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Cefotaxime-induced drug rash with eosinophilia and systemic symptoms syndrome in a 7-year-old boy



Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an unpredictable, life-threatening condition attributable to drugs leading to long-lasting skin eruption and approximately 10% mortality.¹ The classic features are a diffuse maculopapular rash, facial edema, lymphadenopathy, fever, multiple visceral organ involvement, and hematologic abnormalities (eosinophilia, lymphocytosis, and atypical lymphocytes).² Anti-convulsants, allopurinol, and sulfonamides are the most common cause of DRESS syndrome.³ Only 3 cases of cefotaxime-induced DRESS syndrome have been reported in the literature: 2 adult cases and 1 pediatric case.^{4,5} However, there are no reports of patients who underwent a cefotaxime provocation test. We report a case of cefotaxime-induced DRESS syndrome diagnosed based on the classic features, unintentional provocation test result, and delayed-reading intradermal test (IDT) result during the treatment of osteomyelitis in a 7-year-old boy.

A 7-year-old Korean boy was admitted for treatment of acute osteomyelitis of the right distal tibia. He had no chronic comorbidities and no personal or familial history of allergic diseases, including drug hypersensitivity.

We planned to prescribe intravenous vancomycin and cefotaxime for 3 weeks. The patient began an intended 3-week course of intravenous vancomycin (60 mg/kg daily) and cefotaxime (150 mg/kg daily). He tolerated the treatment for the first 14 days, except for sporadic eosinophilia (eosinophil count, 502–707/mm³ [5.8%–6.7%]) from day 3 onward. Starting on treatment day 15, sporadic fever and urticarial rash were observed. The fever was self-limited without use of antipyretics, and pruritic rash persisted despite use of antihistamines (Fig 1A). On day 19, maculopapular rashes developed on the upper extremities and then rapidly fused into a generalized pruritic morbilliform rash over the whole body surface without mucous membrane involvement (Fig 1B). Fever (temperature reached 39°C) persisted, and no hepatosplenomegaly, lymphadenopathy, and respiratory symptoms were observed. Blood tests revealed increased eosinophil percentage (eosinophil count, 494/mm³ [9.5%]), C-reactive protein level (1.07 mg/dL;

reference range, <0.5 mg/dL), erythrocyte sedimentation rate (54 mm/h; reference range, <20 mm/h), lactic acid dehydrogenase level (538 U/L; reference range, <250 U/L), alanine transaminase level (30 U/L; reference range, <40 U/L), aspartate aminotransferase level (48 U/L; reference range, <40 U/L), and total bilirubin level (0.3 mg/dL; reference range, <1.2 mg/dL).

Because of the suspicion of DRESS syndrome, intravenous antibiotic treatment was stopped and oral prednisolone was given on day 20. Three days after antibiotic cessation, fever and skin manifestation improved. Intravenous cefotaxime was readministered on day 22 because of concerns of early antibiotic cessation and the impression that vancomycin was the culprit responsible for the reaction. One day after readministration of cefotaxime, pruritic rashes newly occurred on the trunk and lower extremities. Oral prednisolone was administered for 14 days. The laboratory abnormalities were restored soon after the use of oral prednisolone and intravenous antibiotic cessation. Without exfoliation, skin pigmentation and eosinophilia persisted for more than 7 weeks. The following laboratory tests were performed, and all results were negative: hepatitis A, B, and C virus tests and repeated-measures polymerase chain reactions for human herpesvirus 6 and 7 (HHV-6 and -7), *Mycoplasma pneumoniae*, Epstein-Barr virus, and cytomegalovirus after the onset of morbilliform rash. A delayed-reading IDT to cefotaxime, cefazolin, and cefuroxime (2 mg/mL) according to the European Network on Drug Allergy and European Academy of Allergy and Clinical Immunology Interest Group on Drug Allergy recommendation⁶ was performed 6 weeks after discontinuation of oral prednisolone use. Histamine and saline were used as positive and negative controls, and a positive result to only cefotaxime revealing induration of 10 mm was obtained in the 48-hour reading (Fig 1C). The results of immediate-reading IDTs were negative.

