Clinical and histopathologic review of Schnitzler syndrome: The Mayo Clinic experience (1972-2011)

Olayemi Sokumbi, MD,[a] Lisa A. Drage, MD,[a] and Margot S. Peters, MD[a,b]
Rochester, Minnesota

Background: Schnitzler syndrome is a rare multisystem disorder, defined by urticaria and monoclonal gammopathy, that is associated with malignancy. Considered a neutrophilic urticarial dermatosis, previous reports have included patients with leukocytoclastic vasculitis.

Objective: We sought to better define the clinical features, histopathology, and outcomes of Schnitzler syndrome.

Methods: We retrospectively reviewed clinical records and cutaneous histopathology of all patients with Schnitzler syndrome seen at our institution from January 1, 1972, through July 31, 2011.

Results: Of the 20 patients identified, 80% had IgM κ monoclonal gammopathy; others had IgG λ (10%), IgG κ (5%), or IgM $\kappa+\lambda$ (5%). Patients had fevers (85%), arthralgias (70%), leukocytosis (70%), increased erythrocyte sedimentation rate (70%), bone pain (50%), lymphadenopathy (40%), and organomegaly (5%); 45% developed a hematologic malignancy. Histopathologic examination (n = 14) showed predominantly neutrophilic perivascular and interstitial inflammation (57%) or predominantly mononuclear cell perivascular inflammation (29%), with eosinophils in 50% of cases. None showed leukocytoclastic vasculitis.

Limitations: Our study was limited by its retrospective design.

Conclusion: We added 20 patients to approximately 100 reported cases of Schnitzler syndrome. Neutrophilic urticarial dermatosis was the most common histopathologic pattern, but mononuclear cells were predominant in many cases and the infiltrates often contained eosinophils. A high index of suspicion and careful clinicopathologic correlation are needed to avoid diagnostic delays in this syndrome associated with hematologic malignancy. (J Am Acad Dermatol 2012;67:1289-95.)

Key words: anakinra; hematologic malignancy; hypocomplementemia; lymphoproliferative disease; monoclonal gammopathy; neutrophilic urticarial dermatosis; Schnitzler syndrome; urticaria; Waldenström macroglobulinemia.

Schnitzler syndrome is a rare clinical entity, classically characterized by recurrent, nonpruritic urticaria, monoclonal IgM gammopathy, and at least 2 of the following additional abnormalities: intermittent fever, bone pain, arthralgias or arthritis, lymphadenopathy, hepatomegaly and/or splenomegaly, and leukocytosis. Although patients may have elevated inflammatory indices such as erythrocyte sedimentation rate or C-reactive protein, abnormality in the complement system is rare.[1] The syndrome typically evolves over a long course, and a lymphoproliferative disorder develops in approximately 20% of patients. The cutaneous histopathology of Schnitzler syndrome has been

Abbreviations used:

IL: interleukin
LE: lupus erythematosus
NUD: neutrophilic urticarial dermatosis

From the Departments of Dermatology[a] and Laboratory Medicine and Pathology,[b] Mayo Clinic.
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Reprint requests: Margot S. Peters, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: peters.margot@mayo.edu.
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categorized as a neutrophilic urticarial dermatosis (NUD), which is composed of perivascular and interstitial neutrophilic inflammation with leukocytoclasia but without true leukocytoclastic vasculitis.[2] Although the disease pathogenesis is not established, autoinflammatory mechanisms are favored.[3-5]

Since its initial description in 1972 by the French dermatologist Liliane Schnitzler,[6] approximately 100 cases have been reported, with solitary or small numbers of patients from each source.[3] We retrospectively reviewed clinical records and cutaneous histopathology of all patients with Schnitzler syndrome seen at our institution during a period spanning nearly 4 decades.

CAPSULE SUMMARY

- Schnitzler syndrome is defined by urticaria and monoclonal gammopathy, plus at least 2 minor criteria: fever, bone pain, arthralgias or arthritis, lymphadenopathy, organomegaly, increased erythrocyte sedimentation rate, and leukocytosis.
- Histopathologically, predominantly neutrophilic perivascular and interstitial inflammation (neutrophilic urticarial dermatosis) or predominantly mononuclear cell perivascular inflammation, with or without eosinophils and without true vasculitis, is observed.
- Diagnosis is often delayed and requires a high index of suspicion with clinicopathologic correlation.

METHODS

This study was approved by our institutional review board. Patients were evaluated from January 1, 1972, through July 31, 2011.

Diagnosis of Schnitzler syndrome was established on the basis of documentation of an urticarial rash and monoclonal gammopathy (major criteria) plus at least 2 of the following minor criteria: fevers (recurrent or intermittent), arthralgias or arthritis, bone pain, lymphadenopathy, hepatomegaly and/or splenomegaly, elevated erythrocyte sedimentation rate, leukocytosis, and abnormal findings on bone imaging.[2,6] Other potential diagnoses (eg, hyper-IgD syndrome, adult-onset Still disease, hypocomplementemic urticarial vasculitis, acquired C1 inhibitor deficiency) were considered and eliminated before confirming the diagnosis of Schnitzler syndrome.

We used the institutional medical index and text retrieval system to identify patients with a diagnosis of Schnitzler syndrome and extracted the following data from the medical records: patient characteristics, duration from onset of symptoms and signs to diagnosis of Schnitzler syndrome, presence of major and minor diagnostic criteria, results of cutaneous direct immunofluorescence testing, response to treatment, development of lymphoproliferative disease, and clinical outcome. Formalin-fixed, paraffin-embedded, hematoxylin-eosin–stained tissue sections, obtained during the patients' episodes of care, were examined histopathologically.

RESULTS

We initially identified a preliminary cohort of 72 patients. Those who did not meet the above diagnostic criteria were excluded. The final cohort included 20 patients (65% male; mean age of 59 years [range, 37-84 years]). All fulfilled the 2 major criteria and 3 to 7 minor criteria (fevers [85%], arthralgias [70%], leukocytosis [70%], increased erythrocyte sedimentation rate [70%], bone pain [50%], lymphadenopathy [40%], and organomegaly [5%]). Sixteen patients (80%) fulfilled at least 3 minor criteria; the most common triad was fever, arthralgias or arthritis, and leukocytosis. The diagnosis of Schnitzler syndrome was established 2 to 13 years (mean, 6.1 years) after onset of symptoms. For the 18 patients who had determination of serum complement level, the decreased complement factors were C4 (n = 18 [100%]), C1q (n = 12 [67%]), C2 (n = 6 [33%]), and C3 (n = 6 [33%]).

Medications associated with greatest symptomatic improvement appeared to be corticosteroids (11 of 13 patients), rituximab (2 of 3 patients), and cyclophosphamide (1 of 1 patient). Of 5 patients who received anakinra, 1 reported dramatic improvement and a second patient had minimal benefit; the other 3 patients were lost to follow-up.

Nine patients (45%) developed a malignancy (Table I) at an average of 7.6 years (range, 2-13 years) after onset of symptoms and signs of Schnitzler syndrome. Six patients (67%) with malignancy received chemotherapy. As of manuscript preparation, only 1 of 20 patients had died, of unknown causes.

We reviewed the histopathology of 16 skin biopsy specimens obtained from 14 patients and observed 3 patterns: (1) predominantly neutrophilic perivascular and interstitial inflammation with variable (minimal to brisk) leukocytoclasia in 9 specimens from 8 of 14 patients (57%) (Fig 1); (2) predominantly mononuclear cell perivascular inflammation in 5 specimens from 4 patients (29%) (Fig 2); and (3)

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