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Aztreonam Cell Mediated Hypersensitivity Cross Reactivity with Beta Lactam Antibiotics: The Possibility That It Exists

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Abstract

A 61-year-old female with past medical history of maculopapular rash reaction to ciprofloxacin and amoxicillin being treated for diverticulitis develops the same rash with administration of piperacillin/tazobactam and aztreonam. A diffuse maculopapular rash developed after the administration of piperacillin. It resolved with discontinuation of the drug and the patient was switched to aztreonam and a very similar rash developed subsequently. In a review of the literature, there are no documented cases of a patient with an allergy to both aztreonam and piperacillin/tazobactam despite *in vivo* cross-reactivity. Unfortunately, there are no standardized allergy tests for aztreonam or piperacillin. This case, however, does offer the possibility that aztreonam may not always be the right alternative to persons with beta-lactam antibiotic allergies.

Keywords

Piperacillin; Aztreonam; Cross; Reactivity; Allergy; Amoxicillin; Drug; Rash; Exanthem; Penicillin; Beta; Lactam; Cephalosporin; IgE; Maculopapular Rash

1. Case Description

A 61-year-old Caucasian female presented to the ER with a five-day history of progressively worsening abdominal pain. The patient's only past medical history was anxiety and recently treated diverticulitis with outpatient antibiotics. She had a prior rash due to ciprofloxacin and she was aware of another oral antibiotic that had previously caused a maculopapular rash but she cannot remember what specific antibiotic it was. She had gone to her primary care physician two days prior with the complaint of abdominal pain and fever and was treated empirically with oral doxycycline 100 mg P.O. B.I.D. and metronidazole 500 mg P.O. T.I.D. for presumed diverti-

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culitis.

Her symptoms worsened and she developed a 103˚F fever and worsening abdominal pain. She described this as 8 out of 10 intensity the day prior to admission. In the ER, she denied any nausea, vomiting, diarrhea and had a solid bowel movement the day prior to admission. The urinalysis was unimpressive for infection and the patient's white blood cell count was 8.4×10^9/L. She did have a fever of 101.8˚F orally. Her Basic Metabolic Panel and Liver Function Tests were within normal limit. A CT of the abdomen confirmed diverticulitis. Blood cultures were taken and piperacillin/tazobactam 3.375 grams IV was given once. The patient developed diffuse multiple raised non-pruritic non-blanchable red papules on her lower and upper extremities with no surrounding areas of erythema (No images were secured at that time) several hours later. The patient claims this was the same rash she had with prior antibiotics to which she was told she was "allergic". It was decided not to administer any other antibiotics until the following morning after confirming her drug allergies with her primary care physician. Diphenhydramine and famotidine were administered in response to the rash.

The following morning the patient was afebrile and her purpuric rash had resolved. Her primary care physician suspected her allergies to oral amoxicillin and ciprofloxacin for which she had a nondescript rash. She had received metronidazole in the past without any adverse reactions. The patient was started on aztreonam 2 grams IV every eight hours to cover GI gram negative bacteria and metronidazole 500 mg IV every six hours for anaerobic coverage. Later that evening she developed numerous non-pruritic palpable purpura-like rash on her lower extremities bilaterally and a mild temperature of 100.1˚F (**Figure 1**). She did have sparse similarly looking lesions on the extensor surfaces of her upper extremities. There were no signs of angioedema or hemodynamic instability. There was no mucosal involvement or palm or sole involvement. Her liver function tests and GFR remained within normal reference range during her entire hospital stay. There was no lymphadenopathy or peripheral eosinophilia present during hospitalization.

Infectious Disease consultation suggested starting gentamicin sulfate 300 mg IV daily and clindamycin 600 mg IV every eight hours. By day three, her diverticulitis symptoms were almost fully resolved. The rash was slightly improved. She went home with a PICC line to receive gentamicin 300 mg IV daily and clindamycin 600 mg PO three times a day for a total of five more days. There was no reported rash from the new antibiotic regiment. She was lost to follow up after completing the antibiotic course.

