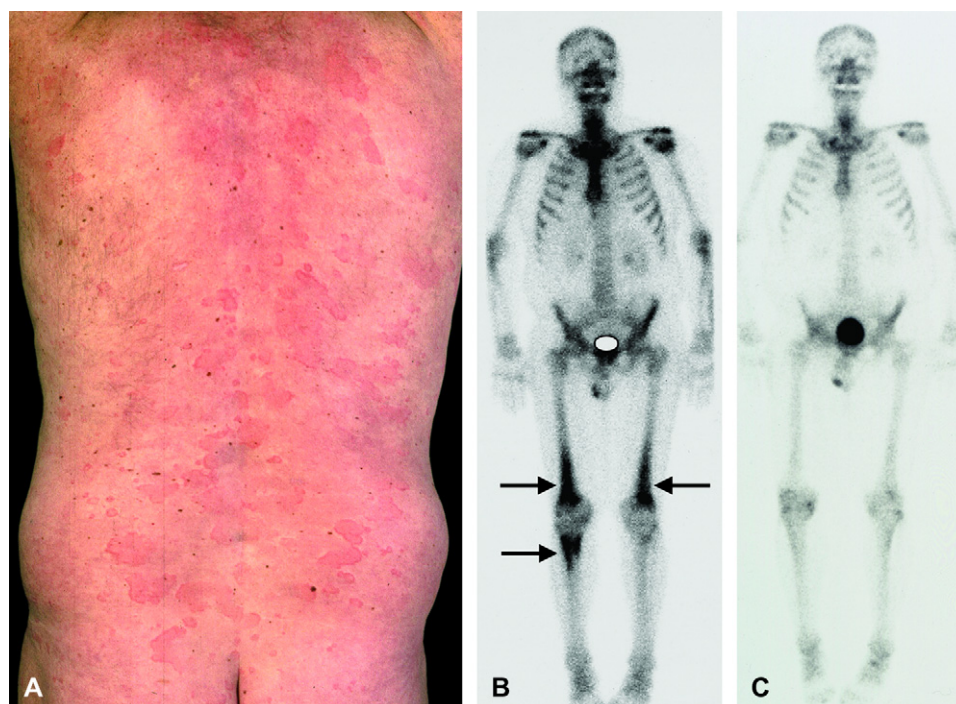


Fig 1. A, Widespread urticaria on the back. B, Bone scintigraphic study before anakinra therapy (3 hours post-injection) showed an abnormal symmetric enhanced isotope uptake in the proximal tibia and bilateral distal femur (arrows). C, Bone scintigraphic study after 5 months of anakinra therapy (3 hours post-injection) showed an almost normal isotope uptake in the proximal tibia and bilateral distal femur.

Table I. Laboratory investigations

	Reference	Before anakinra therapy	During anakinra therapy*
ESR	4-10 mm/h	74	3
CRP	<0.5 mg/dl	16.6	1.7
Fibrinogen	200-400 mg/dl	871	276
Leukocytes	4.0-10.0 Tsd./ μ l	14.3	4.9
Platelets	150-350 Tsd./ μ l	550	245
Ferritin	30-400 μ g/l	636	139
Hemoglobin	14.0-18.0 g/dl	10.4	14.9
Iron	80-150 μ g/l	21	86
Immunofixation (urin)	Negative	Positive Bence-Jones-Kappa	Not done
Immunofixation (serum)	Negative	Positive Paraproteinemia IgM/Kappa	Positive
IgM	40-230 mg/dl	189	Not done
Urine: red blood cells	<5/ μ l	67	Negative
ANA, RF, CK		Negative	Not done

ANA, Antinuclear antibodies; CK, creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin IgM; RF, rheumatoid factor.

*100 mg/day subcutaneously.

Even the combination of the mentioned therapies with prednisolone (20 mg/d) and nonsteroidal anti-inflammatory drugs (rofecoxib and etoricoxib) failed to improve the symptoms. Only high dose prednisolone (above 30 mg/d) abolished the mentioned symptoms within hours. However, additional high dose nonsteroidal anti-inflammatory drugs (etoricoxib 120 mg/d or rofecoxib 37.5 mg/d) were always needed to tolerate the intensive bone pain.

