

A 30-year-old woman with chronic hives, intermittent fevers, and joint pain

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ABSTRACT

Chronic urticaria with concomitant systemic symptoms may be seen in several rheumatologic and autoinflammatory conditions. Although most of these conditions tend to improve with corticosteroids, symptoms often recur with dose tapering. The appearance of the rash in addition to the symptom pattern and laboratory data must be considered to differentiate potential causes. We presented a unique case of chronic urticaria with fevers and arthralgias. A diagnosis was made, and the patient had rapid improvement with targeted therapy.

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CHIEF COMPLAINT

Chronic hives, fevers, and joint pain.

HISTORY OF PRESENT ILLNESS

A 30-year-old woman presented with a chief complaint of chronic hives, intermittent fevers, and joint pain over the past 2 years. Rash occurred daily, which appeared as erythematous nonpruritic macules and slightly raised plaques on her trunk and extremities. Individual lesions lasted for 1–2 days before resolving without scarring or hyperpigmentation. She had tried high-dose antihistamines without relief. She began to experience diffuse arthralgias in addition to her rash. Thus, she was started on prednisone with temporary improvement in symptoms. As the prednisone was tapered, she experienced acute worsening of her urticarial rash, accompanied by fevers, with a temperature up to 39.7°C, and severe pain in her shoulders, elbows, knees, ankles, and hips on weight bearing. She was hospitalized twice, with a negative workup result for infectious etiologies. Her prednisone was again increased with improvement in symptoms and resolution of fever. When prednisone was tapered to <10 mg daily, she noted the return of her rash and onset of palpable joint swelling of her knees.

PHYSICAL EXAMINATION

The patient's vital signs were normal. Results of the patient's head and neck examination were unremarkable. There was no lymphadenopathy. Her lungs were clear, without wheezes, rales, or rhonchi. Her heart was regular rate and rhythm without murmurs or rubs. Her abdomen was soft and nontender, without appreciable organomegaly. Widespread erythematous blanching urticarial macules and plaques were present, which covered much of her back, trunk, arms, and hands (Fig. 1). Bilateral knee pain was elicited, with passive range of motion. Bilateral knee fullness was appreciated, with palpable effusions, left greater than right. The remainder of the examination was unremarkable.

LABORATORY AND OTHER DIAGNOSTIC FINDINGS

Notable findings during a recent hospitalization included leukocytosis, >18,000/μL, with 93% neutrophils and ferritin level of >2000 ng/mL. Erythrocyte sedimentation rate and C-reactive protein values were 84 mm/hour and 123.8 mg/L, respectively. Results of a battery of autoantibody serologies (rheumatoid factor, antinuclear antibody, antidouble stranded DNA, anti-smith, anti-Sjögren's syndrome-related antigen A, anti-Sjögren's syndrome-related antigen B, anti-ribonucleoprotein, anticardiolipin, antineutrophil cytoplasmic antibody), quantitative immunoglobulins, hepatitis viral serologies, and complement levels all were normal. A computed tomography of her abdomen to assess for abscess or malignancy showed only mild splenomegaly. A skin biopsy of her rash was performed, which revealed the unique finding of neutrophilic urticaria, with "low density, interstitial and

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Figure 1. Erythematous macules and slightly raised plaques on the case patient's arms (A) and legs (B).

perivascular inflammatory infiltrate dominated by neutrophils" (Fig. 2). No evidence of vasculitis was found, with a reported absence of leukocytoclasia, perivascular fibrin exudate, and extravasation of red cells.

CLINICAL COURSE QUESTIONS

Question 1

What is the differential diagnosis?

- (a) Systemic lupus erythematosus
- (b) Schnitzler syndrome
- (c) Adult-onset Still disease (AOSD)
- (d) Sweet syndrome

Question 2

What additional laboratory data or investigations would be helpful in arriving at a diagnosis for this patient?

Her history was notably suggestive of Schnitzler syndrome, although serum and urine electrophoreses had not yet been ordered to assess for the presence of a monoclonal M spike. Both were obtained, and the results were negative for monoclonal immunoglobulins by immunofixation electrophoresis. Repeated testing during a mild flare in symptoms showed a polyclonal

increase in immunoglobulins consistent with acute inflammation but was still otherwise normal.

DISCUSSION

Schnitzler syndrome is a rare disorder characterized by persistent urticarial rash, fevers, arthralgia and/or arthritis, bone pain, and lymphadenopathy.¹⁻³ Proposed diagnostic criteria require both urticarial rash and a laboratory finding of monoclonal immunoglobulin M to establish the diagnosis (Table 1).² The term Schnitzler-like syndrome has been used to describe a constellation of symptoms, which is otherwise characteristic but lacks one of the two major diagnostic criteria.¹ There are very few case reports that describe a Schnitzler-like syndrome without monoclonal immunoglobulin M.⁴⁻⁶ Although Schnitzler-like syndrome provides a descriptive label, it has not been established as a unique diagnosis. Here we presented a case of a Schnitzler-like syndrome and discussed whether this may represent a variant of Schnitzler syndrome, an atypical presentation of AOSD, systemic lupus erythematosus, or Sweet syndrome.

