Acute Generalized Exanthematous Pustulosis Caused by Daptomycin in a Critically Ill Burn Victim

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Abstract

Acute generalized exanthematous pustulosis (AGEP) is a self-limiting type of drug eruption that frequently occurs as a reaction to antibiotics, particularly penicillins or macrolides. Daptomycin (DAP) is a newly developed antibiotic that specifically targets methicillin-resistant Staphylococcus aureus infection. We herein present the case of a 77-year-old severe burn victim who was diagnosed with DAP-induced AGEP while receiving treatment in an intensive care unit. Although rare, physicians should be aware that the administration of DAP can cause AGEP, which may complicate the clinical course of patients with a high fever and inflammation.

Key words: acute generalized exanthematous pustulosis, burn, daptomycin, intensive care unit, methicillin-resistant Staphylococcus aureus

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a self-limiting drug eruption that frequently occurs as a reaction to antibiotics, commonly penicillins and macrolides (1, 2). Although its prognosis is generally favorable, AGEP is considered to be similar to severe drug-induced skin reactions, such as drug-induced hypersensitivity syndrome or Stevens-Johnson syndrome (3). AGEP presents with characteristic dermal changes; however, it often goes unnoticed due to its rare incidence.

Daptomycin (DAP), a newly developed lipopeptide antibiotic, is a bactericidal agent that is active against Gram-positive bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA). This drug has been shown to be as effective as vancomycin, a classical anti-MRSA drug (4), and linezolid, a newly developed drug for the treatment of MRSA (5). To the best of our knowledge, only one case of DAP-induced AGEP has been reported to date in Singapore (6). We herein present a case of AGEP caused by DAP in a critically ill patient with approximately 80% skin loss due to severe burns.

Case Report

A 77-year-old man with systemic burns involving approximately 82% of his total body surface area (burn index: 44.5, prognostic burn index: 121.5), primarily on the trunk, back and lower extremities, was admitted to our critical care center. On day 5, meropenem (0.5 g every 6 h) was administered for the treatment of extended spectrum beta-lactamase (ESBL)-producing Escherichia coli cultured from the burn site. On day 16, MRSA was isolated from the burn site. By that time, various drugs, including meropenem, lanzoprazole, magnesium oxide, fentanyl, dobutamine, propofol and carperitide were administered. Suspecting the involvement of burn site infection caused by MRSA, the patient was additively started on 350 mg of DAP on alternate days due to renal insufficiency. Two days later, his body temperature increased to approximately 39°C; however, his general condition was relatively stable, and his hemodynamics were well controlled with a small amount of dobutamine. On the third day of DAP treatment, bilateral axillary and precordial...
pustules appeared. DAP was then discontinued on day 4 under suspicion of a drug-induced rash, and linezolid was administered as an alternative agent. The administration of all other drugs was continued during this time. The pustules gradually became accompanied by diffuse edematous erythema-like erythema (Fig. 1). A microscopic examination of the small pustules did not reveal fungal hyphae or spores, and bacterial cultures were repeatedly negative for pathogenic microorganisms. A histological examination of a skin biopsy specimen obtained from the right axilla revealed a large subcorneal pustule occupying the epidermis (Fig. 2). Laboratory tests showed an elevated white blood cell count of approximately 15,000/μL. Serologic tests (Enzyme Immunoassay) for cytomegalovirus were positive for IgG (7.6) but negative for IgM (0.29), and Epstein-Barr virus nuclear antigen (EBNA) and IgG for viral capsid antigen (VCA) were positive, while VCA-IgM was negative. Blood cultures were negative throughout the patient’s clinical course. A drug-induced lymphocyte stimulation test (DLST) was not performed. The patient was diagnosed with AGEP caused by DAP based on his clinical course and characteristic dermatological and pathological findings of the surviving normal skin. Following the cessation of DAP and the administration of 0.1% topical mometasone furoate, the pustules disappeared after one week. No antihistamine agents were administered. Although the patient recovered from AGEP, he ultimately died of multiple organ failure and sepsis on day 38. His clinical course is summarized in Fig. 3.

