

Cephalosporin Induced Toxic Epidermal Necrolysis and Subsequent Penicillin Drug Exanthem

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ABSTRACT

Background: Drug hypersensitivity is classically divided into IgE mediated and non-IgE mediated disease. We report a rare case of consequent IgE mediated and non-IgE mediated reactions within the beta lactam class of antibiotics.

Case Summary: An 84-year-old man developed toxic epidermal necrolysis (TEN) due to ceftriaxone, a third generation cephalosporin, involving 72% of the body surface area. The patient recovered but within weeks subsequently developed an acute IgE mediated allergic reaction to piperacillin/tazobactam, an extended spectrum penicillin. Further IgE RAST revealed positive results to penicillin major determinant.

Discussion: This case demonstrates the complexity of drug hypersensitivity reactions. While it is accepted that IgE mediated penicillin allergy is a predisposition to cephalosporin allergy, this case displays an unusual correlation between drug hypersensitivity and drug class. There have been few studies that evaluate the cross reactivity with penicillin or other beta-lactams in subjects with primary hypersensitivity to cephalosporins. This clinical scenario emphasizes the need of more studies on cephalosporin allergy in particular as shown by this case of sequential non-IgE mediated cephalosporin induced TEN reaction pursuant by an IgE mediated penicillin allergy.

KEY WORDS

beta-lactams, cephalosporin, penicillin, toxic epidermal necrolysis

INTRODUCTION

Patients with penicillin allergy are at increased risk for an allergic reaction to cephalosporins. Pumphrey *et al.* described the nature of fatal cephalosporin anaphylaxis after penicillin sensitization.¹ Conversely, a documented cephalosporin allergy does not clearly confer a similar increased risk of penicillin allergy. Drug hypersensitivity reactions can be classified within Gell and Coombs immunologic reactions. A correlation has not been established between IgE mediated drug hypersensitivity and the cutaneous eruption spectrum of erythema multiforme. We report a unique case of toxic epidermal necrolysis (TEN) due to ceftriaxone involving 72% of the body surface area including nasal mucosal involvement and lip involvement with subsequent acute IgE mediated skin hypersensitivity to an extended spectrum penicillin, piperacillin/tazobactam, after previous sensitization

with the same drug.

CLINICAL SUMMARY

An 84-year-old man with a history of coronary artery disease, seasonal allergic rhinitis, and atopic dermatitis presented to the emergency department with cough and dyspnea for several days. In the past, he received courses of antibiotics including penicillins and cephalosporins for treatment of sinusitis without incident. Initial evaluation revealed mild hypotension, hypoxia on arterial blood gas (SaO₂ = 86% on room air), and a chest x-ray was remarkable for a left lower lobe infiltrate. After receiving 4 doses of piperacillin/tazobactam 4.5 g IV over 24 hours in the emergency room, he was admitted to the ICU with a diagnosis of sepsis and pneumonia. After 24 hours, piperacillin/tazobactam was discontinued and antibiotics were changed to ceftriaxone 2 g IV q 4 hours. No additional medications were given. Within 12 hours of his

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first dose of ceftriaxone, the patient developed an initially eczematous diffuse dermatitis with scattered pruritic, erythematous patches and papules. Scaling erythroderma was noted on various areas of the body including extensor surfaces of the arms, legs, and trunks. Approximately 72% of the body surface area was involved with skin detachment above 30% of the body surface area and with nasal mucosal involvement, lip involvement, and possible conjunctival involvement. Of note, no hives, ulcers or bullae were noted.

On day 2 of hospitalization, he developed atrial fibrillation with hemodynamic compromise requiring electrical cardioversion. At this time his rash was noted to have increasing erythroderma but in a stable distribution. On day 3 of hospitalization the patient developed bullae and 2nd degree partial thickness involvement with skin loss on the scrotum, sacrum, coccyx, and ischium. Wound margins were irregular, erythematous, and blanched with minimal pressure. Nikolsky's sign was negative. The patient was evaluated by dermatologists who concurred with the diagnosis of TEN secondary to an acute drug reaction. Ceftriaxone was discontinued at this time. The patient's rash became less erythematous and resolved over the next week. However, as a nursing home patient, he was mistakenly dosed with ceftriaxone again within one week of discharge and developed a similar exacerbation of his previous eruption. He was treated immediately with a 60 mg prednisone taper over 7 days with complete resolution of symptoms.

