

## Chronic Urticaria and Arthritis with Polyclonal IgA: Rapid Response and Clinical Remission with Interleukin 1 Blockade

To the Editor:

Interleukin 1 (IL-1) has been identified to mediate several autoinflammatory diseases with features of chronic urticaria, polyarthritis, and systemic inflammation<sup>1</sup>. A case clinically resembling Schnitzler's syndrome but with polyclonal IgA is described. The rapid response to IL-1 blockade with clinical remission indicates a critical role of IL-1 in the pathogenesis of this disorder.

A 54-year-old white woman presented with chronic urticaria and joint pain. Urticaria began at 9 years of age and bilateral knee joint pain began 3 years later. These symptoms had been recurrent and appeared more frequently with age, from once a week to once every 2–3 days, and lasted longer, from one day to 2–3 days and at times sustained for one week. One year before presentation, mildly pruritic urticaria appeared daily, first in the trunk, and spread to the extremities. Her joint pain was associated with rash and involved knees, ankles, shoulders, elbows, and occasionally wrists and proximal interphalangeal joints. Inflammatory synovial fluid without crystals was detected in the left knee 5 months prior to presentation. Finger-clubbing was noted over the past 7 years. She had fatigue and night sweat, but no fever. She had borderline splenomegaly. Skin histopathology was consistent with urticaria with neutrophil infiltrate. Trials of immunosuppressants in the past, including methotrexate, sulfasalazine and cyclosporine, were unsuccessful. High-dose prednisone (60–80 mg/day) suppressed urticaria and improved arthritis. But symptoms returned when prednisone was tapered to 10 mg/day. Antihistamine agents had no effects on urticaria or arthritis. On examination, she had finger-clubbing without cyanosis or edema of lower extremities. There was no synovitis or joint effusion. She had small and large areas of erythematous maculopapular rash on her trunk, extremities, and neck, but not her face. Her white blood cell count was 15,300/mm<sup>3</sup>, hemoglobin 11.8 g/dl, platelets 482,000/mm<sup>3</sup>, absolute number of neutrophils 12,900 mm<sup>3</sup>, erythrocyte sedimentation rate (ESR) 105 mm/h, C-reactive protein (CRP) 151 mg/l (normal < 6 mg/l), ferritin 472 ng/ml, and IgA 703 mg/dl (normal 70–400 mg/dl; Figure 1). IgG and IgM levels were normal. Monoclonal gamma-globulin was not evident on immunofixation. She had tested negative for autoantibodies to nuclear antigens, neutrophil cytoplasm, and IgE receptor and rheumatoid factor. Serum IgE and complement levels were normal.

Anakinra 100 mg daily by subcutaneous injection was started. Three hours after the first dose of anakinra, the rash resolved completely and her joint pain began to improve. Continuing with daily anakinra, the urticaria did not recur and the arthritis resolved. Two weeks after initiation of anakinra, the leukocytosis resolved; hemoglobin, CRP, and ferritin were normalized; and ESR was markedly improved. Her serum IgA level initially declined slightly, but reached a plateau and was not normalized (Figure 1). Continuation of daily anakinra sustained the clinical therapeutic effects and improvement of laboratory measures of systemic inflammation. She remained in remission at 8 months after initiation of anakinra. However, her finger-clubbing remained with no changes.

The clinical constellation of this case fits the spectrum of autoinflammatory diseases and closely resembles Schnitzler's syndrome. However, the major distinction of this case from Schnitzler's syndrome was the lack of monoclonal IgM or IgG that is a major criterion for diagnosis<sup>2</sup>; instead, she had elevated polyclonal IgA. There is one case report that a 58-year-old woman with chronic urticaria associated with polyclonal IgG and IgA had complete resolution on anakinra<sup>3</sup>. Several reported cases indicate the efficacy of anakinra in treating Schnitzler's syndrome<sup>4–9</sup>. The significant therapeutic effect and rapid onset of response to IL-1 blockade indicates that IL-1 is the effector molecule in the pathogenesis of Schnitzler's syndrome. Ironically, virtually no increased plasma level of IL-1 is detected in those cases of proven IL-1-mediated inflammatory diseases, although *ex vivo*-stimulated peripheral blood mononuclear cells from these patients produced strikingly increased amounts of IL-1<sup>9</sup>. A recently discovered positive feedback of IL-1 $\beta$  stimulating its own produc-