Perhaps the most striking and potentially diagnostic feature of this case is the neutrophilic urticaria described on histopathology. The term neutrophilic urti-

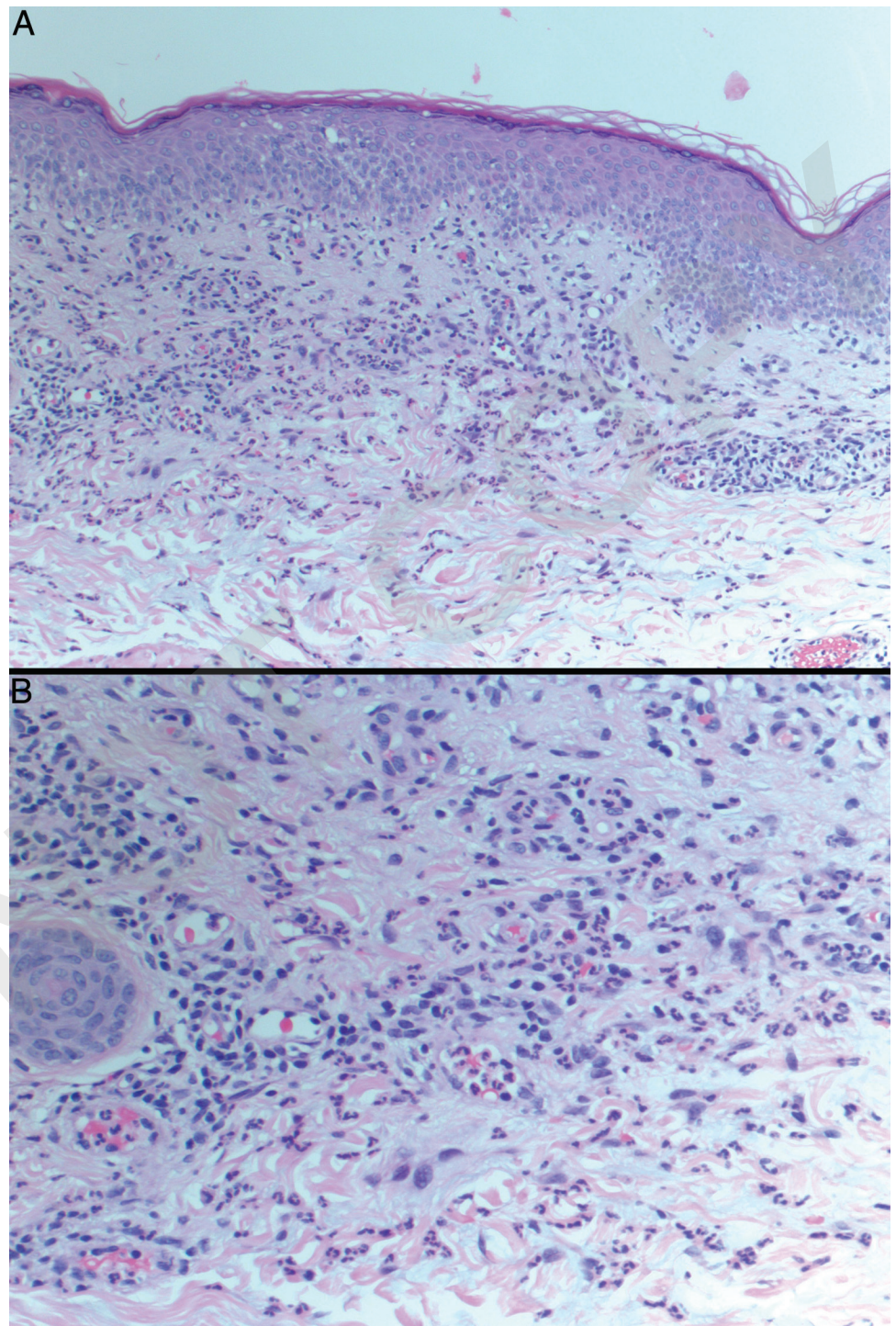


Figure 2. Representative histopathologic findings of a skin biopsy are depicted at mid-power (A) and high-power (B); inflammatory infiltrate in the dermis is dominated by neutrophils.

carial dermatosis has been used to categorize this rare finding and the diseases associated with it.⁷ Schnitzler syndrome, AOSD, and, less often, systemic lupus erythematosus have been associated with neutrophilic urticarial dermatosis.^{1,3,7,8} These syndromes are sometimes easily distinguished based on the appearance and frequency of rashes as well as by serology and multisystem involvement in the case of systemic lupus erythematosus. Neutrophilic dermatosis is also ob-

served with Sweet syndrome, although lesions are not generally urticarial and are described as brightly erythematous or violaceous. Schnitzler syndrome presents with chronic, sometime daily urticaria, which is moderately erythematous in appearance,^{1,2} whereas the rash of AOSD is classically salmon colored, maculopapular, and evanescent, often appearing and disappearing in correlation with quotidian fevers.^{8,9} Urticaria is a rare manifestation of AOSD, although at least