Four weeks after discharge, the patient was re-evaluated at the emergency room for a low grade temperature of 99.8°F, hypotension 81/45, tachycardia 111, and oxygen saturation of 84% on room air. Chest x-ray revealed a new left lower lobe infiltrate. He received piperacillin/tazobactam 3.375 mg IV and within 15 minutes had a diffuse erythematous rash on his back, neck, arms, and the entire legs bilaterally. The rash was pruritic with intermittent wheals on the trunk. Within one hour of drug administration, he became hypotensive, tachycardic and hypoxic to 78% oxygen saturation. He received decadron 4 mg IV and was ultimately intubated and placed on mechanical ventilation. He received Ranitidine 150 mg bid, diphenhydramine 25 mg q6 hrs, and a tapering dose of hydrocortisone 100 mg q8 hrs for 7 days. His sputum culture grew *Staphylococcus aureus* and *Klebsiella* which was treated with vancomycin and amikacin. His rash dramatically improved within 72 hours. He was extubated and discharged back to the nursing home in stable condition.

PATHOLOGICAL FINDINGS

The patient was evaluated in our allergy clinic as an outpatient 6 months after discharge. Without availability of penicillin major determinant, ImmunoCAP testing for penicillin G (major determinant) and peni-

cillin V (minor determinant) was performed through ARUP Labs (Salt Lake City, Utah). Penicillin G was interpreted as Class 3 positive (level 9.41 kU/L) and penicillin V was interpreted as negative (<0.35 kU/L). Based upon the patient's medical history and lab results, he was labeled with an IgE mediated penicillin allergy allowing for desensitization if necessary. However, the TEN reaction to cephalosporins precluded the use of this drug class in the future.

DISCUSSION

Drug allergies can be categorized into IgE-mediated (type I/immediate-type) and non-IgE mediated hypersensitivity reactions. IgE-mediated reactions include anaphylaxis, angioedema, urticaria, and bronchospasm and occur within 72 hours after drug administration. Non-IgE mediated hypersensitivity reactions include hemolytic anemia, interstitial nephritis, thrombocytopenia, serum sickness, drug fever, morbilliform eruptions, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis and occur most commonly after 72 hours of drug administration.²

TEN is defined as extensive detachment of full-thickness epidermis most often related to an adverse drug reaction.³ The mechanism of the TEN phenomenon is not completely understood. Originally, it was hypothesized that the major factor involved CD8+ cytotoxic T cells,^{4,5} although more recently it is believed that fatty acid synthetase (FAS) and FAS ligand (FASL) are more responsible for keratinocyte death.^{6,7} FASL has been found to be elevated in sera and expressed on keratinocytes of skin sections from TEN, SJS, and maculopapular rash although the degree of elevations does not correlate with severity of skin rash.⁸ This can interact with FAS (CD95), a death receptor constitutively expressed on keratinocytes and upon crosslinking, results in rapid apoptosis.⁹ TEN is considered a severe form of the erythema multiforme spectrum. The spectrum is distinguished by surface area with Steven-Johnson syndrome defined by a limit of 10% body surface. Skin detachment of 10–30% is designated SJS-TEN overlap syndrome, and TEN is defined by 30% or more skin detachment.¹⁰

Skin reactions in cephalosporin drug allergy are approximated to occur between 1% to 3% of patients. However, the overall incidence of severe skin reactions to cephalosporins is lower than with penicillins.¹¹ Case reports of exfoliative dermatitis due to ceftazidime, cephalexin, cefoxitin and cefotaxime therapy have been published.¹²⁻¹⁵

While type I hypersensitivity cross reactivity is known with beta lactams, TEN may occur with both penicillins and cephalosporins in an undefined mechanism. IgE mediated crossreactivity between cephalosporin and penicillins may be due to the beta-lactam ring, specific side chains, or other unknown

haptenic determinants. Cephalosporin allergy occurs in 8.1% of those with a history of penicillin allergy as compared with 1.9% of those without such a history.¹⁶ There have been few studies, however, which have evaluated the cross reactivity with penicillin or other beta-lactams in subjects with primary hypersensitivity to cephalosporins.^{17,18} Romano *et al.* determined the IgE response in subjects with known immediate hypersensitivity reactions to cephalosporins and evaluated the cross-reactivity to different cephalosporins and penicillins. All 30 subjects displayed a history of immediate reactions to injectable cephalosporins and positive skin test or RAST to either cephalosporins or penicillins. Of these 30 subjects, 29 had skin tests positive for cephalosporins. Of 30 subjects, 86.7% displayed skin test negativity to penicillin determinants. The remaining 13.3% of patients had skin RAST positive to penicillin determinants (half from penicilloyl-polylysine and half from ampicilloyl-polylysine). The former group was further analyzed to be 57.7% positive to only the culprit cephalosporin and 42.3% positive to a different non-culprit cephalosporin.¹⁹