We report a case of a 7-year-old boy with cefotaxime-induced DRESS syndrome. Because of the rare association with cefotaxime, initially we suspected vancomycin as the culprit drug. On the basis of fever (temperature of 39°C), morbilliform rash, eosinophilia, exclusion of other potential causes, and hepatic cytolysis, the patient was considered to have a probable case (score of 5) suggested by the European Registry of Severe Cutaneous Adverse

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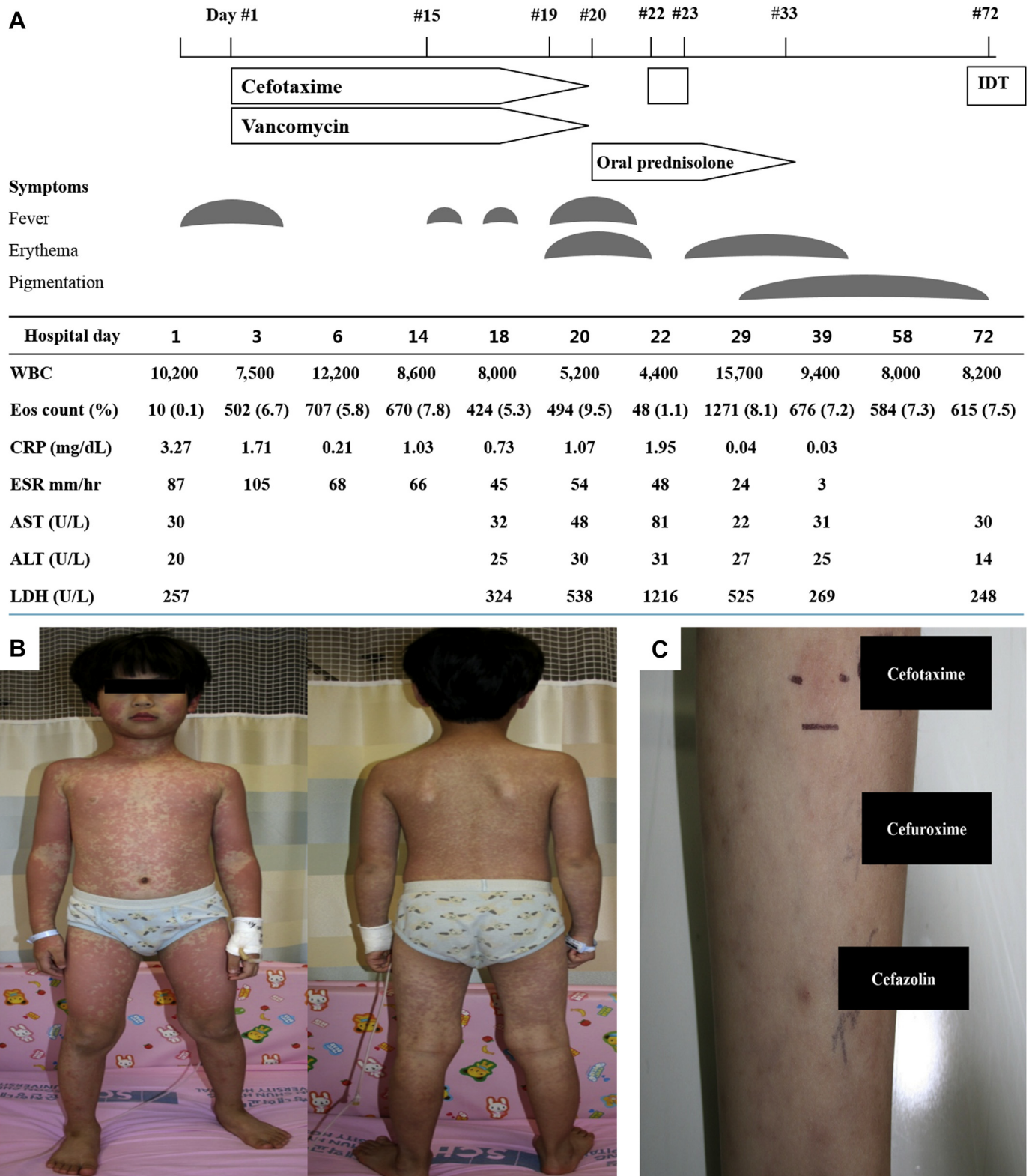


Figure 1. (A) Hospital course. On day 19 after starting intravenous vancomycin and cefotaxime therapy for the treatment of osteomyelitis of the right distal tibia, fever and pruritic morbilliform rash developed. Three days after antibiotic cessation and initiation of oral prednisolone (1 mg/kg) therapy, fever and skin manifestation were improved. However, skin manifestation was worsened when intravenous cefotaxime was readministered on day 22. A total 14-day course of oral prednisolone at a tapered dose successfully treated the drug rash with eosinophilia and systemic symptoms syndrome. The delayed-reading intradermal test result was positive for cefotaxime (induration of 10 mm) 6 weeks after discontinuation of oral prednisolone treatment. (B) Morbilliform, pruritic rash was noted on the face, trunk, and extremities. (C) Intradermal skin test result with delayed reading at 48 hours. A positive result to cefotaxime with a 10-mm induration was observed, whereas negative results to cefuroxime and cefazolin were obtained. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; Eos, eosinophil; ESR, erythrocyte sedimentation rate; IDT, intradermal test; LDH, lactate dehydrogenase; WBC, white blood cell.

