



Letters

Chronic urticaria with monoclonal IgG gammopathy: a clinical variant of Schnitzler syndrome?

Schnitzler syndrome (SS) is a rare entity originally described as chronic urticaria associated with intermittent fever, arthralgias, and monoclonal immunoglobulin (Ig) M gammopathy.¹ We describe two patients seen in our allergy clinic who were diagnosed with SS. Both patients demonstrated similar symptoms along with a monoclonal gammopathy. However, one displayed an IgM gammopathy; the other, an IgG. This paper illustrates that SS can present similarly with both types of monoclonal gammopathy.

Patient 1, a 51-year-old woman, was evaluated for complaints of daily hives of 4 months' duration. She started taking hydroxyzine nightly for the past month without symptom relief. She also experienced generalized myalgias, arthralgias, and several febrile episodes 1 week before evaluation. On presentation, the patient was afebrile, and physical examination was notable for urticarial papules on her chest. Laboratory analysis was significant for positive antinuclear antibody (1:160 speckled pattern) and increased anti-Ro and anti-La antibody levels. Serum protein electrophoresis indicated a monoclonal spike with an increased kappa/lambda ratio of 3.78. The quantitative immunoglobulin assay demonstrated an elevated IgG level of 2,640 mg/dL (normal, 844–1,912). Results of serum chemistries, beta-2-microglobulin, hepatic function panel, complement levels, and thyroid function tests were unremarkable. The patient was started on doxepin 10 mg daily for her chronic urticarial symptoms and referred to the hematology department for monitoring of her monoclonal gammopathy. On follow-up 3 months later, the patient reported improved urticaria on the new treatment regimen.

Patient 2 was a 52-year-old woman with chronic urticaria, arthralgias, and daily bone pain for approximately 20 years. Previous symptoms were notable for urticarial lesions commencing on postpartum day 1 after the delivery of her first child and bilateral lower extremity arthralgias starting 6 months after her third child was born. Both symptoms increased in frequency over the past decade until they became daily occurrences. She also experienced occasional fevers. On presentation, the patient was afebrile, and physical examination was significant for non-blanching urticarial lesions on the chest and bilateral forearms. Laboratory testing was remarkable for an elevated IgM of 391 mg/dL (normal, 40–230) and serum protein electrophoresis revealing an M-spike of 0.5 g/dL. Serum chemistries, beta-2-microglobulin, hepatic function panel, antinuclear antibody, and complement levels were unremarkable. The patient was started on twice-daily antihistamine therapy. On follow-up 1 month later, she reported improvement in all of her symptoms.

Both of our patients were diagnosed with SS. Theoretically, monoclonal gammopathy of undetermined significance could coexist with chronic urticaria and thereby mimic the syndrome. However, our diagnosis was based on a set of diagnostic criteria (Table

Table 1

Diagnostic criteria for schnitzler syndrome: two major criteria in addition to at least 2 of the minor criteria are necessary for the diagnosis²

Major criteria (both required)	Minor criteria (at least 2 required)
Chronic urticarial skin rash	Intermittent fever
Monoclonal gammopathy (IgM or IgG)	Arthralgias or arthritis
	Bone pain
	Palpable lymph nodes
	Liver or spleen enlargement
	Elevated erythrocyte sedimentation rate
	Leukocytosis
	Bone abnormalities on radiological imaging or histological investigation

1) set forth by Lipsker et al in 2001² and subsequently accepted by de Koning et al¹ in 2007 after reviewing 94 cases. Because SS is defined by a specific constellation of clinical and biologic signs with a diagnostic criteria well accepted in the literature, we feel confident in our diagnosis and that it is unlikely to be a coincidence.

Although its pathogenesis remains unclear, SS may be categorized as an immune-mediated inflammatory disease with features of autoimmunity.³ Pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6 have been implicated in SS.⁴ Uncontrolled activation of IL-1 has been suggested to play a role, although the exact mechanism remains unknown. The effects of IL-6 on B-cell differentiation might contribute to the gammopathy in SS.⁴ Usually a monoclonal IgM gammopathy is observed; however, a rarer variant SS has been reported, characterized by IgG gammopathy.¹ Deposits of IgM in the skin may be the cause of the cutaneous manifestation of SS via immune complex formation and complement activation.⁵ Skin biopsies of urticarial lesions show heterogeneous histopathological findings ranging from neutrophilic urticaria to spongiotic dermatitis.^{3,6} Skin biopsies were not performed in our patients because they are not required for diagnosis.

