

Letter to the Editor

IL-1 blockade in Schnitzler syndrome: *Ex vivo* findings correlate with clinical remission

To the Editor:

Schnitzler syndrome is a disease characterized by chronic urticaria with intermittent fever, arthralgia, and a monoclonal gammopathy. Recently, the use of IL-1 inhibitors has been advocated on the basis of clinical observations.¹ In this report, we examine the *ex vivo* production of cytokines and effect of inhibition of IL-1 in Schnitzler syndrome.

A 50-year-old white woman with an 8-year history of increasingly severe urticaria presented for evaluation. She initially noticed intermittent, scattered, nonpruritic “hive”-like rashes presenting for a few hours at a time. The rash gradually progressed to chronic persistent urticaria with significant pruritus, affecting her entire body with the exception of her face. She had a 3-year history of intermittent fever up to 39°C, with associated fatigue, myalgia, and arthralgia affecting her lower limbs. She denied perioral edema or dyspnea. Previous trials of numerous medications, including antihistamines and montelukast, were unsuccessful; high doses of steroids resulted in temporary improvement. Past history included hypothyroidism for which she was on an adequate dose of levothyroxine.

On examination, she had indurated erythematous papules and plaques, ranging in size from 0.5 to 4 cm in diameter, with the most prominent involvement on the central body (Fig 1, A). No pigmentary disturbance, bruising, or epithelial change was noted. Laboratory tests revealed anemia (hemoglobin 101 g/L), thrombocytosis (platelets $749 \times 10^9/L$), and white cell count of $6.9 \times 10^9/L$. Complement levels, including functional assays, were normal. Biochemistry was normal except for elevated alkaline phosphatase at 146 U/L and IgM gammopathy with a total IgM of 9.22 g/L on serum protein electrophoresis, with no paraprotein peak on urine protein electrophoresis. Bone marrow biopsy demonstrated no increase in lymphocytes, blast cells, or plasma cells. Flow cytometry showed no clonal population. Bone scintigraphy showed increased uptake in both tibiae. Biopsy of affected skin demonstrated a neutrophilic dermatosis with no evidence of vascular damage.

A diagnosis of Schnitzler syndrome was reached. This syndrome bears similarities to Muckle-Wells syndrome (MWS), an inherited disease in which symptoms usually begin in childhood and mutations in the *CIAS1* gene are found. Sequencing of the entire gene in this patient revealed no mutations.

Within hours of the introduction of anakinra 100 mg daily, an IL-1 receptor antagonist, our patient had resolution of skin rash (Fig 1, B), fevers, malaise, and bone pain. This effect has now been sustained for 1 year. Laboratory testing demonstrates normalization of her hematologic parameters and alkaline phosphatase, but the IgM gammopathy persists.

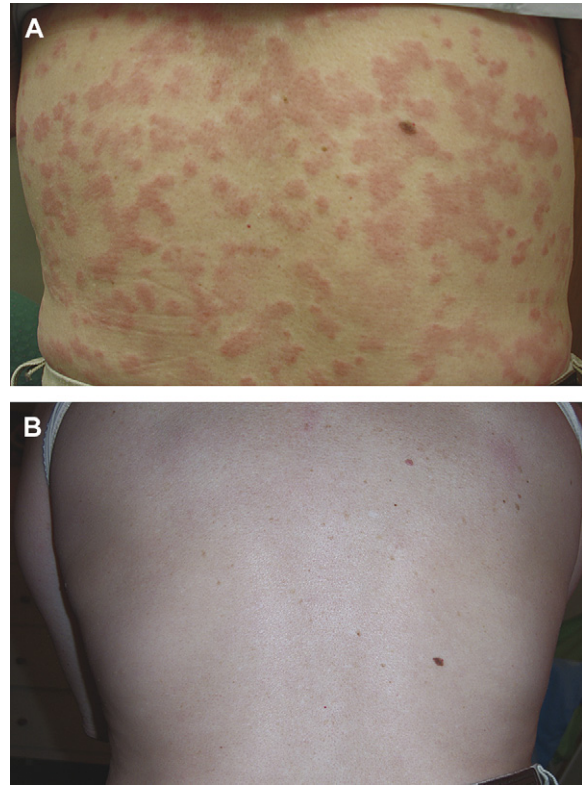


FIG 1. A, Urticarial lesions on trunk. B, Within 24 hours of commencing anakinra, these lesions had resolved.

