Refractory Urticaria with Raised Antistreptolysin O (ASO) Titer: An Intriguing Case of Adult-Onset Still’s Disease

Patient: Female, 26-year-old
Final Diagnosis: Adult-onset Still's disease
Symptoms: Fever • urticaria
Medication: —
Clinical Procedure: —
Specialty: Dermatology • Rheumatology

Objective: Rare disease
Background: Adult-onset Still’s disease (AOSD) is a rare systemic autoinflammatory disease with a myriad of clinical presentations. The diagnosis is often challenging because there is no specific confirmatory test. Uncommon presentations can delay the proper diagnosis and management.

Case Report: A 26-year-old woman presented with a history of urticaria for 2 years that had failed to respond to many types of treatment. Cutaneous biopsy showed neutrophilic urticaria. A diagnosis of AOSD was made after infectious, drug-related, neoplastic, and rheumatic etiologies had been excluded and based on the triad of fever, evanescent rash, and joint pain. Besides leukocytosis and increased levels of inflammatory markers, the patient’s laboratory results showed an extremely high D-dimer concentration and an increased antistreptolysin O (ASO) titer. Treatment with prednisolone and methotrexate resulted in resolution of the woman’s symptoms. Once clinical remission had been achieved, all laboratory markers returned to normal, yet the patient’s ASO titer remained elevated during 18 months of follow-up.

Conclusions: Urticaria is a rare cutaneous manifestation of AOSD. Histopathology typically shows predominant neutrophilic infiltrates, which is a unique entity called neutrophilic urticarial dermatosis (NUD). Identifying diseases associated with NUD will facilitate prompt diagnosis and treatment of AOSD, as therapies for it largely differ depending on the underlying cause. Known etiologies of AOS include systemic lupus erythematosus (SLE), Schnitzler syndrome, hereditary autoinflammatory periodic syndromes, and serum sickness-like drug eruption. An elevated ASO titer is unusual, and in our case, it did not seem to follow the patient’s clinical course. An elevated D-dimer concentration can be an indicator of disease activity and testing might be beneficial in a subset of patients with normal ferritin levels.

MeSH Keywords: Skin Diseases • Still’s Disease, Adult-Onset • Urticaria

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Background

Adult-onset Still’s disease (AOSD) is a rare systemic autoinflammatory disease with a myriad of clinical presentations. Properly diagnosing it is challenging because it mimics many conditions, which must be excluded before the diagnosis is made. Several diagnostic criteria have been validated, the mostly widely accepted of which are the Yamaguchi criteria [1–3]. Among varied clinical features, AOSD typically presents with a classic triad of periodic high-spiking fever, arthralgia/arthritis, and an evanescent, salmon-pink, maculopapular rash. Clinicians often rely on the rash to make the diagnosis, yet atypical skin manifestations often have been reported and they may hinder identification of AOSD. Urticaria was reported in 11 of 81 cases of AOSD (14%) in the literature that involved atypical cutaneous manifestations [4]. We report on a 26-year-old woman with urticaria that was refractory to many treatments.

Case Report

In October 2018, a 26-year-old Yamani woman was referred from the Dermatology Service at King Khalid University Hospital to the Rheumatology Service because of refractory urticaria, generalized joint pain, and fever. She reported having a sore throat and fever 2 weeks earlier, but no cough or runny nose. She denied having contact with ill people or animals, traveling, or ingesting raw milk. The patient’s fever subsequently abated and then returned, along with pruritic urticaria and generalized joint pain. The urticaria and pain had started 18 months earlier, but the trigger was not clear. The patient was taking dapsone but had been off steroids for 4 months. She had responded well to 50- to 60-mg doses of prednisolone, but her symptoms reappeared whenever the drug was stopped. Various antihistamines had been tried as well, with limited success. Up to that point, the top diagnoses in the differential were Schnitzler syndrome and familial Mediterranean fever (FMF).

Upon evaluation, the patient had generalized joint pain that involved the hands, wrists, and knees, with no synovitis. Confluent pruritic urticarial plaques involved areas of the face, ears, and upper and lower extremities and resolved within 24 to 48 hours (Figure 1). Pharyngeal erythema was observed with no tonsillar exudates. The patient’s fever subsequently abated whenever the drug was stopped. Various antihistamines had been tried as well, with limited success. Up to that point, the top diagnoses in the differential were Schnitzler syndrome and familial Mediterranean fever (FMF).