Reactions.⁷ Furthermore, results of the unintentional provocation and delayed-reading IDT to cefotaxime supported the cefotaxime-induced DRESS syndrome.

Cefotaxime is known to be a safe drug and rarely associated with mild adverse reactions. In the previously reported case of cefotaxime-induced DRESS syndrome in a child, the drug lymphocyte stimulation test and patch test were used as diagnostic tools; however, the patch test is recommended as an additional test method when no intravenous drug solutions are available for an IDT, and it has a lower sensitivity than delayed-reading IDT in the diagnosis of nonimmediate hypersensitivity reactions.⁸

Usually, DRESS syndrome is a severe, life-threatening drug hypersensitivity, and it commonly involves multiple internal organs. However, previous cases of cefotaxime-induced DRESS syndrome in a 52-year-old man and a 11-year-old girl revealed minimal internal organ involvement.^{4,5} Although some mechanisms, such as deficiency of drug-metabolizing enzyme, T-lymphocyte activation, reactivation of herpesviruses, and genetic predisposition with specific HLA complex, have been proposed to play key roles in the pathogenesis of DRESS syndrome, they are not fully understood.¹

Since Marviridin et al⁹ reported that amoxicillin induced HHV-6 replication in vitro, it has been believed that the use of antibiotics and reactivation of HHV-6 are strongly associated with the development of DRESS syndrome. Dysphagia, mucous membrane involvement, cervical lymphadenopathy, facial edema, and atypical lymphocytosis have been suggested as the early signs and symptoms of HHV-6 reactivation.¹ However, our case did not reveal any of these signs and symptoms or herpesvirus infection and reactivation. Our patient had mild clinical manifestations and a good response to drug discontinuation and corticosteroid treatment. Absence of association with HHV-6 reactivation may explain the mild form of DRESS syndrome.

Although immediate withdrawal of the culprit drug and initiation of high-dose systemic corticosteroids have been recommended,¹⁰ we used a minimum dose of oral prednisolone (1 mg/kg) and gradually tapered it during 2 weeks because of concerns of reactivation of herpesviruses and worsening of osteomyelitis.

To the best of our knowledge, only 3 cases of cefotaxime-induced DRESS syndrome have been reported in the literature. However, none were confirmed by a provocation test. In this case, the syndrome was confirmed by the unintentional provocation test and IDT results. Furthermore, we suggest that preceding mild

eosinophilia and an unexpected episode of fever and urticarial rash during cefotaxime therapy with a tolerable response may be early signs of DRESS syndrome.

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Omalizumab in the treatment of antihistamine-resistant chronic urticaria in adults



Chronic urticaria is characterized by hives and/or angioedema that occurs for more than 6 weeks at a time.¹ Although the use of high doses of second-generation histamine₁ antihistamines has recently been proposed as a treatment for this condition, biological therapy against IgE has also emerged as a new alternative for the treatment of chronic spontaneous urticaria.^{2–6}

This study assessed the effectiveness of omalizumab to treat spontaneous or inducible urticaria in the Mexican population. The ethics and research committees of the Hospital Regional “Lic. Adolfo López Mateos,” Instituto de Seguridad y Servicio Sociales de los Trabajadores del Estado approved our study, and each patient provided written informed consent to participate. When building our cohort, we included patients 18 years or older who had inducible or spontaneous chronic urticaria and those who had a refractory response to antihistamines at a standard dose after 2 weeks, as defined by a Urticaria Activity Score 7 (UAS-7) score of

16 points or more. We excluded all patients with a history of asthma or allergic rhinitis, anaphylactic reactions or hypersensitivity to omalizumab, neoplasms, greater than 10% weight loss in the 6-month period before the study, and autoimmune disease, women who were pregnant or breastfeeding, and patients using systemic or topical corticosteroids. Consecutive patients were recruited by nonprobability sampling from March 1, 2014, through February 29, 2015. All the patients in our study were initially treated with 5 mg/d of levocetirizine for 2 weeks to control urticaria (157 patients). The 82 patients who responded to the treatment were excluded. The 76 patients who continued to have chronic urticaria with a UAS-7 score greater than 16 points went to a second phase of treatment with 20 mg/d of levocetirizine (4 times the common dose) for 4 weeks. Patients who achieved control of urticaria with this dose (50 patients) did not participate in the final stage. Patients who did not achieve control or had inadequate