

Case Report

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Hypersensitivity vasculitis induced by cefoperazone/sulbactam

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Abstract

Background: Cefoperazone has not been reported to cause vasculitic complications before. Here, we report a case of hypersensitivity vasculitis associated with cefoperazone/sulbactam.

Case presentation: A 13-year-old girl with appendicitis developed hypersensitivity vasculitis on the fifth day of cefoperazone/sulbactam therapy. Hypersensitivity vasculitis resolved gradually after removal of the agent on the seventh day and did not recur. Although hypersensitivity vasculitis has multiple causes, coexistence of hypersensitivity vasculitis and cefoperazone treatment, and the quite resolution of the disease after removal of the drug, strongly favours a causative relationship.

Conclusion: To our knowledge, this is the first report of a hypersensitivity vasculitis associated with cefoperazone.

Background

Cefoperazone is a common antibiotic drug used mainly to treat serious infections. Reported adverse effects of this drug include urticaria, maculopapular and erythematous skin rash and rarely anaphylaxis and bronchospasm [1,2]. Cefoperazone has not been reported to cause vasculitic complications before. We report a case of hypersensitivity vasculitis associated with cefoperazone/sulbactam.

Case Presentation

A 13-year-old girl was admitted to Ondokuz Mayıs University Hospital with a 3-day history of abdominal pain and fever. She had no history of allergic reactions, connective tissue disease, respiratory tract infection and/or use of antibiotics or another drug. Physical examination revealed abdominal tenderness and defense, and positive

Rovsing's sign in the right lower quadrant. The white-cell count was 20.700 per cubic millimeter with 78 percent neutrophils, 20 percent lymphocytes and 2 percent monocytes. Hemoglobin was 12.1 g/dl. Erythrocyte sedimentation rate (ESR) was slightly elevated at 46 mm/hour. The patient was referred to the pediatric surgery department and acute perforated appendicitis was considered. Cefoperazone/sulbactam 100 mg/kg/day two in divided doses was initiated on the first day of admission. Abdominal exploration was performed on the second day of admission and a gangrenous appendicitis with adhesions to peripheral tissue and purulent material around the caecum was observed. Biopsy specimen revealed necrosis of mucosa, excessively lymphocyte, neutrophil, plasma cell infiltration in the layers of appendix, and gangrenous appendicitis. No vasculitic changes were ob-

served. *E. coli* was detected in the peritoneal fluid culture. On the fifth day of admission, an erythematous maculopapular rash without edema developed symmetrically along the legs and feet. By the 7th day the rash gradually spread to buttocks and changed to slightly elevated palpable purpuric lesions 3 to 8 mm in diameter, all at the same stage and which did not blanch on pressure. On the 7th day of admission, assuming the antimicrobial agent was the causative agent, cefoperazone/sulbactam regimen was changed to ampicillin (200 mg/kg/day in four divided doses) plus netilmycin (5 mg/kg/day in three divided doses) and an antihistaminic (clemastine, 2 × 1 mg/per day) was initiated. The patient was afebrile after the 6th day of admission. The patient had no vomiting, melena, abdominal pain, arthritis or arthralgia. Antinuclear antibody (ANA), anti-deoxyribonucleic acid (anti-DNA) and rheumatoid factor were negative. Serum complements (C3, C4), prothrombin time, partial thromboplastin time, urinalysis, platelet and white blood cell counts were normal. Kidney and liver function tests were within normal limits. A skin biopsy of a new purpuric lesion from the anterior of the leg was done on the second day of the rash and was revealed a cutaneous vasculitis characterized by perivascular mononuclear cell infiltration. Direct immunofluorescence revealed IgA, IgG and fibrin deposits on the vessel walls. The cutaneous lesions faded within a few days and disappeared on seventh day after discontinuation of cefoperazone/sulbactam therapy. Ampicillin and netilmycin as well as antihistaminic agent were administered for ten days. The patient was discharged on the 18th day of hospitalization. On periodic controls, she is quite well and purpura no recurred.

