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CASE REPORT

Acute Angioedema Triggered by Daptomycin

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ABSTRACT

Introduction: Daptomycin is a cyclic lipopeptide antibiotic, frequently administered for *Staphylococcus aureus* bloodstream infections. Numerous studies have shown that daptomycin is relatively safe and well tolerated. Serious adverse events possibly related to this antimicrobial compound are rare. We report a case of acute angioedema triggered by daptomycin.

Case Report: A 60-year-old woman with *S. aureus* bacteremia without identified source was treated intravenously with high-dose beta-lactams at our institution. Because *S. aureus* bacteremia persisted on day 6, and in parallel, acute kidney injury developed, antimicrobial treatment was switched to a combination therapy with daptomycin and ceftriaxone. Shortly after completion of the first daptomycin administration, the patient developed lip and tongue swelling and dyspnea. Acute angioedema was clinically evident. Antibiotic therapy was switched to vancomycin, and the further clinical course was favorable. An intradermal test showed a significant wheal diameter for daptomycin, but negative results for ceftriaxone.

Conclusion: The association with daptomycin in this case is either probable or certain. Clinicians should be aware that daptomycin can cause immediate-type hypersensitivity reactions, including acute angioedema, even upon first administration.

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INTRODUCTION

Daptomycin is a cyclic lipopeptide antibiotic approved for the treatment of complicated skin and skin structure infections, as well as for *Staphylococcus aureus* bloodstream infections, including those occurring with right-sided infective endocarditis [1, 2]. Data analyses from the EU-CORE registry consisting of 6075 patients indicate that daptomycin is relatively safe and well tolerated, even at high doses (>6 mg/kg/day) [3]. Serious adverse events possibly related to daptomycin occurred in ≤2% of patients, but hypersensitivity reactions were rare [3]. The precise clinical manifestations of these hypersensitivity reactions are not described. These registry data are important, in particular when facing a previously undescribed adverse event to a compound. Here, we report a case of acute angioedema triggered by daptomycin.

CASE REPORT

A 60-year-old woman was admitted to our hospital because of immobilizing lumbar back pain and elevated inflammatory markers in blood tests. Spine infection was suspected, and after obtaining blood cultures, the patient was treated empirical therapy with ceftriaxone (2 g once daily). Growth of Gram-positive cocci was detected in all blood culture samples. Antimicrobial treatment was switched to amoxicillin/clavulanate (2.2 g every 4 h on days 3 and 4 of hospitalization), and then streamlined to flucloxacillin (2 g every 4 h) after identification of methicillin-susceptible *S. aureus*. Despite 2 MRI scans, a PET-CT scan, an anti-granulocyte scintigraphy and several transesophageal echocardiographies, the source of bacteremia was not identified. On day 6, blood cultures were still positive for *S. aureus*. Thus, persistent *S. aureus* bacteremia without identified source was postulated. In parallel, acute kidney injury developed. Because of persistent bacteremia and renal impairment, antimicrobial treatment was switched to a combination therapy with daptomycin (10 mg/kg body weight) and ceftriaxone (2 g once daily) [4]. Shortly after completion of the first daptomycin administration (60 min infusion), the patient developed lip and tongue swelling and dyspnea. After adrenaline inhalation and intravenous administration of clemastine and methylprednisolone, symptoms and findings resolved. No skin eruption or diffuse lymphadenopathy was noted in clinical examinations, and results of laboratory investigations showed no elevated eosinophil counts, atypical lymphocytosis or increased serum alanine aminotransferase. Thus, the differential diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) appeared unlikely, and a diagnosis of acute angioedema was made.

Antibiotic therapy was switched to vancomycin and continued for 4 weeks. Doses were adapted according to the gradually recovering renal function, and monitored by vancomycin trough levels in serum. Blood cultures showed no growth on day 9 and results remained negative on day 12. The further clinical course was favorable.

The workup of the case included investigations into the cause of angioedema and renal failure. The timely occurrence of the latter and the histopathological characteristics of the kidney biopsy result were consistent with acute interstitial nephritis [5]. High-dose beta-lactam exposure during the first 4–6 days

of hospitalization was considered the most likely cause.

After intermittent hemodialysis (days 10–19) and corticosteroid treatment, renal function values returned to normal on the day of discharge (day 32).

