Fever and Rash in a Young Woman

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A 25-year-old woman presents with fever, rash, mild headache, and decreased appetite. Six days after being prescribed TMP/SMX for urinary tract symptoms, fever developed and her temperature has been gradually rising since then.

A 25-year-old woman presents with fever, rash, mild headache, and decreased appetite. About 1 week earlier, she had dysuria, urgency, and suprapubic pain. Trimethoprim/ sulfamethoxazole (TMP/SMX) was prescribed, and the urinary tract symptoms quickly resolved. However, 3 days later, fever developed and her temperature has been gradually rising since then. She denies cough, sputum, urinary symptoms, nausea, emesis, and diarrhea.

HISTORY
The patient was previously healthy. Current medications are TMP/SMX and an oral contraceptive. She denies any allergies.

PHYSICAL EXAMINATION
Temperature is 39.3°C (102.8°F); heart rate, 100 beats per minute; and blood pressure, 100/60 mm Hg. There is a 1-cm ulcer on the right buccal mucosa. Lymph nodes in the cervical, axillary, and supraclavicular regions are not enlarged. Chest is clear, and heart rhythm is regular. Abdomen is nontender, without masses or organomegaly. Extremities show no signs of arthritis. A maculopapular rash is evident on both upper extremities, and diffuse erythema is noted on her upper torso. The patient comments that the redness on her torso is new—in fact, she has not noticed it until now—although her arms have been pruritic for the past day or two.

LABORATORY AND IMAGING RESULTS
A serum biochemistry profile, chest film, and results of urinalysis are all normal. Hemogram reveals a hemoglobin level of 13.7 g/dL; a platelet count of 162,000/µL; and a white blood cell count of 1800/µL, with about 50% polymorphonuclear neutrophils and 50% lymphoid forms.

Which of the following is the most appropriate management strategy?
A. Administer intravenous vancomycin for methicillin-resistant Staphylococcus aureus (MRSA) infection.
B. Administer intravenous antibiotics and fluids for toxic shock syndrome.
C. Obtain Lyme disease titers.
D. Discontinue the TMP/SMX.
CORRECT ANSWER: D
The clinical findings in this case suggest an allergic reaction to an antibiotic. The skin is the most frequently affected organ in such reactions; 2 large studies show that rash occurs in 2.2% to 3.6% of patients given antibiotics.1,2 The agents most often implicated are sulfa drugs, ampicillin, and amoxicillin.1

The typical allergic drug eruption is maculopapular and has a predilection for the trunk and proximal extremities. A rash with this pattern suggests involvement of T lymphocytes, whereas urticaria points to an IgE-mediated mechanism.3 A maculopapular drug eruption usually takes several days to as long as a few weeks to develop; urticaria tends to develop much more quickly.

With continued drug exposure, a more full-blown hypersensitivity syndrome—which may include fever and eosinophilia—can occur and can eventually evolve into the more serious Stevens-Johnson syndrome (mucosal ulceration) and even toxic epidermal necrolysis (sloughing of the skin). The latter 2 syndromes are associated with a high risk of mortality.

Diagnosis of drug eruption. There are few diagnostic tests for drug allergy. Skin testing has been used but is effective only for identifying an IgE-mediated allergy. A mixed lymphocyte proliferation test for the more common T cell-mediated allergy is used in Europe but is not available in the United States. Thus, the history and physical findings remain the mainstays of diagnosis. This patient's syndrome occurred while she was taking an antibiotic known to induce allergic reactions, and it developed in the proper time frame. In addition, the truncal distribution of the maculopapular rash is typical. Her fever and beginning mucosal ulceration suggest evolution toward...
a more severe condition, such as Stevens-Johnson syndrome. Her severe neutropenia may also be a part of this evolution, although sulfa drugs have a high propensity for inducing leukopenia even without other allergic findings.

**Management.** With a delayed adverse reaction to antibiotics, management is usually expectant, and resolution typically occurs within days. Note the allergy prominently in the medical record, and educate the patient about the need to avoid further exposure.

**Other causes of fever and rash.** The other choices here represent other conditions that frequently present with fever and a rash. The rash of early Lyme disease (choice C), termed erythema migrans, occurs in about 80% of patients with the disease. It is typically localized and round, with central clearing at the site of the tick bite; it is quite different from the more generalized maculopapular rash seen here.

Toxic shock syndrome (choice B) is caused by toxin-producing *S aureus* or *Streptococcus* species and is most often linked to infections involving tampons and vaginal birth control methods and infected wounds. Patients are usually far more ill than this woman, with emesis, diarrhea, and symptomatic hypotension accompanying the fever. The rash is sunburn-like—a diffuse, flat, branching erythroderma—rather than truncal and maculopapular.

In recent years, community-acquired MRSA infections have become more common. MRSA infections usually develop on the skin; initially they appear as a pimple or boil. As they progress, the inflammation and cellulitis may be extensive enough to resemble a rash. However, the infection is typically asymmetric and localized, and swelling, pain, and perhaps even purulence are present.

**Outcome of this case.** A presumptive diagnosis of hypersensitivity reaction to a sulfa drug (TMP/SMX) was made, and the antibiotic was immediately stopped (choice D). Surveillance cultures of urine and blood were negative. The patient was treated symptomatically with acetaminophen and intravenous fluids. Use of granulocyte colony-stimulating factor was entertained but proved unnecessary.

The rash quickly began to abate, and no new mouth lesions developed. After 72 hours, she was afebrile and the rash had faded. By day 4, her total white blood cell count was 3800/µL, with an absolute neutrophil count of 1900/µL.


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