**Discussion**

AGEP is generally a self-limiting type of skin eruption that is most frequently (approximately 90% of cases) triggered by drugs. It has been reported that the use of antibiotics, especially penicillins, quinolones and macrolides, is most frequently associated with this condition (2). The duration between the administration of the causative drug and the appearance of pustules is relatively short, usually one to three days. Other causes include infections caused by viruses, such as enterovirus, coxsackie virus, parvovirus B19, adenovirus, cytomegalovirus, Epstein-Barr virus and hepatitis B virus, as well as hypersensitivity reactions to mercury,
chromium compounds and vaccination (7, 8). Because no definitive diagnostic markers for AGEP exist, various scoring systems have been proposed to help diagnose the disease, although these systems are still not well established (2). Currently, AGEP is diagnosed based on the presence of a combination of clinical and pathological findings. The most important factor for the diagnosis of AGEP is the prompt improvement of characteristic areas of skin eruption following the cessation of the causative drug.

Only one case of DAP-induced AGEP has been reported to date (6). In that report, the authors described a 57-year-old man with MRSA infection associated with osteomyelitis and bacteremia. The patient was treated with DAP for 24 days and developed a non-pruritic generalized maculopapular erythematous rash on the trunk and limbs. The onset of symptoms in that case was relatively delayed; however, the clinical and pathological findings were consistent with AGEP.

In the present case, due to its high permeability to soft tissues and bactericidal effect against MRSA, DAP was chosen as the preferred antimicrobial agent to treat the MRSA burn site infection. The rash that appeared after the start of DAP therapy was characteristic of AGEP, and the patient’s condition matched the characteristics observed in AGEP cases. That is, the condition suddenly emerged (three days after the administration of DAP) then rapidly disappeared (promptly resolving after the cessation of DAP) with erythema and small multiple pustules primarily in axillary regions accompanied by fever and neutrophilia. In addition, the histological findings showed subcorneal pustules with infiltration of neutrophils, consistent with the findings of AGEP. Differential diagnoses of AGEP include psoriasis, anticonvulsant hypersensitivity syndrome, subcorneal pustular dermatosis, superficial fungal infections, Sweet’s syndrome, toxic epidermal necrolysis and erythema multiforme (9). Although clearly distinguishing the condition from forms of bacterial pustulosis, especially pustular miliaria, was difficult in this case, the negative results of the microscopic examination and bacterial culture of the pustules, as well as the improvement observed following the administration of topical steroids, indicated that such a diagnosis was unlikely. At the time of the emergence of the pustules, other drugs were being administered; however, each drug had been given throughout the patient’s clinical course (more than two weeks). Therefore, these drugs were considered not to be causative of AGEP in this case.

There are no specific serum markers for the diagnosis of AGEP. As Leng et al. reported (6), we consider that the combination of clinical and dermatological characteristics and the exclusion of other possible etiologies of pustules are the only clues to the diagnosis of AGEP. Although the usefulness of DLST and/or patch tests as supportive means for diagnosing AGEP is of note, the diagnosis of AGEP secondary to DAP was reliably made in this case without these tests due to the typical presentation. We consider that the important issue for clinicians is to regard any antibiotics as possible culprits for the occurrence of AGEP.

Pre-existing bacterial infections, such as tonsillitis, otitis, pneumonia and parotitis may act as promoting factors (10, 11). Some researchers have speculated that a cytokine production pattern associated with drug-specific T cells evoked by bacterial infection is implicated in the occurrence of AGEP. In the present case, the severe systemic burn itself and the subsequent ESBL-producing E. coli and MRSA infections at the burn sites may have promoted the development of AGEP. Dermatological changes were fortunately observed in the surviving normal skin of the axilla and precordia in this case. However, if all sites with a predilection for AGEP had been involved with the burn sites, obtaining a definitive diagnosis would have been delayed or even impossible.

Currently, DAP is commonly used as the key drug in the treatment of MRSA infection. Myopathy, peripheral nerve injury and hypersensitivity pneumonitis are well-known side effects of DAP. However, due to the drug’s short history of clinical use, other as yet unidentified side effects may be associated with its administration. MRSA infection exhibits various presentations in critically ill patients; therefore, DAP is often administered in clinically complicated cases. Hence, we consider the possible side effects of DAP observed in this case to be important. Although rare, physicians should be aware that DAP can be a causative drug in cases of AGEP, which may complicate the clinical course in patients with a high fever and inflammation.

The authors state that they have no Conflict of Interest (COI).

References


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