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CASE REPORT

Piperacillin/Tazobactam-Associated Hypersensitivity Syndrome with Overlapping Features of Acute Generalized Exanthematous Pustulosis and Drug-Related Rash with Eosinophilia and Systemic Symptoms Syndrome

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Acute generalized exanthematous pustulosis (AGEP) is a rare disorder characterized by acute onset of erythematous and edematous eruptions with sterile pustules, accompanied by fever, and a self-limiting condition thought to be caused by drugs, in particular, antibiotics. Drug-related rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug-induced reaction, characterized by a generalized skin rash associated with hypereosinophilia, lymphocytosis, and internal organ involvement. These reactions differ in causative agents, as well as clinical presentation, prognosis, and treatment. Therefore, appropriate diagnostic measures should be rapidly undertaken. Herein, we described a patient who developed overlapping features of hypersensitivity syndromes, AGEP and DRESS, with the use of piperacillin and the beta-lactamase inhibitor sodium tazobactam. Coexistence of AGEP and DRESS in the same patient is quite rare. To the best of our knowledge, there have been no previous reports on the coexistence of AGEP and DRESS associated with piperacillin/tazobactam. **(Ann Dermatol 28(1) 98～101, 2016)**

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-Keywords-
Acute generalized exanthematous pustulosis, Drug hypersensitivity syndrome, Piperacillin

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare disorder characterized by acute onset of erythematous and edematous eruptions with sterile pustules, accompanied by fever, and a self-limiting condition thought to be caused by drugs, in particular, antibiotics[1]. Drug-related rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug-induced reaction, characterized by a generalized skin rash associated with hypereosinophilia, lymphocytosis, and internal organ involvement[2]. Herein, we describe a patient who developed overlapping features of these hypersensitivity syndromes with the use of piperacillin and the beta-lactamase inhibitor sodium tazobactam.

CASE REPORT

A 74-year-old woman with metastatic renal cancer was admitted to our hospital for treatment for pneumonia. She developed fever (38.5°C) and rash after 9 days of treatment with piperacillin/tazobactam. The rash consisted of diffuse pruritic erythematous eruptions with nonfollicular pinhead-sized pustules on the neck, trunk, and both upper and lower extremities, sparing the mucous membranes (Fig. 1A～C). She had no known drug allergies. Blood tests revealed a white blood cell count of $9.89\times10^3/\mu l$

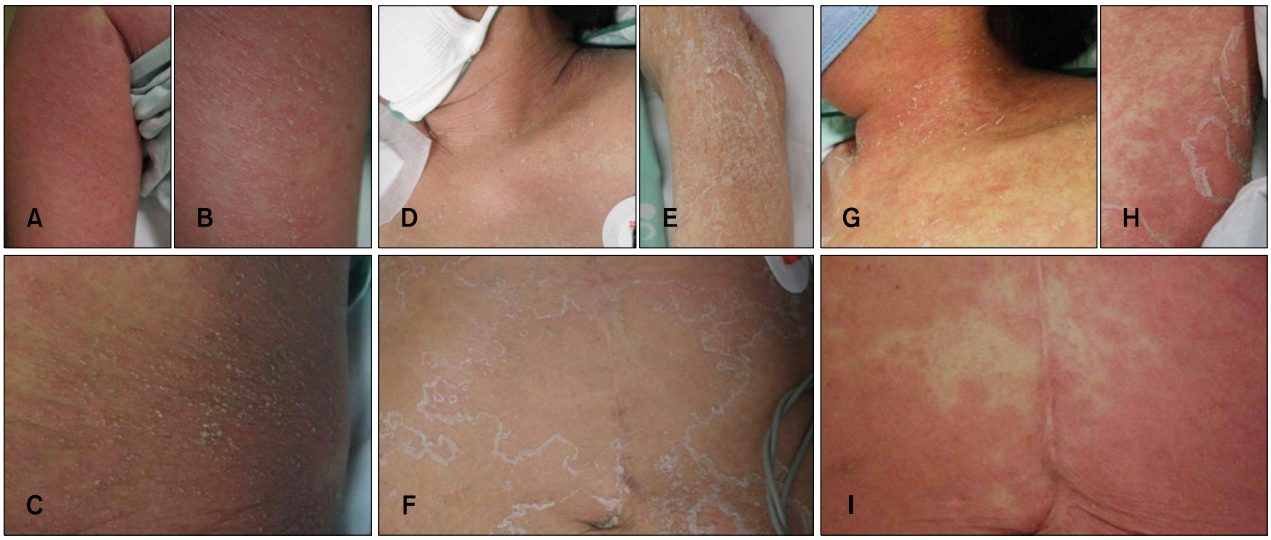

Fig. 1. Diffuse erythematous eruption with nonfollicular pinhead-sized pustules on both extremities and the trunk appearing after 9 days of treatment with piperacillin/tazobactam (A～C), subsequent improved status of the skin with desquamations on the neck, arm, and abdomen (D～F), and erythematous patches with previous desquamations on the 20th day after initiation of the antibiotic therapy (G～I).