This case exemplifies the complexity of multiple drug reactions. This patient was given diagnoses of several drug reactions in a span of a few weeks. He had a clear history of atopic skin disease and rhinitis preceding his first hospitalization. He had previous exposure to beta-lactam antibiotics without incident during his lifetime. This history of atopy by itself does not seem to be an independent risk factor for antibiotic allergy although it may predispose patients to more severe and even fatal reactions in the event of anaphylaxis.²⁰

This patient showed evidence of type I hypersensitivity. This patient was sensitized to beta lactams prior to his first hospitalization. Since he developed no reaction to penicillin drugs upon initial admission while receiving zosyn, he was sensitized to penicillins, but not at a high enough antigen load to trigger an IgE response. However, after the ceftriaxone based reaction, he became "hypersensitive" to penicillin and developed an acute drug reaction. During his second hospitalization, he displayed an immediate type hypersensitivity to piperacillin/tazobactam which responded to discontinuation of the drug and anaphylaxis therapy. In addition, ImmunoCAP testing supports the diagnosis.

Of greater interest, this patient appeared to have a severe exfoliative erythroderma that developed while on another beta lactam, ceftriaxone. To our knowledge, there have been no case reports linking a type I hypersensitivity reaction to a beta lactam to that of TEN. In toxic epidermal necrolysis, T lymphocytes present at the site of lesions, exhibit a drug specific cytotoxicity against autologous target cells, or allogeneic cells that shared the same HLA than autologous cells. This MHC class I restriction and mediation of death by perforin/granzyme release, is the classical

behavior of cytotoxic T lymphocytes, like those operating in the rejection of a transplanted organ. As previously reported, MHC restriction could explain the key role of HLA genes as predisposing factors to severe drug reactions. Also, although FASL was not measured in this patient's sera, this patient may have a genetic predisposition leading to an increase of FASL which has been found to be increased in both maculopapular rashes, SJS, and TEN. Nevertheless, the FAS/FASL hypothesis does not elucidate whether this patient's underlying atopic predisposition conferred a setup for such a response.

Ideally, this patient should have been skin tested to both major and minor determinants of penicillin. However, our facility did not have access to these determinants. In addition, with the history of TEN, skin testing with penicillin G and the major determinants would be precluded. Although RAST testing was helpful in this case, less than 20% of patients with a history of penicillin have detectable penicillin specific IgE antibodies at the time of testing.²¹ Also, lymphocyte transformation testing (LTT), a measurement of proliferating T lymphocytes to a drug in vitro could have been performed for confirmatory testing. However, this is not routinely performed because LTT requires experience with cellular techniques, special equipment, and the results are difficult to interpret.²² Also the positivity of LTT varies by the type of allergic reaction being tested, more likely to be positive in generalized exanthema such as maculopapular, bullous, pustular, and less likely positive in TEN reactions.²² Of note, our facility did not have access to LTT. Cephalosporin skin tests are not routinely available, although anti-cephalosporin IgE antibody assays are available to some clinicians in other countries. In addition, specific haptenic determinants in hypersensitivity are only recently being identified. For example a degradation product of cefaclor and cephalexin, a pyrazinone conjugate, has been identified as a potential cephalosporin allergen by Venemalm in 2001.²³

This case demonstrates the lack of a discrete algorithm in the diagnosis of drug hypersensitivity. Commercially available diagnostics to truly distinguish classes of drug hypersensitivity and specific antibiotic drug allergy are needed. A focused approach to the cephalosporin reaction would have been helpful in this case. However, cephalosporin allergenic determinants have not been identified fully, and cephalosporin conjugates are reported to be unstable.²⁴ Few studies have reported delayed hypersensitivity reactions to cephalosporins, but patch testing for cephalosporins have shown to be diagnostically useful in case-reports.²⁵ Although our correlation of this case is primarily clinical, it demonstrates the variability of beta lactam hypersensitivity and provides a clinical example of concurrent IgE mediated and non-IgE mediated reactions within a class of antibiotics. It

further suggests a possible yet undelineated mechanism of cross reactivity and hypersensitivity between beta lactam classes.

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