Laboratory examination revealed a hemoglobin level of 11 g/dL (normal: 12–16), mean corpuscular volume of 77 (normal: 80–100), platelet count of 265 000 (normal: 150,000 to 450 000), and white blood cell count of 14 000 mm\(^3\) (normal: 4,000 to 10 000), with 86% neutrophils. The total protein level was 6.6 g/dL and albumin 37.3 g/dL; results of serum electrophoresis were unremarkable. The patient’s erythrocyte sedimentation rate was 60 mm/h, her C-reactive protein level was 60 mg/dL (normal: 0.0–0.8), and her serum ferritin level was 3.20 mg/L (normal: 10 to 200). Results from liver and renal function testing, a coagulation profile, and a urinalysis were unremarkable. The woman’s lactic acid dehydrogenase level was 310 U/L (normal: 140 to 280) and her D-dimer concentration was 22 µg/mL FEU (normal: 0.22 to 0.45). Testing for antinuclear antibodies was mildly positive at 1: 40. However, testing for rheumatoid factor, complements, anti-double stranded DNA, anti-cyclic citrullinated peptide, and anti-neutrophil cytoplasmic antibodies was negative. Testing for brucella, HIV, syphilis, Epstein-Barr virus, cytomegalovirus, hepatic virus, mycoplasma, and herpes simplex was negative. The patient’s anti-streptolysin O (ASO) titer was 414 (normal: 0 to 200 IU/mL). Her immunoglobulin levels were normal. Cultures from a throat swab and blood were negative. Computed tomography scans of the neck, chest, abdomen, and pelvis were unremarkable, as were X-rays of the patient’s hands, wrists, and knees. An echocardiogram also was normal.

The patient’s skin biopsy revealed perivascular and interstitial cellular infiltrates of lymphocytes, neutrophils, and a few eosinophils (Figure 2). In the absence of family history and after excluding infectious, drug-related, neoplastic, and rheumatic
dant eosinophils, and perivascular and interstitial neutrophilic features of classic eosinophilic urticaria, which typically has abundant eosinophils, and perivascular and interstitial neutrophilic infiltrates [5,6]. Furthermore, NUD has a unique differential diagnosis profile, which includes systemic lupus erythematosus (SLE), Schnitzler syndrome, hereditary autoinflammatory periodic syndromes, and serum sickness-like drug eruption, in addition to AOSD [7]. Management of NUD largely depends on the clinical context in which it occurs. A recent review by Gusdorf et al. delineated treatment of different categories of NUD. In patients without underlying autoimmune diseases or malignancies, management usually is with neutrophil migration inhibitors, such as dapsone and colchicine, with varying degrees of success. However, if an underlying cause is present, management of NUD differs. In the setting of AOSD, nonsteroidal anti-inflammatory drugs, corticosteroids, or methotrexate usually are effective for NUD, and the highest success rates are seen with anakinra or tocilizumab. For Schnitzler syndrome and cryopyrin-associated periodic syndrome, treatment that targets interleukin-1 blockade results in a remarkable response. For FMF and SLE, success has been reported with dapsone and colchicine [8].

One challenging aspect of the present case was the elevated ASO titer, which made rheumatic fever a possibility. However, the patient had no evidence of cardiac involvement, and biopsy is crucial to distinguish from the classic erythema marginatum rash, which suggests rheumatic fever. Our patient’s rash frequently involved her face and was pruritic, whereas in erythema marginatum, it is generally nonpruritic and spares the face in [9]. Besides these variables, a raised ASO could be a false positive, not specific for group A Streptococcus, which would be evidenced by a negative throat swab culture. A more specific test is needed for anti-DNase B. Unfortunately, that testing was not conducted in our case. In 1 notable case of AOSD, the patient had a clinical course similar to ours, with full clinical and laboratory remission but an elevated ASO titer [10]. Other reported cases suggest that the increase in the titer is a trigger for AOSD [11], while in 1 case, the titer fell after the disease was controlled [12]. Our understanding remains limited about whether the pathogenesis of AOSD and group A Streptococcus are related, and the titer remains high after a clinical response in some patients but not in others.

The other clue to the diagnosis in our case was the extremely elevated D-dimer concentration in a relatively stable patient, with no other explanation, such as macrophage activation syndrome (MAC) or disseminated intravascular coagulation (DIC). In a case series of 20 patients with AOSD, a markedly elevated D-dimer concentration was noted in 4 patients [13]. Authors of a case report about a patient with AOSD described a highly elevated D-dimer concentration without MAC or DIC, which suggests it could be an indicator of early steroid introduction [14]. As in our case, it was not correlated with the disease course or severity, yet the D-dimer concentration merits its attention in future research, which could shed light on its...
role in pathogenesis, diagnosis, and usefulness as a clinical marker in a certain subset of patients, especially those with normal levels of serum ferritin (as reported in 30% of cases of AOSD) [15]. Low serum ferritin levels, as in our case, are unusual but best explained by a concomitant iron deficiency state.

Conclusions

NUD should be differentiated from classic urticaria because it usually is associated with an underlying systemic inflammatory condition. Therefore, promptly identifying any diseases associated with it will alleviate any unnecessary delay in diagnosis. More importantly, treatments for NUD differ, usually but not necessarily depending on the underlying cause. As with AOSD, therapeutic agents that target disease control usually are effective. An elevated ASO titer is unusual in patients with AOSD, and in the present case, it did not seem in keeping with the clinical course. An elevated D-dimer concentration could be an indicator of disease activity and testing for it could be beneficial in a subset of patients who have a normal ferritin level.

Conflicts of Interest

None.

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