with neutrophilia (80%) and a normal eosinophil count (1%) and increased liver enzyme levels (aspartate aminotransferase, 45 IU/L; alanine aminotransferase, 78 IU/L; alkaline phosphatase, 873 IU/L). Wound and blood cultures showed no growth. Histopathology revealed subcorneal pustules with epidermal spongiosis and perivascular inflammation of lymphocytes and eosinophils in the upper dermis (Fig. 2). Antibiotics were discontinued, and a topical steroid was applied. The pustules and neutrophilia rapidly resolved (Fig. 1D～F). Based on the clinical and histopathological findings, the patient was diagnosed with AGEP. However, on the 20th day of antibiotic therapy, she developed a generalized erythematous rash, again with desquamations that occurred after pustules (Fig. 1G～I). The patient showed severe facial edema and fever (38.5°C). Blood tests revealed eosinophilia (36%, Fig. 3), atypical lymphocytes, and an increase in liver enzyme levels (aspartate aminotransferase, 90 IU/L; alanine aminotransferase, 64 IU/L; alkaline phosphatase, 568 IU/L). The results of mycoplasma immunoglobulin (Ig) M and IgG, cold agglutinin, hepatitis B surface antigen and anti-hepatitis B core antibodies (HBc Ab), anti-hepatitis C virus Ab, anti-human immunodeficiency virus Ab, rapid plasma reagin, and influenza tests were all negative. The patient was treated with systemic corticosteroids. The skin rash responded partially, but neither eosinophilia nor hepatic dysfunction resolved in the following days. She expired due to exacerbation of pneumonia.

DISCUSSION

The classic diagnostic triad of AGEP includes nonfollicular intraepidermal or subcorneal pustules (< 5 mm) arising on widespread edematous erythema, fever with a temperature of greater than 38°C, and a neutrophil count greater than 7,000 cells/μl[1]. Based on the clinical findings of relatively acute onset, nonfollicular pustules, and fever with neutrophilia, the patient had been diagnosed with AGEP before skin lesions appeared again with facial edema. After that, blood tests revealed eosinophilia instead of neutrophilia, and atypical lymphocytes were shown with increased liver enzyme levels. A Japanese consensus group has established seven criteria for the diagnosis of DRESS syndrome[3]. Our case fulfilled five of the seven criteria, and was consistent with atypical DRESS.

Considering the histological findings, which showed subcorneal pustules and perivascular inflammation of lymphocytes and eosinophils in the upper dermis and a positive clinical response to discontinuation of antibiotics, we diagnosed this patient with hypersensitivity syndrome with overlapping features of AGEP and DRESS by the use of piperacillin/tazobactam. We excluded this case from the diagnosis of DRESS syndrome with pustulation because the eosinophilic skin rashes appeared with desquamations after all pustules had subsided. A lymphocyte transformation test, patch test, and skin prick test helped to identify the drug causing the hypersensitivity reaction. However, in this case, these tests could not be performed due to the patient's poor condition.

