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### CASE PRESENTATION

A 67-year-old white man with a history of type 2 diabetes mellitus and peripheral vascular disease that necessitated amputation of the left great toe and right second toe is admitted to the hospital with a clinical diagnosis of cellulitis surrounding a necrotic lesion on the dorsum of his right foot (Figure 1). He is started on empiric intravenous treatment with piperacillin/tazobactam. When his clinical condition does not improve, the patient undergoes amputation of the right second transmetatarsal, and vancomycin is added to his regimen postoperatively.

Subsequently, the patient's renal function worsens, and because of possible drug-induced nephropathy, his intravenous treatment with piperacillin/tazobactam is changed to an oral dose of ciprofloxacin. On day 7 of hospitalization, the patient develops an erythematous skin rash with palpable purpuric lesions on his left lower extremity (Figure 2). The vancomycin is changed to clindamycin because drug-induced skin rash was suspected.

Skin biopsy of the rash is performed; results reveal perivascular neutrophilic infiltrates (Figure 3), and direct immunofluorescent (DIF) analysis of a biopsy specimen is positive for IgA and C3. The patient requires hemodialysis for worsening renal function. The patient has no history of drug allergies or tobacco or alcohol use. Laboratory evaluation reveals a total leukocyte count of  $13.6 \times 10^3/\text{mm}^3$ , blood urea nitrogen level of 63 mg/dL, and serum creatinine level of 5.1 mg/dL (serum creatinine was within the normal range at the time of hospitalization). Enzyme-linked immunosorbent assay for HIV and serology for hepatitis were negative, as were tests to detect antinuclear antibodies, cytoplasmic antineutrophilic cytoplasmic antibodies, and serum cryoglobulin. Other laboratory test results were as follows: erythrocyte sedimentation rate, greater than 100 mm/h; C3 complement, 55 mg/dL (normal range, 90–180 mg/dL); C4 complement, 23 mg/dL (normal range, 10–40 mg/dL). A culture of the patient's foot wound grew group B streptococci.

### WHAT IS YOUR DIAGNOSIS?

- A) Cryoglobulinemia
- B) Drug-induced cutaneous vasculitis
- C) Henoch-Schönlein purpura
- D) Meningococcemia
- E) "Red-man" syndrome



Figure 1. Erythema surrounding the necrotic lesion on the dorsum of the patient's right foot.

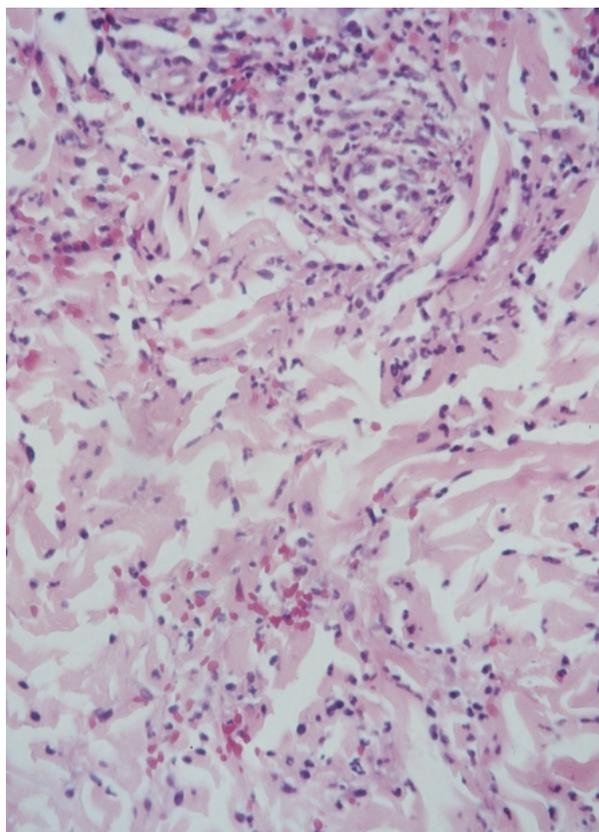
### WHAT IS THE APPROPRIATE TREATMENT?

- A) Change the antibiotic therapy to an intravenous dosage of penicillin G
- B) Discontinue antibiotic treatment and observe
- C) Initiate corticosteroid treatment
- D) Perform plasmapheresis

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**Figure 2.** Erythematous skin rash with purpuric lesions on the left foot.



**Figure 3.** Biopsy tissue taken from the patient's skin rash showing perivascular neutrophilic infiltrates (hematoxylin-eosin stain; original magnification  $\times 160$ ).

## ANSWERS

The correct answers are Henoch-Schönlein purpura (C), and discontinue antibiotic treatment and observe (B). The diagnosis of Henoch-Schönlein purpura is based on the skin biopsy results, which are consistent with leukocytoclastic vasculitis, and on DIF analysis of a biopsy specimen, which revealed IgA and C3 deposits in the cutaneous vessel wall.