A detailed review of the drug charts strongly suggested a timely association between angioedema and daptomycin. The role of other compounds (nonsteroidal anti-inflammatory drugs, opioids) in causing direct histamine release or immunoglobulin E (IgE)-mediated reaction was also reviewed. These compounds were repeatedly challenged without an obvious clinical reaction. Because no similar case was previously described in the literature, the differential diagnosis included a more commonly known reaction to ceftriaxone, although exposure to ceftriaxone in the preceding week spoke against such a reaction. Also, the workup of the patient's history revealed that she was exposed to 1st and 2nd generation cephalosporins in the previous years without any notable reaction. Daptomycin re-exposure was considered in the intensive care unit (ICU). An intradermal test (IDT) was performed first. The results were positive for daptomycin (5 mg/mL, wheal diameter 5 mm after 20 min), but negative for ceftriaxone (2 mg/mL). One healthy control produced no reaction to IDT with daptomycin at the same concentration. Acute angioedema shortly after daptomycin infusion and the positive IDT result suggested an immediate hypersensitivity reaction to daptomycin. Informed consent was obtained from the patient for being included in this case report.

DISCUSSION

To the best of our knowledge, this is the first report of angioedema after daptomycin exposure. A literature review identified only three published cases of immediate-type hypersensitivity reactions to daptomycin. Bagwell et al. [6] reported a 24-year-old woman with multiple antibiotic allergies. She had experienced hypersensitivity reactions to daptomycin previously, and after re-exposure, pruritus and shortness of breath developed. Metz and Thyagarajan described a 33-year-old man who did not tolerate vancomycin because of a diffuse urticarial eruption [7]. After the third daptomycin administration, he developed a generalized urticarial rash (no lip or tongue swelling or shortness of breath). His symptoms improved with diphenhydramine, but the urticarial rash returned after each subsequent dose. On the basis of the reported patient history, it is unclear whether this reaction was IgE mediated or nonspecific (e.g., mast cell activation). The third case illustrates desensitization to ceftaroline in a 32-year-old woman with multiple allergies, including anaphylaxis to daptomycin (not further specified) [8]. In contrast to these cases, our patient had no known allergy, and angioedema developed acutely after the first dose. In addition, the association with daptomycin was suggested by a positive IDT result.

Daptomycin was first approved by the US Food and Drug Administration (FDA) in September 2003. After the hallmark study on daptomycin for *S. aureus* bacteremia and endocarditis was published in 2006 [9], numerous safety data on this agent became available [3, 10–13]. In addition to known adverse events (e.g., myotoxicity), an association of daptomycin with eosinophilic pneumonia has been raised through an FDA drug safety communication [1]. Moreover, rare clinical manifestations such as acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms have been reported [14]. Anaphylaxis and angioedema are

labeled as reactions of unknown frequency and causality [1, 2]. Worldwide, 72 immediate-type hypersensitivity reactions to daptomycin have been reported to WHO pharmacovigilance centers [15]. In 20 of these cases, the reaction occurred on the first day of daptomycin treatment.

In the present case, the more frequently reported association of beta-lactams with hypersensitivity reactions [16] and the lack of a similar case report associated with daptomycin were misleading. When performing an IDT, a procedure with sequent dilutions is recommended (10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}) [17]. We performed the IDT in the ICU with a 10^{-1} dilution of the original vial concentration (50 mg/mL) and all necessary precautions were taken in case emergency treatment was needed. As done in our investigations, healthy volunteers with or without previous exposure to the drug can be used as negative controls to evaluate nonspecific skin reaction [17]. Although one healthy control may be insufficient to draw firm conclusions, the IDT result and a negative control was a helpful tool—together with the clinical observation and detailed time analyses of drug application—in pointing towards a daptomycin-associated hypersensitivity reaction. Because of the clinical circumstances, no in vitro testing with specific IgE level measurements to daptomycin could be performed, and no tryptase was measured. Although, in our view, IgE-mediated reaction is likely, it cannot be ascertained. Therefore, the association with daptomycin is either probable or certain.

CONCLUSION

Daptomycin is relatively safe and well tolerated. Serious adverse events are rarely reported. Nevertheless, clinicians should be aware that daptomycin can cause immediate-type hypersensitivity reactions. Our case report indicates that acute angioedema can be triggered by daptomycin, even upon first administration.

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