2. Discussion

Cross reactivity between beta-lactam antibiotics and aztreonam with cell-mediated allergy is thought to be virtually non-existent [1]. In reviewing the literature penicillin and cephalosporin IgE mediated cross reactivity is between 1% - 10% depending on which literature and analysis study is referenced. Cross reactivity between the beta lactam class and the monobactam class is lacking in data, with the exception of cross reactivity between ceftazadime and aztreonam [2]. Ceftazadime and aztreonam cross reactivity is hypothesized to be due to a nearly identical side chain causing a Type I reaction [3]. Other studies reveal that in patients with confirmed immunological beta lactam allergy there is no cross reactivity with aztreonam [4] [5]. *In vivo* studies have confirmed no IgE mediated cross reactivity [6]. Although many of these studies use a small patient population, it does support a strong case for little cross-reactivity. In the mid 1980's when aztreonam was first introduced to the market, cross-reactivity was shown to be less than 0.001% with known minor and major determinant penicillin IgE [7]. In fact, the amount of aztreonam to illicit a cross-reactivity, requires a 10,000 fold increase in order to achieve a similar block with anti-penicillin and anti-cephalothin antibodies [8]. One study, has shown cross reactivity between cephalosporins and aztreonam to be as high as 3.1% in skin testing only [9]. This case represents a rare instance where a patient exhibited similar dermatologic response to both aztreonam and piperacillin/tazobactam. The time between onset of the rash and the administration of the antibiotics support the reaction being a type I hypersensitivity. The initial reaction with the piperacillin/tazobactam resolved within twelve hours after discontinuation of the antibiotic while the dermatologic lesions with aztreonam persisted for several days before complete resolution. There were no other clinical findings suggestive of additional processes. There was no end organ damage, hematologic abnormalities or hemodynamic instability. Both antibiotics were in a 5% dextrose solution. The rash was purpura-like which raises the possibility of a hypersensitivity vasculitis. Unfortunately a biopsy was not performed to confirm vasculature neutrophilic invasion. Beta lactams are notorious for this reaction. This typically occurs after one week of exposure but there are cases as soon as two days after. Purpura alone is an adverse reaction attributed to aztreonam.

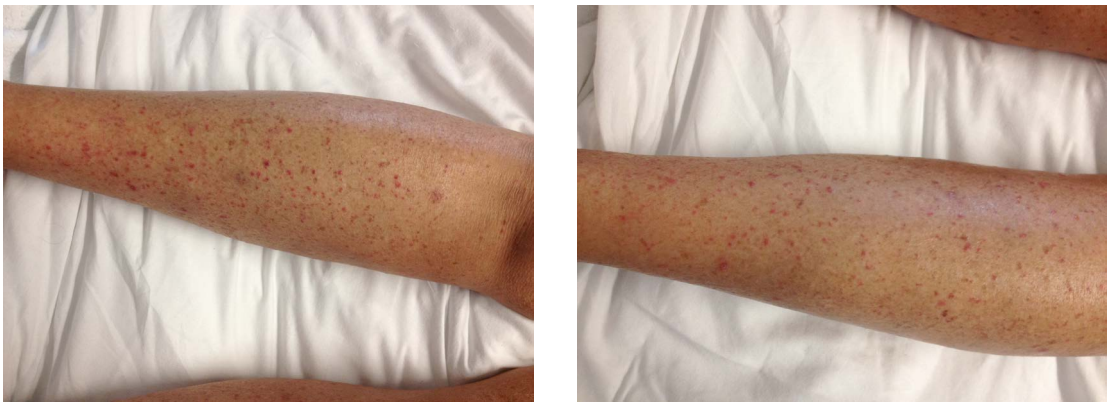

Figure 1. 12 hours after administration of first dose of aztreonam. An almost identical rash presented several hours after Piperacillin/tazobactam administration.

Penicillin skin testing is indicated in presumed penicillin IgE mediated reaction. Other antibiotics however have no standardization for skin testing. Skin testing has been known to be a confirmatory test of monobactam and penicillin cross reactivity [5] [9]. It is indicated in this case for this patient to undergo skin testing to confirm her antibiotic hypersensitivity in order to determine proper antibiotic regiments for her in the future, however she was lost to follow up [10].

In this case, there was a mild transient drug exanthema that resolved quickly with discontinuation of the antibiotic. Whether or not this was an IgE mediated response as opposed to an antibiotic related vasculitis is unknown, and due to the patient's poor follow up, allergy testing was never performed. There are instances of IgE immediate and nonimmediate hypersensitivity reactions in the literature for beta-lactams. In early immunologic studies of aztreonam cross reactivity with penicillin confirmed allergic patients, aztreonam appeared safe, even in patients with positive RAST and skin testing to aztreonam [6].

Perhaps administration of aztreonam in a confirmed penicillin allergic patient may need to be performed with caution if there is a severe reaction. This should be interpreted in a case by case basis. If patient has had previous ceftazidime allergy, there may be increased risk of an allergic reaction as previously described in the literature [1] [11]. This is merely a single case exhibiting the possibility that aztreonam may not be as benign in beta-lactam allergic individuals.

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