## DISCUSSION

Henoch-Schönlein purpura (HSP) is an IgA-mediated, autoimmune, nonthrombocytopenic, hypersensitivity vasculitis characterized by diverse symptoms including purpuric skin rash, arthritis, abdominal pain, and renal impairment. A report of the first case of HSP was published in 1801. In 1837, Johann Lukas Schönlein described the association of joint pain and purpura and named it “purpura rheumatica.” Eduard Heinrich Henoch, who was a student of Schönlein, subsequently

underscored the importance of gastrointestinal and renal involvement in this syndrome.<sup>1</sup>

## Epidemiology

Although it is well documented in adults, HSP occurs much more frequently in children.<sup>2</sup> HSP affects males more often than females, and it is uncommon in black patients.<sup>3</sup> HSP is a seasonal disorder, occurring most often in the spring, winter, and fall months and preceded in 50% of affected children by upper respiratory tract infections.<sup>2</sup>

## Pathogenesis

The presumptive pathogenic mechanism for HSP is immune-complex deposition. A number of inciting agents have been suggested, including upper respiratory tract infections, various drugs, foods, insect bites, and immunizations. IgA is the antibody class most often seen in the immune complexes and has been detected in renal biopsies of patients with HSP.<sup>4</sup>

### **Clinical Manifestations**

HSP usually presents with a skin rash, typically followed by purpura, abdominal pain, arthritis, and nephritis<sup>5</sup>; children younger than 2 years typically have a milder course. Almost all patients develop a skin rash classically characterized by urticarial wheals, erythematous maculopapules, and larger, palpable, ecchymosis-like lesions, appearing on the lower extremities and buttocks. These lesions are accentuated in areas of pressure and can also involve the upper extremities, face, and trunk.<sup>1</sup> In adult patients with HSP, 33% may develop joint involvement, and 19% may develop gastrointestinal involvement.<sup>2</sup> Gastrointestinal involvement is characterized by abdominal pain that is usually colicky in nature and may be associated with vomiting. Arthritis is characterized by warmth, tenderness, and swelling of the joints, particularly the large joints.<sup>1</sup> The incidence of renal involvement in adult patients with HSP is 23% to 49%.<sup>6</sup> Predictive factors for renal involvement include a recent history of infectious disease, fever, the spread of purpura to the trunk, and biological markers of inflammation.<sup>6</sup> The most common manifestation of renal disease in HSP is hematuria.<sup>1</sup> Rare manifestations of HSP include hepatosplenomegaly, myocardial infarction, pulmonary hemorrhage, and pleural effusions.

### **Diagnosis**

Diagnosis of HSP in adult patients requires the presence of 2 of the following clinical criteria: palpable purpura, age less than 20 years at onset, diffuse abdominal pain, and the presence of vessel wall granulocytes on biopsy.<sup>7</sup> The presence of IgA deposits in vessel walls on cutaneous DIF analysis has not yet been described as an essential part of the syndrome.<sup>6</sup>

No specific laboratory test is available to aid in the diagnosis of HSP. Serologic studies have documented elevated levels of IgA in 50% of affected patients, with activation of the alternate pathway of the complement system. Levels of the C4 and C3 complement components are within the normal range, and histopathology of the skin and other affected organs usually reveals polymorphonuclear cells in the vessel wall, with IgA, C3, and immune complexes seen in venules, arterioles, and capillaries.<sup>2</sup> The erythrocyte sedimentation rate and platelet count may be elevated in patients with HSP. Transient hematuria is the most common renal manifestation of the disorder.<sup>2</sup> The presence of an underlying infectious etiologic agent should be excluded if suggested by clinical signs.

### **Differential Diagnosis**

Antibiotic allergy, cryoglobulinemia, sepsis, and

“red-man” syndrome should be considered in the differential diagnosis of the case patient. Although the antibiotic ciprofloxacin is generally well tolerated, it can cause a cutaneous rash in approximately 1% of patients receiving it. A few cases of cutaneous vasculitis also have recently been reported<sup>8,9</sup>; patients with ciprofloxacin-induced vasculitis developed a skin rash within 10 days of taking ciprofloxacin. The rash usually involves the trunk and limbs and resolves within 1 to 4 weeks of discontinuing the causative drug. In one report, the rash was associated with worsening renal function.<sup>8</sup>

Piperacillin is known to cause interstitial nephritis, which is characterized by fever, eosinophilia, hematuria, proteinuria, or pyuria. A few reports exist that document delayed hypersensitivity characterized by generalized erythema and a pruritic, maculopapular rash; in one report, the skin rash was also associated with fever and eosinophiluria.<sup>10</sup>

Vancomycin is associated with “red-man” syndrome, which is characterized by pruritus, an erythematous rash involving the face, neck, and upper torso, and occasionally hypotension. The rash usually occurs within hours of or soon after the completion of dosing and resolves spontaneously after slowing the infusion rate or discontinuing administration of the antibiotic.<sup>11</sup>

### **Treatment**

No specific treatment exists for HSP. Bed rest and supportive care, such as assuring adequate hydration, are helpful. Nonsteroidal anti-inflammatory drugs can be used for symptomatic relief. A few patients have reportedly benefited from colchicine or dapsone therapy for skin manifestations of HSP. The use of corticosteroids in patients with HSP is controversial. In cases of renal involvement, it is unclear whether treatment during the early stages might be effective in delaying or preventing progressive renal disease. High-dose immunoglobulin therapy can temporarily arrest the disease in some patients with severe IgA glomerulonephritis of HSP.<sup>12</sup> In the absence of renal disease and central nervous system involvement, the prognosis for patients with HSP is excellent. **HP**

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