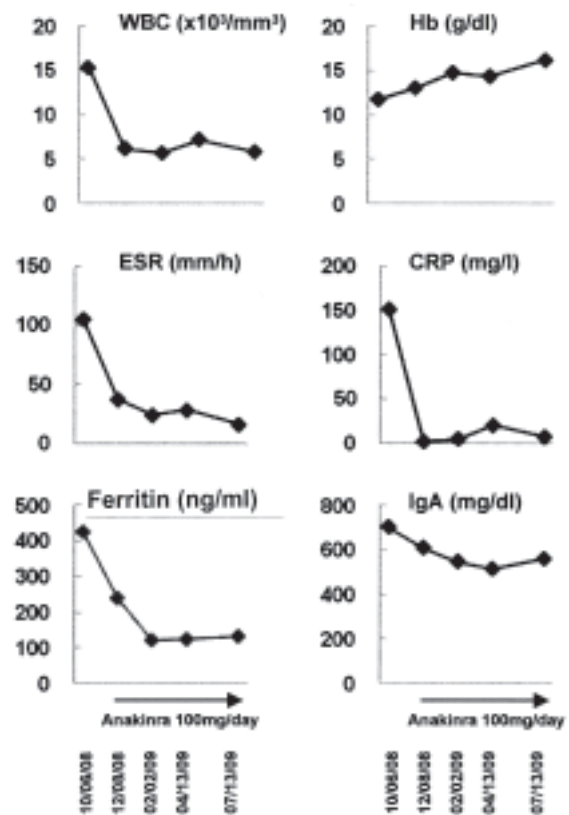


Figure 1. Laboratory values and response to anakinra therapy. WBC: white blood cells; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IgA: immunoglobulin A.

tion *in vivo* in patients with cryopyrin-associated periodic syndrome may explain why seemingly little detectable IL-1 is needed to cause the symptoms of autoinflammatory diseases<sup>10</sup>.

This case and the previous one<sup>3</sup> with increased polyclonal IgA or IgG and high efficacy of IL-1 blockade suggest a broader spectrum of Schnitzler's syndrome-like disorders associated with elevated Ig (monoclonal or polyclonal) and increased IL-1 activity. It would not be surprising that more Schnitzler's syndrome-like cases will be recognized among patients with chronic urticaria refractory to standard treatments. The criterion of monoclonal IgM or IgG<sup>2</sup> for diagnosis of Schnitzler's syndrome may need to be revised to include polyclonal Ig.

It remains to be determined how elevated Ig and increased IL-1 activity are related in Schnitzler's syndrome. As seen in this case and others<sup>2,9</sup>, blocking IL-1 has little or no effect on elevated Ig concentrations. This suggests that IL-1 does not contribute to the elevated Ig. On the other hand, little is known about whether monoclonal or polyclonal Ig contributes to IL-1 production<sup>2</sup>. Alternatively, we may speculate that a third factor(s), such as IL-6, drives both increased Ig and IL-1 production.

CONG-QIU CHU, MD, PhD, Assistant Professor of Medicine, Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University and Portland VA Medical Center, Portland, Oregon, USA. Address correspondence to Dr. C-Q. Chu, Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, OP09, Portland, OR 97239, USA. E-mail: chuc@ohsu.edu

## REFERENCES

1. Dinarello CA. Immunological and inflammatory functions of the

- interleukin-1 family. *Annu Rev Immunol* 2009;27:519-50.
2. de Koning HD, Bodar EJ, van der Meer JW, Simon A. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007;37:137-48.
  3. Treudler R, Kauer F, Simon JC. Striking effect of the IL-1 receptor antagonist anakinra in chronic urticarial rash with polyclonal increase in IgA and IgG. *Acta Derm Venereol* 2007;87:280-1.
  4. Asli B, Bienvenu B, Cordoliani F, Brouet JC, Uzunhan Y, Arnulf B, et al. Chronic urticaria and monoclonal IgM gammopathy (Schnitzler syndrome): report of 11 cases treated with pefloxacin. *Arch Dermatol* 2007;143:1046-50.
  5. Devlin LA, Wright G, Edgar JD. A rare cause of a common symptom, anakinra is effective in the urticaria of Schnitzler syndrome: a case report. *Cases J* 2008;1:348.
  6. Klemmer N, Lenain P, Balguerie X, Le Loet X. Effectiveness of anti-IL-1 in Schnitzler's syndrome. *Joint Bone Spine* 2007; 74:509-10.
  7. Lipsker D. The Schnitzler syndrome — a treatment at last? *Dermatology* 2002;205:1-2.
  8. 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. *Arthritis Rheum* 2005;52:2226-7.
  9. Ryan JG, de Koning HD, Beck LA, Booty MG, Kastner DL, Simon A. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission. *J Allergy Clin Immunol* 2008;121:260-2.
  10. Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, et al. In vivo regulation of interleukin 1 beta in patients with cryopyrin-associated periodic syndromes. *J Exp Med* 2009;206:1029-36.
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