Therapies for SS have shown variable results. In most cases, high-dose corticosteroids are able to decrease symptoms.¹ However, the use of steroids as long-term treatment is limited because of their side effects.¹ Other treatment modalities including immunosuppressant agents have been used.^{5,7} Anakinra, an IL-1 receptor antagonist, was successfully used in several cases of SS.⁸ The success of Anakinra has provided key insights into the mechanisms of this disease. The next step in increasing our understanding of SS is genetic analysis, because in many aspects it resembles genetically determined auto-inflammatory syndromes.³ Efforts are currently underway to search for genetic factors in an international clinical study (<http://clinicaltrials.gov/ct2/show/NCT00933296>). Although SS is typically associated with an IgM gammopathy, our two case presentations high-

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light the similarities between chronic urticaria and monoclonal gammopathy of either IgM or IgG. The diagnostic criteria for SS may therefore be extended to include the IgG variant.

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What should drive the choice of allergen for immunotherapy in polysensitized patients?

Polysensitization has always been an obstacle to prescription of allergen immunotherapy. Actually, 2 attitudes are dominant: to renounce to such treatment or to perform it by mixtures of all allergens giving a positive result to allergy tests. Both approaches are inappropriate, because the former has no real basis, whereas the latter was demonstrated to be ineffective.¹ In particular, the cited study might be a paradigmatic example of inappropriate prescription, because there were some possible biases, including the following: (1) The patients that were selected for this research trial did not have severe allergies; therefore the improvement with immunotherapy was not significant; (2) the patients were medicated or overmedicated, which possibly contributed to masking the benefit of immunotherapy, and (3) there was a question about the quality of the allergy extracts that were used in the study.

Calderon and colleagues² have recently revised the issue concerning immunotherapy strategy in polysensitized patients. In large-scale clinical trials of grass pollen sublingual tablets, polysensitized patients benefited at least as much from allergen

immunotherapy as did monosensitized patients. Sublingual and subcutaneous multiallergen immunotherapy in polysensitized patients requires more supporting data to validate its efficacy in practice.

Our studies confirmed the first statement; we found that in polysensitized subjects treated with sublingual immunotherapy for 1 year, using 1 to 2 single allergen extracts, a significant decrease of rhinitis severity occurred.^{3,4} Further analyzing the data, we noted an important aspect, represented by the discrepancy between the prevalence of specific sensitization and the relative prescription. We evaluated a group of adult patients with polysensitizations. The Figure shows that the allergens most frequently causative were grasses (82%), followed by *Parietaria* (48%), mites (47%), and *Betulaceae* (39%).⁵ The data concerning the allergen extracts prescribed for immunotherapy showed that most sensitizations to mites (>80%) become a prescription for immunotherapy, whereas fewer than 50% of grasses' sensitizations lead to prescription. This phenomenon was more evident for other pollens, such as *Parietaria* and olive tree (approximately one third of sensitized patients were treated with immunotherapy), and *Betulaceae* (only 20% of patients were

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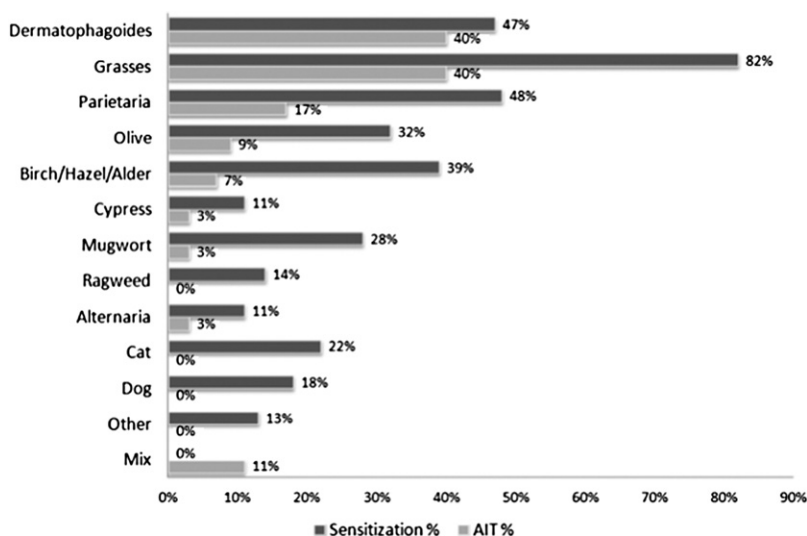


Fig. 1. Frequencies of allergen sensitization (dark bars) and allergen prescription for allergen immunotherapy (light bars) in patients with polysensitization. AIT, allergen immunotherapy.