Case report

Fatal ampicillin-sulbactam anaphylaxis in a 34-year-old male

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A 34-year-old man receiving his first dose of ampicillin-sulbactam for osteomyelitis in a hospital setting experienced fatal drug-induced anaphylaxis. (J Allergy Clin Immunol Global 2023;2:100136.)

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Abbreviation used
MDM: Minor determinant mixture

A 34-year-old male with a history of daily intravenous fentanyl use, asthma, seasonal allergic rhinitis, atopic dermatitis, obesity, and hyperlipidemia presented for evaluation of a chronic 7 × 8-cm right forearm wound related to intravenous fentanyl use. Physical examination revealed exposed necrotic muscle and bone; in addition, there was laboratory evidence of systemic infection and inflammation (see Table E1 in the Online Repository at www.jaci-global.org), and radiographic evidence of osteomyelitis of the proximal ulna. The patient underwent surgical debridement and began receiving broad antibiotic coverage with intravenous vancomycin, cefepime, and metronidazole. Operative cultures grew *Proteus mirabilis*, ampicillin-sensitive *Enterococcus*, and *Bacteriodes fragilis*. Once the culture and sensitivities returned, the patient was transitioned to ampicillin-sulbactam monotherapy.

Within minutes of the patient's first 3-gram ampicillin-sulbactam dose, his nurse was alerted (by his hospital roommate) that he needed medical assistance. On entering the patient's room, the nurse found the patient unconscious and unresponsive. A code protocol was initiated, and the ampicillin-sulbactam was stopped. Approximately 12 minutes after the ampicillin-sulbactam infusion had been started, the patient received his first intravenous dose of epinephrine and naloxone. After being unable to regain a reperfusing rhythm after multiple rounds of epinephrine and cardiopulmonary resuscitation, the code team cannulated the patient for extracorporeal membrane oxygenation and quickly regained a rhythm. During the cannulation and intubation process, the anesthesia team heard wheezing and reported low tidal volumes, difficulty with ventilation, and persistent hypotension refractory to high-dose vasopressors. No flushing, rash, angioedema, vomiting, or diarrhea were reported. No other medications were administered within 4 hours of this event. The patient's tryptase levels 4 and 5 hours after the acute event were 57.5 ng/mL and 35.8 ng/mL, respectively (Fig 1).

Five days after the event, penicillin skin testing was performed. Percutaneous and then intradermal testing for penicillin G, ampicillin, and benzylpenicilloyl polylysine allergy was performed. No testing was performed for allergy to amoxicillin or sulbactam. The testing revealed a positive wheal and flare at the site of ampicillin intradermal testing (8 × 11 mm) with a negative wheal and flare at the site of benzylpenicilloyl polylysine and penicillin G (Table I and see Fig E1 in the Online Repository at www.jaci-global.org). Ten minutes after the ampicillin intradermal testing, the patient developed acute hypotension, tachypnea, respiratory instability, and an upward deviated eye gaze. His norepinephrine drip, which had been at 4 μg per minute the entire day, was increased to 20 μg per minute, and 2 boluses of hydromorphone were required for sedation. The patient's tryptase level measured during the event was 6.8 ng/mL, which was down from 35.8 ng/mL 5 days earlier. However, his tryptase level was 2.2 ng/mL on day 7 after the acute event (Fig 1). A peripheral blood sample was negative for the *KIT* Asp816Val mutation, the most common *KIT* oncogene point mutation at codon 816 which results in substitution of aspartic acid with valine in the protein.

The patient denied any history of allergies, including antibiotic allergies. In view of his limited medical records, whether he had received ampicillin-sulbactam before this hospitalization is unclear. According to his primary care provider and pharmacy, he had not been prescribed any antibiotics over the past 2 years.

After the initial resuscitation, the patient developed myoclonic movements and extensor posturing, and a portable head computerized tomography scan showed loss of gray-white matter differentiation, hypoxic ischemic injury, and mass-effect over the brainstem, consistent with a severe and irreversible anoxic brain injury. An electroencephalogram showed a burst suppression

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Informed consent has been obtained with regards to using the patient's history, laboratory results, and pictures. The patient's proxy has given permission to allow publication of the case report.

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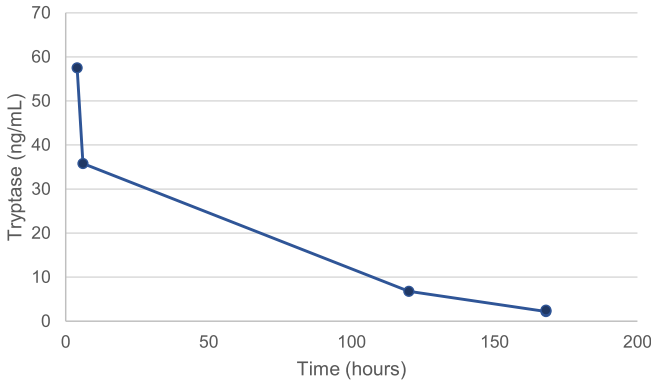

FIG 1. Tryptase levels throughout hospitalization.