Table 1 Diagnostic criteria for Schnitzler syndrome and AOSD

	Schnitzler Syndrome Criteria*#	Case Patient	AOSD Criteria§¶	Case Patient
Major criteria				
	Chronic urticarial rash	×	Fever, temperature of $\geq 39^{\circ}\text{C}$ for ≥ 1 wk	×
	Monoclonal IgM		Arthralgia, ≥ 2 wk	×
			Rash (macular or maculopapular nonpruritic salmon-pink eruption, usually with fever)	
			Leukocytosis ($\geq 10,000/\text{mm}^3$) with $>80\%$ granulocytes	×
Minor criteria				
	Intermittent fever	×		
	Arthralgia or arthritis	×		
	Bone pain		Sore throat	
	Lymphadenopathy		Lymphadenopathy	
	Hepatomegaly, splenomegaly	×	Splenomegaly	×
	Elevated ESR level	×	Liver dysfunction	
	Leukocytosis	×	Negative RF and ANA	×
	Bone abnormalities			
Criteria met?		No		Yes

AOSD = Adult-onset Still disease; IgM = immunoglobulin M; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ANA = antinuclear antibody.

*From Ref. 2.

#The diagnosis of Schnitzler syndrome requires both major criteria plus two or more minor criteria as well as exclusion of other possible causes.

§From Ref. 9.

¶The diagnosis of AOSD requires five or more criteria, including two or more major criteria with exclusion of other possible causes.

28 cases have been previously reported with urticarial lesions.^{8,10}

Analysis of the epidemiologic data also reveals striking differences between Schnitzler syndrome and AOSD. Schnitzler syndrome has a male predominance, with mean age of onset of 51 years, rarely occurring before age 35 years.¹ In contrast, AOSD is more common in female patients and tends to present between 16 and 35 years of age.⁸ Analysis of the epidemiologic data favors AOSD over Schnitzler syndrome. Because Schnitzler syndrome and AOSD exhibit an assortment of overlapping features (Table 1), abnormal laboratory data may aid in differentiating the two. Specifically, urticaria with monoclonal immunoglobulin M is virtually pathognomonic for Schnitzler syndrome,¹⁻³ whereas marked elevation of the ferritin level is more suggestive of AOSD.¹ In fact, a case series of 16 patients with Schnitzler syndrome noted normal ferritin values in all of their patients.³ Our patient had a ferritin level of >2000 ng/mL, with normal immunofixation electrophoresis on two separate occasions.

In summary, although our patient had a daily urticarial rash suggestive of Schnitzler syndrome, analysis of epidemiologic and laboratory data strongly favored an atypical presentation of AOSD. Although pathophysiology of these diseases is not well understood, both are thought to involve dysregulation of the inflammasome, which leads to increased interleukin-1 production.¹ Anakinra, an interleukin-1 receptor antagonist, has been used therapeutically for both diseases as well as other autoinflammatory disorders, with rapid resolution of symptoms and normalization of inflammatory markers.^{1,3,5,7} Given the potent efficacy of anakinra in treating both diseases, the necessity of a definitive diagnosis may be questioned. However, prognosis and disease course differ dramatically between the two diseases, with AOSD generally remitting, whereas Schnitzler syndrome leads to chronic persistent symptoms.¹ Schnitzler syndrome has also been associated with lymphoproliferative disorders in $\sim 20\%$ of patients, which warrants ongoing monitoring for malignancy.¹ These distinctions highlight the utility in identifying a definitive diagnosis. Ultimately, we treated our patient

with anakinra subcutaneous daily injections. She experienced rapid improvement in her arthralgias and urticarial rash, with corresponding normalization of inflammatory markers. Her rapid and complete response confirmed that she has an interleukin-1-mediated disease. Although the appearance and chronicity of her rash was certainly Schnitzler-like, epidemiologic and laboratory data support the diagnosis of AOSD.

FINAL DIAGNOSIS

AOSD.

CONCLUSION

Chronic urticaria accompanied by fevers and arthralgias warrants a thorough evaluation for rheumatologic and autoinflammatory conditions. Although the clinical presentation may guide an initial workup, skin biopsy may prove invaluable. A histologic finding of neutrophilic urticaria should prompt narrowing of the differential diagnosis, with epidemiologic and laboratory data weighed to determine the final diagnosis. AOSD can present with a broad range of cutaneous manifestations⁸ and may clinically appear as a Schnitzler-like syndrome. Note that anakinra is not approved by the U.S. Food and Drug Administration for AOSD or Schnitzler syndrome.

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