PBMCs were isolated by Ficoll (MP Biomedicals LLC, Solon, Ohio) from this patient 48 hours after withdrawal of anakinra and from a healthy control following institutional review board approval and written informed consent. PBMCs were incubated with 100 pg/mL lipopolysaccharide (LPS; ultrapure *Salmonella minnesota* LPS, List Biological Laboratories, Campbell, Calif), with or without 30 minutes preincubation with YVAD (Z YVAD-FMK; Kamiya Biomedical Company, Seattle, Wash), an inhibitor of caspase-1, IL-1 trap (Regeneron Pharmaceuticals, Tarrytown, NY), an inhibitor of IL-1, or adalimumab (Abbott Laboratories, North Chicago, Ill), an inhibitor of TNF. After 14 hours, we collected supernatant and determined concentrations of IL-1, IL-6, and TNF by cytokine bead array (BD Biosciences, San Diego, Calif).

There was no spontaneous secretion of cytokines, but the concentration of all 3 cytokines upon stimulation with LPS was significantly elevated in the patient versus control (Fig 2, A). Both the IL-1 trap and the caspase-inhibitor YVAD were effective in inhibiting the hypersecretion of all 3 cytokines, whereas adalimumab had only a very limited effect (Fig 2, B). The effect of the IL-1 trap on IL-1 secretion cannot be directly demonstrated in this model as it interacts with this IL-1 detection assay.

Schnitzler syndrome is defined as a combination of chronic urticaria, IgM gammopathy, and at least 2 of the

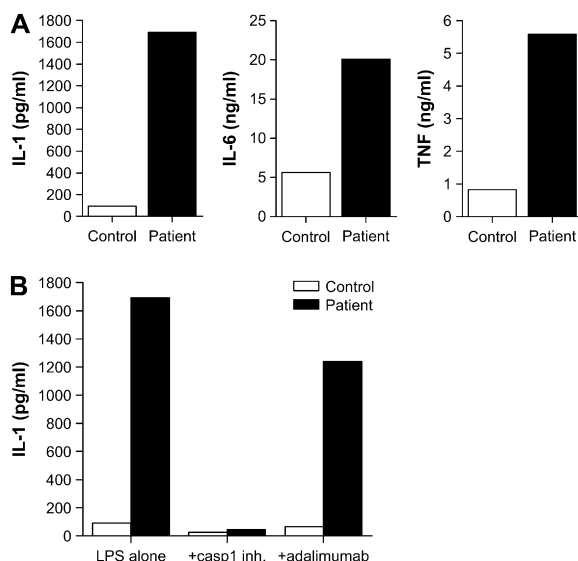


FIG 2. A, Cytokine production by PBMCs on LPS stimulation is significantly increased in patient (4-fold for IL-6, 15-fold for IL-1). **B,** Caspase-1 inhibitor YVAD had the most profound effect on LPS-induced IL-1 and also on IL-6 and TNF (not shown), more than TNF inhibitor adalimumab.

following criteria: recurrent fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepatomegaly or splenomegaly, leukocytosis, an elevated erythrocyte sedimentation rate, and abnormalities in bone morphology.^{1,2} As in the present case, there is usually a diagnostic delay of years. Long-term follow-up is warranted because some patients progress to Waldenström macroglobulinemia.¹ Schnitzler syndrome is of unknown etiology; biopsy of skin lesions is generally in keeping with neutrophilic urticaria.³ The clinical response of patients with cryopyrinopathies such as MWS led to the use of anakinra in Schnitzler syndrome.^{4,5} To date, anakinra has resulted in complete remission of symptoms in all patients with Schnitzler syndrome; it does not seem to affect the IgM gammopathy.¹ Most patients require daily dosing to prevent recurrence of symptoms, although intermittent dosing has sufficed in isolated cases. The safety of anakinra has been evaluated in a randomized controlled trial in patients with rheumatoid arthritis. Adverse events included injection site reactions and a 2% risk of serious infections in the anakinra arm compared to a 1% risk in those receiving placebo. The effect of IL-1 inhibition on the risk of developing malignancy is still unknown.

There have been 2 reports on the use of TNF inhibitors in Schnitzler syndrome: in one report, etanercept gave a partial remission⁶; in another patient, inhibition of TNF

by either adalimumab or etanercept seemed to result in an exacerbation of disease.⁷ Our *ex vivo* results support these clinical observations (Fig 2).

The case presented in this report highlights the advances that have transformed Schnitzler syndrome from an incurable, incapacitating curiosity to a disorder with a successful and rational therapy. Schnitzler syndrome should be considered in patients with chronic urticaria who fail to improve with standard therapies. A careful history with regard to systemic symptoms and serum protein electrophoresis can lead to a diagnosis. Monotherapy with an inhibitor of IL-1 is the treatment of choice. This report provides *ex vivo* evidence to support clinical observations.

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