TABLE I. Penicillin skin testing results

Drug	Prick testing	Intradermal testing (0.02 mL)	Intradermal testing (0.02 mL)
Penicillin G (10,000 U/mL for prick testing and 1,000 and 10,000 U/mL for intradermal testing)	0 mm	0 mm	0 mm
Benzylpenicilloyl polylysine	0 mm	0 mm	0 mm
Ampicillin (25 mg/mL)	0 mm	8 × 11 mm	
Histamine (6 mg/mL)	11 × 25 mm	7 × 10 mm	
Saline	0 mm	0 mm	

pattern at a 100% burst suppression ratio. The decision was made for him to become an organ donor via donation by cardiac death. The patient did not undergo an autopsy.

DISCUSSION

The patient's acute cardiac arrest in the setting of ampicillin infusion with elevated tryptase levels and a positive ampicillin skin testing result suggests that anaphylaxis in response to ampicillin was a contributor to or cause of his fatal acute decompensation.

Although the rate of reported drug anaphylaxis is low and decreasing, antibiotics account for approximately 40% of drug anaphylaxis fatalities, with β-lactams being the most commonly implicated antibiotic class.[1] Penicillins remain the most commonly reported drug class causing anaphylaxis.[2] Fatal drug anaphylaxis in the United States is extremely rare; the fatality rate is estimated at less than 1 death per million people per year. In the United Kingdom, only 1 fatal amoxicillin reaction was reported over a 35-year period.[3]

Ampicillin and amoxicillin are aminopenicillins, defined as 2-amino derivatives of benzylpenicillin. This similar R1 side chain motif is shared with cephalosporins such as cefaclor, cephalexin, cefadroxil, and cefprozil. Although different patterns of penicillin allergy have been described, anaphylaxis due to penicillin may be side chain–specific.[4,5] In a multisite US study across 63 subjects with positive skin testing tests, 4 patients (6%) tested positive to amoxicillin alone and 13 (21%) tested positive to both amoxicillin and minor determinant mixture (MDM).[6] Given that intravenous amoxicillin and MDM are not available for skin testing in the United States, we use intradermal ampicillin to improve detection of aminopenicillin allergy and dual sensitization to amoxicillin and MDM in high-risk patients.[7] Our patient's skin testing results were positive to ampicillin and negative to benzylpenicilloyl polylysine and penicillin G, suggesting sensitization to an antigenic determinant specific to ampicillin's R1 side chain, which is an uncommon pattern in the United States.[8,9]

Penicillin allergy evaluation begins with a drug allergy history, followed by skin testing in high-risk patients.[7,9] Penicillin skin testing has a sensitivity of 30.7% (95% CI = 18.9%-45.9%) and a specificity of 96.8% (95% CI = 94.2%-98.3%);[10] ampicillin skin testing has a sensitivity of 33% and specificity of 99%.[11] Systemic reactions to penicillin skin testing are extremely rare but previously appreciated in the allergy literature.[11] Given that nonirritating concentrations range from 2.5 to 25 mg/mL,[9] using an additional dilution may have reduced the severity of this patient's reaction during skin testing.

Multiple risk factors for fatal drug anaphylaxis have been identified; they include age, cardiovascular disease, obstructive pulmonary disease, prior drug allergy, systemic mastocytosis, and Sjögren syndrome.[1,2,12,13] Our patient's only known risk factor for fatal drug anaphylaxis was asthma. Asthma, however, is also a well-described risk factor for fatal anaphylaxis beyond drug allergy.[14] We are unsure whether the patient's chronic use of opioids may have contributed to his anaphylaxis. His clinical presentation was inconsistent with a mast cell disorder, with a tryptase test that returned to normal levels and a negative *KIT* Asp816Val result.

This case of fatal ampicillin anaphylaxis in a young male might increase awareness of drug anaphylaxis at a time in the United States when clinicians are correctly delabeling patients with inaccurate penicillin allergy histories. This case is a humbling reminder that although penicillins are among our safest and most effective antibiotics, they are also the most commonly reported cause of fatal drug anaphylaxis, and as we advocate for broad delabeling of inaccurate allergies, we must also advocate for an improved understanding of drug anaphylaxis for improved medication safety.

DISCLOSURE STATEMENT

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