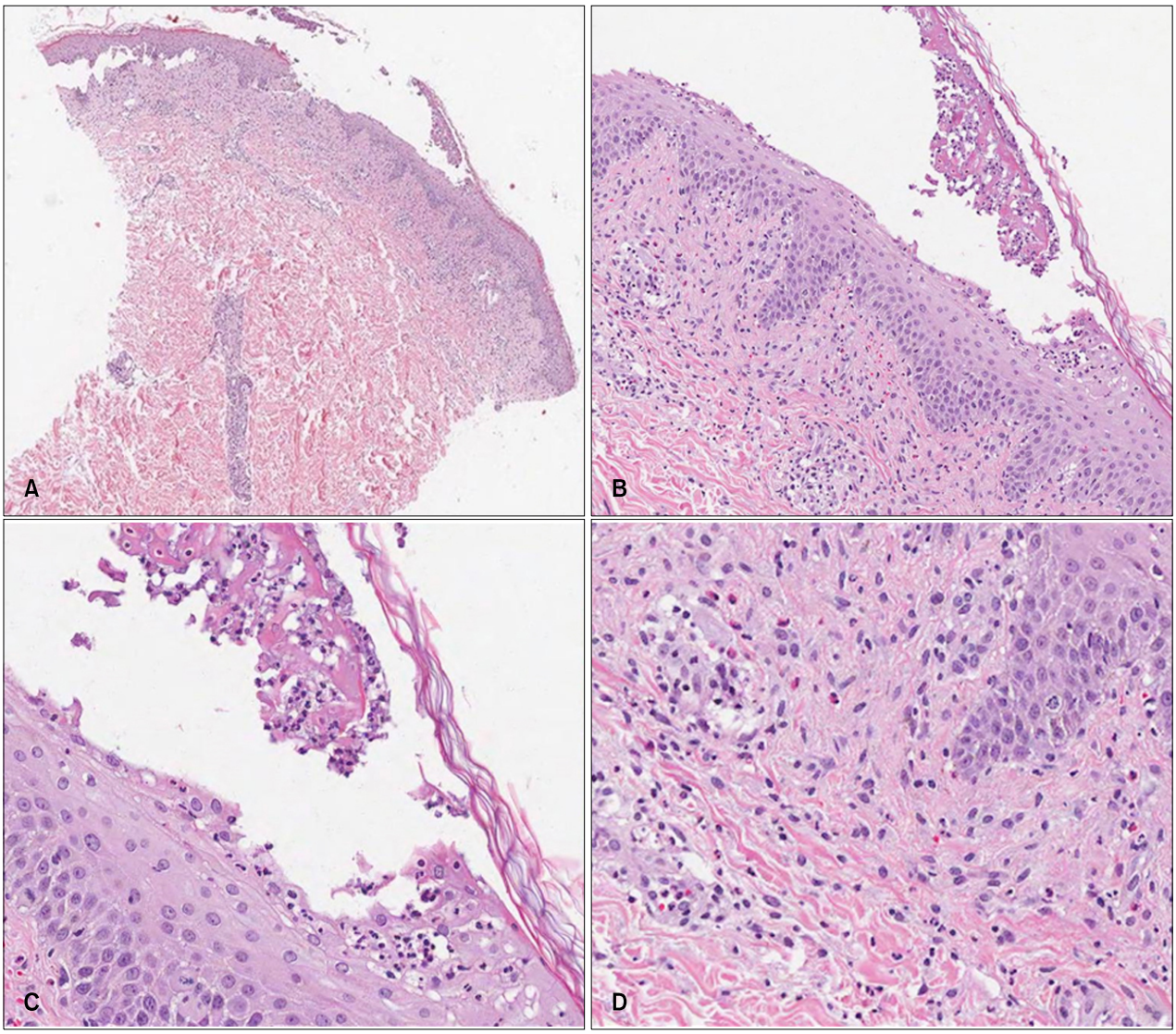

Fig. 2. Histopathology showing a subcorneal pustule with epidermal spongiosis and perivascular inflammation of lymphocytes and eosinophils in the upper dermis (H&E; A: ×40, B: ×100, C and D: ×200).

The spectrum of severe drug-induced skin reactions includes Stevens-Johnson syndrome and toxic epidermal necrolysis, generalized bullous fixed drug eruptions, AGEP, and DRESS. These reactions differ in their causative agents and clinical presentation, prognoses, and treatments. Therefore, appropriate diagnostic measures should be rapidly undertaken[4]. In AGEP, the onset of disease follows antibiotic use, and the time between antibiotic administration and onset of eruption is around 2∼3 days[1]. DRESS is categorized as a disorder associated with eosinophilia and is clinically differentiated from other hypersensitivity disorders[5]. Although AGEP and DRESS syndrome have different clinical presentations, they have a common T-cell–mediated pathogenesis[4], and we suggest that this mechanism allows for the presentation of overlapping features of the two diseases. A previous report demonstrated overlapping features of two drug-associated diseases by vemurafenib[6].

The drugs most frequently associated with AGEP include penicillin and related antibiotics[7]. In contrast, aromatic anticonvulsant drugs and allopurinol are the most frequently reported drugs associated with DRESS syndrome[3]. Although there are previous cases of AGEP or DRESS syndrome caused by piperacillin/tazobactam[8-10], the coexistence of AGEP and DRESS in the same patient is quite rare, and to the best of our knowledge, there have been no previous reports on the coexistence of AGEP and DRESS associated with piperacillin/tazobactam. Although AGEP is a self-limiting condition with a good prognosis, close monitoring is needed depending on the causative drug and the patient's

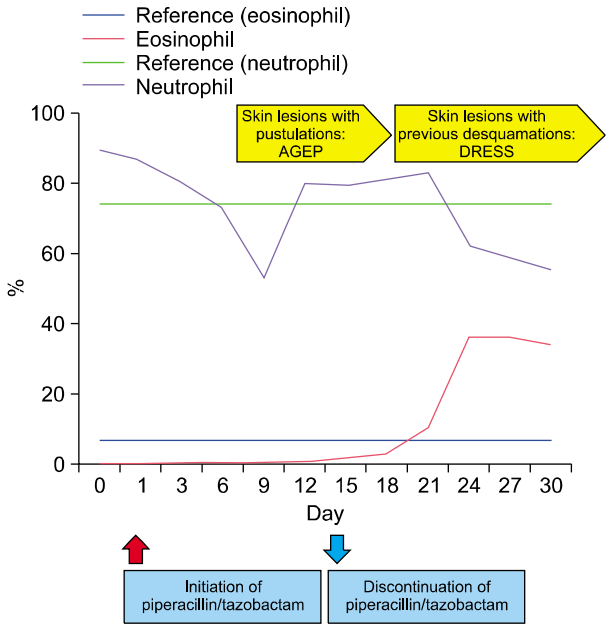

Fig. 3. Eosinophil and neutrophil percentages with references according to day. Day 0 indicates the day before treatment with piperacillin/tazobactam, and day 1 indicates the first day of treatment. AGEP: acute generalized exanthematous pustulosis, DRESS: drug-related rash with eosinophilia and systemic symptoms.

immune status, as in the case of this patient.

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