

Case Letter

Successful Treatment of Schnitzler Syndrome With Canakinumab

To the Editor:

Schnitzler syndrome occurs with a triad of chronic urticaria, recurring fevers, and monoclonal gammopathy. It was recognized as a clinical entity in 1972; now nearly 200 patients are reported in the medical literature.¹⁻³ Flulike symptoms, arthralgia, bone pain, lymphadenopathy, and hepatosplenomegaly also are clinical findings.^{4,5} The erythrocyte sedimentation rate (ESR) often is markedly elevated, as are other acute phase reactants. Leukocytosis with neutrophilia and IgM and IgG monoclonal gammopathies have been described.⁴

Schnitzler syndrome shares many clinical characteristics with a subset of autoinflammatory disorders referred to as cryopyrin-associated periodic syndromes (CAPS), which includes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. These syndromes are associated with mutations in the cold-induced autoinflammatory syndrome 1 gene, *CIAS1*, which encodes the NALP3 inflammasome, leading to overproduction of IL-1 β .⁵ A gain-of-function mutation in *CIAS1* has been described in a patient with Schnitzler syndrome.⁶

Treatment of urticaria and constitutional symptoms associated with Schnitzler syndrome is challenging. Antihistamines are ineffective, though high-dose systemic glucocorticosteroids control most of the clinical manifestations. Methotrexate sodium, cyclosporine, and tumor necrosis factor antagonists are utilized as glucocorticosteroid-sparing agents. Anakinra, an IL-1 receptor monoclonal antibody that is approved for use in CAPS, has been reported to induce complete resolution of Schnitzler syndrome when administered daily; however, it is not approved by the US Food and Drug Administration for this disorder.⁷ Canakinumab, an IL-1 β monoclonal antibody that is dosed every 8 weeks, was approved

by the US Food and Drug Administration in 2009 for the treatment of CAPS. Given the similar clinical characteristics and genetic mutations found in CAPS and Schnitzler syndrome, canakinumab may be an effective treatment of both disorders. We report successful treatment with this monoclonal antibody in 2 patients with Schnitzler syndrome.

A 63-year-old man reported having night sweats and fatigue but had no arthralgia or arthritis. He had a 1-year history of severe urticaria and recurrent fevers (temperature, up to 38.4°C) and he also had type 1 diabetes mellitus, hypothyroidism, and celiac disease. Physical examination revealed an elevated temperature (38.4°C) and generalized urticaria but no evidence of hepatosplenomegaly, adenopathy, or arthritis. Leukocytosis was revealed (white blood cell count, 12,400/ μ L [reference range, 4500–11,000/ μ L]) with neutrophilia (88.5% [reference range, 56%]), elevated ESR (81 mm/h [reference range, 0–20 mm/h]), and IgM κ monoclonal gammopathy (0.37 g/L [reference range, 0.4–2.3 g/L]). Clinical examination as well as laboratory and imaging studies did not show evidence of malignancy or autoimmune disease. A skin biopsy identified neutrophilic urticaria without vasculitis. Prednisone 20 mg daily controlled the urticaria and fever, but symptoms recurred within days of glucocorticosteroid withdrawal.

A 47-year-old woman presented with a 7-year history of severe urticaria, fever (temperature, 38.9°C), myalgia, and arthralgia. She had a medical history of allergic rhinitis, gastroesophageal reflux disease, chronic pain syndrome, and depression. Physical examination revealed generalized urticaria with cervical and axillary lymphadenopathy 1 to 2 cm in size but no hepatosplenomegaly or arthritis. Prior evaluations for fever of unknown origin as well as autoimmune and malignant disorders were negative. Skin biopsies reported neutrophilic urticaria without vasculitis, and a lymph node biopsy from the left axilla revealed neutrophilic inflammation. A white blood cell count of 17,800/ μ L with 61.6% neutrophils, elevated C-reactive protein (153.4 mg/L [reference range, 0.08–3.1 mg/L]) and ESR (90 mm/h), and an IgG λ monoclonal gammopathy were present. She was previously treated with etanercept, methotrexate sodium, golimumab,

Dr. Pesek is from the University of Arkansas for Medical Sciences, Little Rock. Dr. Fox is from the University of South Florida, Tampa, and the James A. Haley Veterans' Hospital, Tampa.

The authors report no conflict of interest.

Correspondence: Robbie Pesek, MD, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, 13 Children's Way, Slot 512-13, Little Rock, AR 72202 (rdpesek@uams.edu).

and adalimumab, with only a partial response. For more than 5 years, prednisone 20 to 50 mg daily was necessary to control her symptoms. Cyclosporine 200 mg twice daily was added as a corticosteroid-sparing drug with partial response.

Both patients were diagnosed with Schnitzler syndrome and were started on canakinumab 150 mg administered subcutaneously in the upper arm every 8 weeks. Resolution of the urticaria and fevers occurred within 2 weeks, and all other medications for the treatment of Schnitzler syndrome were withdrawn without recurrence of symptoms after 3 years. The neutrophil count and acute phase reactants returned within reference range in each patient, but the monoclonal gammopathies remained unchanged. Patient 2 noted worsening of arthralgia after initiation of canakinumab, but long-term corticosteroid withdrawal was considered the cause. Patient 1 has been able to increase the interval of dosing to every 3 to 4 months without recurrence of symptoms. Patient 2 has not tolerated similar changes in dosing interval.

Canakinumab given at 8-week intervals was a safe and effective treatment of Schnitzler syndrome in this open trial of 2 patients. Anakinra also induces remission, but daily dosing is required. Cost may be a notable factor in the choice of therapy, as canakinumab costs substantially more per year than anakinra. Further investigation is required to determine if treatment with canakinumab will result in long-term

remission and if less-frequent dosing will provide continued efficacy.

Robbie Pesek, MD
Roger Fox, MD

REFERENCES

1. Schnitzler L. Lésions urticariennes chroniques permanentes (érythème pétaaloïde?). *Cas cliniques. n° 46 B. Journée Dermatologique d'Angers*. October 1972.
2. Schnitzler L, Schubert B, Boasson M, et al. Urticaire chronique, lésions osseuses, macroglobulinémie IgM: maladie de Waldenström. *Bull Soc Fr Dermatol Syphiligr*. 1974;81:363.
3. Simon A, Asli B, Braun-Falco M, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy*. 2013;68:562-568.
4. de Koning HD, Bodar EJ, van der Meer JW, et al. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment [published online ahead of print June 21, 2007]. *Semin Arthritis Rheum*. 2007;37:137-148.
5. Lipsker D, Veran Y, Grunenberger F, et al. The Schnitzler syndrome. four new cases and review of the literature. *Medicine (Baltimore)*. 2001;80:37-44.
6. Looock J, Lamprecht P, Timmann C, et al. Genetic predisposition (NLRP3 V198M mutation) for IL-1-mediated inflammation in a patient with Schnitzler syndrome. *J Allergy Clin Immunol*. 2010;125:500-502.
7. Ryan JG, de Koning HD, Beck LA, et al. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission [published online ahead of print October 22, 2007]. *J Allergy Clin Immunol*. 2008;121:260-262.