

Itching Like Mad

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PRESENTATION

Minor infection led to a significant new entry in one 34-year-old man's medical history. The patient was admitted to the Medicine Service at Strong Memorial Hospital, with edematous, annular, erythematous plaques with central clearing; diffuse pruritus; and angioedema of the face and neck. He had been well until 10 days earlier, when he developed an abscess of the upper palate following a routine dental cleaning. The abscess was drained, and the patient was prescribed a 7-day course of amoxicillin, 500 mg, 4 times per day.

On the day following completion of the antibiotic course, the patient noticed several well-defined, edematous, annular, erythematous, pruritic lesions with central clearing on the right side of his abdomen and chest. He subsequently presented to a local community hospital, where he was treated with diphenhydramine and low-dose oral corticosteroids for a suspected type I hypersensitivity reaction to amoxicillin.

He was discharged several hours later with complete resolution of the lesions. However, the pruritic lesions reappeared on the right side of his abdomen and chest the next day, rapidly spreading to his face, scalp, upper and lower extremities, and back within a few hours. In addition, the patient had myalgias; arthralgias; angioedema of his hands, feet, neck, and face; chills; night sweats; and generalized weakness.

ASSESSMENT

On admission, the patient had a temperature of 99.5° F (37.5° C), a blood pressure of 136/82 mm Hg, and a pulse of 112 beats per minute. Pruritus from the lesions was

causing him considerable distress, as is consistent with diffuse urticaria. His past medical history was notable for depression. He denied any known allergies. In fact, the patient had taken amoxicillin as a child for otitis media and had no skin or systemic reaction. Current medications included the antidepressant fluoxetine and a multivitamin.

The diffuse rash consisted of well-demarcated, circumferentially-growing, annular, blanching, edematous plaques with pale central clearing; they ranged in size from 2 cm to greater than 15 cm, and only the patient's palms, soles, and mucous membranes were spared (Figures 1-3). Angioedema was most prominent in the lateral aspect of his hands and feet, his neck, and around the opening of his mouth (Figure 4).

An oral examination was notable for a 0.25-cm white pustule on the roof of his mouth, approximately 1-cm posterior to the upper incisors. Mild, nontender, cervical lymphadenopathy was present. He had full range of motion in all joints, and no deformities, swelling, or warmth were noted. Manual palpation of his proximal muscles reproduced his myalgias. Strength was assessed in all muscle groups as 4/5. The remainder of the physical examination was normal.

The patient's eosinophil count, white blood cell count, and creatine kinase level were normal. An antinuclear antibody titer was negative. Serology disclosed decreased levels of C3 complement component (70 mg/dL; normal, 79-152 mg/dL), C4 complement component (12 mg/dL; normal, 16-38 mg/dL), and total hemolytic complement (CH50). His C-reactive protein level was highly elevated at 172 mg/L (normal, 0-10 mg/L). In addition, his lactate dehydrogenase level was elevated at 306 U/L (normal, 120-246 U/L). Urinalysis showed moderate proteinuria and glucosuria, but no evidence of urinary tract infection, acute renal failure, or intrinsic renal disease. Tests for human immunodeficiency viruses 1 and 2, Lyme disease, and herpes simplex viruses 1 and 2 were negative, as were 2 sets of blood and urine cultures taken on admission. The residual upper palate abscess was re-evaluated by the dentistry department. Computed tomography of the neck, orbits, and maxillofacial area was normal.

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Figure 1 Lesions covered the patient's right leg. Note variations in the size of the plaques.

DIAGNOSIS

A diagnosis of serum sickness-like reaction secondary to treatment with amoxicillin was based on the patient's symptoms—urticarial rash, consisting of well-demarcated plaques with central clearing, myalgias, arthralgias, and weakness appearing 8 days after initial exposure to the drug—and the findings of an increased C-reactive protein level and mildly decreased complement level. Serum sickness-like reaction is named for its clinical similarity to serum sickness, in which immune complexes are deposited in the skin, joints, and other organs. True serum sickness, a type III hypersensitivity reaction, results in fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances, proteinuria, and significant decreases in serum complement levels; it was originally described after patients were infused with equine immunoglobulins.¹ In contrast, serum sickness-like reactions are specific drug reactions that are not associated with circulating immune complexes.