Because of the severe side effects of long-term prednisolone therapy, we decided to use the IL-1 antagonist anakinra (Kineret; Amgen, Thousand Oaks, Calif) for the treatment of refractory SS. In October 2005, anakinra (100 mg/day subcutaneously) was started in addition to 20 mg/day prednisolone and etoricoxib (120 mg/d). After the second injection of anakinra, our patient noticed a dramatic improvement in bone pain, fever, and urticaria. Within 6 weeks of daily anakinra injections, prednisolone was reduced by the patient to 2.5 mg/day. Etoricoxib was no longer required after the second injection of anakinra. In addition, serologic parameters, such as erythrocyte sedimentation rate, ferritin, C-reactive protein level, anemia, and leucocyte count normalized (Table I). Tapering of glucocorticosteroids and cessation of analgesics were well tolerated without flare-up of SS. During anakinra therapy we monitored clinical and routine blood chemistry. We did not observe injection site reactions or any infection. The only side effect of 6 months of therapy was a periodic headache subsiding upon ongoing therapy with anakinra. Moreover, a repeated three-phase bone scintigraphic study after 5 months of therapy shows an almost normal isotope uptake in the proximal right tibia and bilateral distal femur (Fig 1, C). We intend to taper anakinra at first to injections every other day.

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 1.¹⁰⁻¹² Anakinra has proven to be effective in the treatment of rheumatoid arthritis and other autoinflammatory disorders.^{2,11,12} As recently reported, anakinra may be a promising option for the treatment of refractory SS^{2,5,13} as was also shown in our patient.

We conclude that IL-1 blockade with anakinra may be an effective option for the treatment of recalcitrant, severe SS with only discrete side effects.

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Funding sources: None.

Conflicts of interest: None declared.

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doi:10.1016/j.jaad.2006.05.057

Acquired digital arteriovenous malformation: Ultrasound imaging and response to long-pulsed neodymium:yttrium-aluminum-garnet treatment

To the Editor: Acquired digital arteriovenous malformation, also previously described in the literature as periungual and subungual arteriovenous tumor, is a rare vascular anomaly involving the digit, most commonly the periungual region. The lesion is characterized by an abnormal endothelial-lined connection between arterioles and venules supplied by the digital artery.¹⁻³

Two cases are presented here that responded to treatment with the long-pulsed neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. One case was imaged by ultrasound before treatment.

Case 1

A 49-year-old woman presented with a 5-month history of an intermittently bleeding, painless, enlarging, pulsatile lesion involving the lateral periungual region of her right fourth finger. Examination

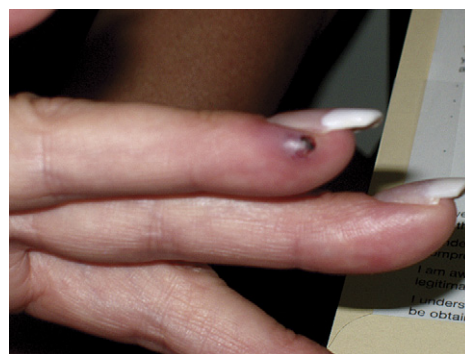


Fig 1. Case 1 before treatment demonstrating blood blister-like swelling.



Fig 2. Longitudinal ultrasound image of palmar surface of distal digit demonstrating well-defined hypoechoic lesion with mild surrounding hyperechogenicity in pulp of digit.

revealed a 3- × 5-mm raised bluish red lesion with a small area of black scab involving the distal aspect. The surrounding skin was pink (Fig 1).

An ultrasound study revealed a well-defined 3- × 11- × 3-mm hypoechoic lesion immediately deep to the skin (Fig 2). Color Doppler imaging demonstrated that the lesion and adjacent tissue were highly vascular (Fig 3, A). The lesion was not related to the neurovascular structures. Visualized pulsation could be seen overlying the lesion.

The radiologist's report was consistent with a vascular lesion. An arteriovenous malformation was considered to be the most likely diagnosis as the pulsed Doppler assessment of the lesion showed arterial and venous waveforms within it (Fig 3, B).

The patient was treated once only with the long-pulsed Nd:YAG laser 3-mm spot at 250 J/cm² and 55-millisecond pulse with a skin contact cooled tip (Lyra, Laserscope, San Jose, Calif).

Clearance with scar-free healing was complete at 5 weeks (Fig 4).

Case 2

A 41-year-old man presented with a 10-year history of a recurrently bleeding, vascular lesion on