Hypersensitivity vasculitis presents usually as drug or infection induced purpura and involves dominantly the small vessels. The disease has been reported to be triggered by many factors including bacterial infections, drugs, immun complexes, blood stasis and systemic disease [3]. The criteria of the classification of hypersensitivity vasculitis are age at disease onset >16 years, medication at disease onset, palpable purpura, maculopapular rash and biopsy showing granulocytes in a perivascular or extravascular location. The presence of any 3 or more criteria has been shown to have a sensitivity of 71% and a specificity of 84% [4]. Our patient meets three of five criteria (medication at disease onset, palpable purpura and maculopapular rash) for hypersensitivity vasculitis.

In hypersensitivity vasculitis, the pathogenic mechanism responsible for the blood vessel injury seems to be a type III immun complex reaction or a type IV cell mediated reaction. When the triggering antigen is drug, the term "hypersensitivity" seems apt [5]. The vascular damage is believed to be triggered by the deposition of immun complexes in vessel walls, with activation of complement cas-

cade. Polymorphonuclear leukocytes then migrate to the area and release lysosomal enzymes that damage blood vessels, leading to extravasation of erythrocytes, fibrin deposition, and necrosis. Because leukocytoclastic inflammation is such a prominent feature, these lesions are referred to as "leukocytoclastic vasculitis". Hypersensitivity vasculitis can be divided into neutrophilic and lymphocytic subtypes. The former is frequently associated with hypocomplementemia, whereas the latter is not [6]. Our patient was of lymphocytic type and complement level was normal. In the literature, it is reported that lymphocytic infiltration might represent the resolving phase of an immun complex-mediated neutrophilic vasculitis in lesions more than 48 hours old [7]. On the other hand, there was no relationship between appendicitis and vasculitis. Although IF characteristically shows IgA deposits within vessel walls in HSP while, in most other types of leukocytoclastic vasculitis, IgG or IgM deposits are seen [8]. In our patient, lymphocytic infiltration may be due to delayed biopsy in resolving phase and IgA and IgG deposits do not exclude a leukocytoclastic vasculitis.

Drugs are implicated in up to 10–30% of cases of hypersensitivity vasculitis. Penicillins and sulfonamids are most frequently associated with such a reaction, but many other agents have been implicated as well [3,9]. The other more common agents are antihypertensives, antiarrhythmics, allopurinol, cimetidine, furosemid, hydantoin, penicillins, phenylbutazone, hydralazine and sulfonamides [10].

Since its introduction in 1985, the third generation cephalosporin antibiotic cefoperazone has gained widespread use, and much information has accumulated about its possible adverse effects. Hypersensitivity reactions are the most common side effects. Urticaria, maculopapular and erythematous rash are more common reactions than other immediate reactions such as anaphylaxis and bronchospasm [1,2,11,12]. Although some anecdotal cases of vasculitis have been reported related with cephalexin, cefuroxim and cefprozil, cefoperazone has not been reported to cause vasculitic complications before [13–15].

Conclusion

In the case presented here, occurrence of the typical skin lesions after five days of intake of cefoperazone, in addition to resolution of lesions on discontinuation of cefoperazone are strong evidence in support of a role of cefoperazone in the development of vasculitis. To our knowledge, this is the first reported case of hypersensitivity vasculitis associated with cefoperazone. We believe that cefoperazone may be considered among the possible drugs causing hypersensitivity vasculitis.

Authors' contributions

II followed the patient as hypersensitivity vasculitis and wrote this case report. SB made pathologic investigations and revised edition of this article. AOK followed clinically the patient as gangrenous appendicitis. EA followed clinically the patient as gangrenous appendicitis and helped to editing this report. NG followed the patient as hypersensitivity vasculitis and helped to editing this case report

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Written consent was obtained from the patient or their relative for publication of study.

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