Although the exact pathogenesis is poorly understood, serum sickness-like reactions are thought to originate from



Figure 2 Central clearing was evident in lesions on the patient's left leg.



Figure 3 The rash also spread across the patient's back.

an abnormal inflammatory reaction that occurs in response to defective metabolism of drug byproducts generated during pharmacologic therapy; the metabolic flaw could be a maternally-inherited trait.² In vivo hepatic drug biotransformation studies have shown greater lymphocyte killing in subjects with a known history of serum sickness-like reac-



Figure 4 Angioedema was pronounced on the lateral aspects of the patient's hands.

tions than in control subjects. The reaction generally includes a constellation of fever; urticarial polycyclic wheals with central clearing on the trunk, extremities, face, and lateral borders of the hands and feet; oral edema without mucosal involvement; lymphadenopathy; arthralgias; myalgias; and mild proteinuria. Case reports have noted the absence of fever in serum sickness-like reactions to amoxicillin.¹ Laboratory abnormalities include normal or mild decreases in serum C3, C4, and CH50 levels, and mild proteinuria, all of which were identified in our patient.^{1,3-5} In contrast to true serum sickness, renal and hepatic involvement is rare. Significant decreases in serum C3, C4, and CH50, reported in the literature for true serum sickness, are rarely described in serum sickness-like reaction.

Agents that have been implicated in serum sickness-like reactions include cefaclor, amoxicillin, sulfonamides, tetracyclines, ciprofloxacin, nonsteroidal anti-inflammatory drugs, barbiturates, carbamazepine, propranolol, thiouracil, and allopurinol.¹ Metabolites of these drugs might bind with tissue proteins inappropriately, eliciting an acute inflammatory response that typically develops 7-14 days after initiation of the offending agent. It is interesting that this patient received amoxicillin as a child, yet never developed a systemic inflammatory response. It is possible that serum sickness-like reactions are dose-responsive, so that only higher doses produce sufficient metabolites to bind to tissue proteins and spur the characteristic symptoms.

Serum sickness-like reactions to amoxicillin have previously been reported to occur at a rate of less than 1 in 10 million.⁶ In Australia, 18% of drug-induced serum sickness-like reactions in the pediatric population were attributed to amoxicillin.⁷ The differential diagnosis for serum sickness-like reaction includes erythema multiforme, urticaria multiforme, and Stevens-Johnson syndrome. Clinical differentiation of these disorders can be accomplished with a careful history that documents the exact time course of symptom onset following drug therapy and with a thorough physical examination.

MANAGEMENT

Serum sickness-like reaction is an acute self-limited reaction with an ultimately favorable outcome.⁸ Treatment is typically symptomatic, but hospitalization may be required for severe cases. While optimal treatment strategies for serum sickness-like reactions are not clearly defined in the literature, discontinuation of the suspected agent combined

with use of antihistamines and corticosteroids for symptom control is an appropriate therapeutic route.^{3,9} Case reports have shown that treatment with prednisone, 60 mg daily, and high doses of H₁ and H₂ antihistamines help resolve the arthralgias and myalgias within 24 hours and the remaining symptoms within 48-72 hours.¹ It is unclear whether patients who experience a serum sickness-like reaction should be advised to avoid ingesting all medications that have been linked with the condition. The question of cross reactivity should be explored in more depth; since multiple antibiotic classes are associated with serum sickness-like reaction, the potential for antimicrobial therapy may be limited in patients with a known history.

Our patient was initially treated with intravenous methylprednisolone, 60 mg every 12 hours. His pruritus was very difficult to control, despite administration of intravenous diphenhydramine, 25 mg, every 2 hours and intravenous famotidine, 20 mg, every 12 hours. Better symptom management was obtained by adding oral doxepin, 10 mg once daily, to the antihistamine regimen. Substantial dermatologic improvement was noticed within 48 hours, with many of the lesions resolving completely. The pruritus had improved substantially 72 hours after admission.

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