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A Case of Vancomycin-Induced Drug Reaction with Eosinophilia, Systemic Symptoms and Multiorgan Involvement Proven Using Lymphocyte Transformation Test

Kyung Bae Chung, Ji-Hye Hwang, Doyoung Kim

Department of Dermatology and Cutaneous Biology Research Institute, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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Corresponding Author
Doyoung Kim
Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2080
Fax: +82-2-393-9157
E-mail: dykim@yuhs.ac
https://orcid.org/0000-0002-0194-9854

Drug-induced hypersensitivity syndrome (DiHS), also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), is a rare but potentially life-threatening condition induced by drug hypersensitivity that leads to significant morbidity and mortality and often occurs in patients undergoing combination antibiotic therapy. Due to a recent increase in the incidence of methicillin-resistant *Staphylococcus aureus* infections, the occurrence of vancomycin-induced DiHS/DRESS has increased rapidly. However, because of insufficient pharmacogenetic data on vancomycin-induced drug eruptions in Asians coupled with the risk of re-eliciting the symptoms by provocation tests, confirmation of the culprit drug in vancomycin-induced DiHS/DRESS is often challenging. Here, we report a case of vancomycin-induced DiHS/DRESS, where the causal relationship was confirmed using a lymphocyte transformation test (LTT). A 51-year-old woman was treated with combination antibiotics, including vancomycin, for infective pericarditis. The patient subsequently developed fever, facial edema, generalized rash followed by multiple internal organ involvement, including the kidney, lung, liver, and heart. Thus, based on the International Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria, the case was diagnosed as 'definite' DiHS/DRESS, although the culprit drug was obscured by combination antibiotic therapy. The LTT confirmed that vancomycin, but not other glycopeptide antibiotics, specifically induced T-cell proliferation in this case. Collectively, our case suggests that clinicians can utilize LTT to identify the causative medication of DiHS/DRESS when the clinical information is limited to defining the culprit drug.

Keywords: Drug eruptions, Drug hypersensitivity, Drug hypersensitivity syndrome, Lymphocyte activation, Vancomycin

INTRODUCTION

The combined use of antibiotics, particularly in critically ill patients, may lead to the development of severe cutaneous adverse reactions (SCARs), which complicate the future decision of a safe antibiotic regimen. Notably, drug-induced hypersensitivity syndrome (DiHS), also called drug reaction with eosinophilia and systemic symptoms (DRESS), is a SCAR with a variable and unpredictable course that commonly occurs after a long incubation period; therefore, the identification of the culprit antibiotics is often challenging[1,2]. *In vivo* drug provocation tests should be avoided in SCARs; thus, an *in vitro* approach such as a lymphocyte transformation test (LTT) could be employed to identify the causative medication[1,3]. In certain antimicrobials such as beta-lactams, anti-tuberculoids, sulfamethoxazole, or dapsone, the sensitivity and specificity of LTT have been widely analyzed[1,4].

Recently, there have been a few reports on DiHS/DRESS provoked by vancomycin, which is a drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) infections[5,6]. However, the usefulness of LTT for glycopeptide antimicrobials such as vancomycin and teicoplanin has not been widely

verified, particularly in DiHS/DRESS. Here, we report a case of vancomycin-induced DiHS/DRESS, presenting with multiple internal organ involvement, where the causal relationship was confirmed using LTT.

CASE REPORT

A 51-year-old woman visited a cardiology department for the treatment of dextrocardia, situs inversus, and large atrial septal defect (ASD), which caused migraine with aura, dyspnea, and atrial fibrillation. After surgical intervention with ASD patch repair, tricuspid valvuloplasty, and maze operation, she was administered ceftriaxone (a third-generation cephalosporin). However, 2 weeks after the operation, she developed fever with increased pericardial effusion. The pericardial fluid was drained by pericardiocentesis, and she was administered piperacillin/tazobactam with levofloxacin to control the acute condition. Fortunately, the patient was discharged without additional complications on the 34th day of admission. However, 5 days after discharge, she presented to the emergency department with a high fever (39.3℃), and a blood test revealed neutrophilia (89.9%, 7,060/μl) and increased serum C-reactive protein (CRP) (185.3 mg/L). Based on chest computed tomography (CT) and echocardiography, bacterial pericarditis was suspected. Therefore, combined antibiotics, including rifampicin, gentamicin, and vancomycin, were administered. The general condition had improved, and she was afebrile until day 14.

Fifteen days after antibiotic administration, she showed elevated levels of creatinine (0.92 mg/dl) and CRP (42.8 mg/dl). She also showed an increase in eosinophil number, which peaked at 1,230/μl (12.9% of total leukocytes) on day 35. Atypical lymphocytes were also found in the blood. She presented with fever on day 18 and displayed a generalized morbilliform skin rash and facial swelling on day 21 (Fig. 1). Due to consistent fever even with antibiotic treatment, the antibiotics were changed to teicoplanin. Multiple enlarged lymph nodes with diffuse body wall edema and pleural effusion were detected on a CT scan (Fig. 2). Along with radiological findings, dyspnea with negative bacterial culture in sputum suggested pulmonary involvement of a non-infectious inflammatory process. Moreover, she showed a continuous increase in creatinine level (1.71 mg/dl) with a decrease in estimated glomerular filtration rate, suggesting renal dysfunction, followed by elevation of liver enzyme levels (aspartate transaminase and alanine transferase levels peaked at 658 IU/L and 146 IU/L, respectively). Serology for hepatitis A, B and C virus ruled out viral origin. Furthermore, a cardiac marker, NT-proBNP, was elevated to 3,465 mg/dl with increased pericardial effusion. Thorough workup including infection (i.e. *Mycoplasma*) or autoimmune conditions revealed negative. Based on the International Registry of SCAR (RegiSCAR) criteria for the diagnosis of DiHS/DRESS, the patient was finally diagnosed with definite DiHS/

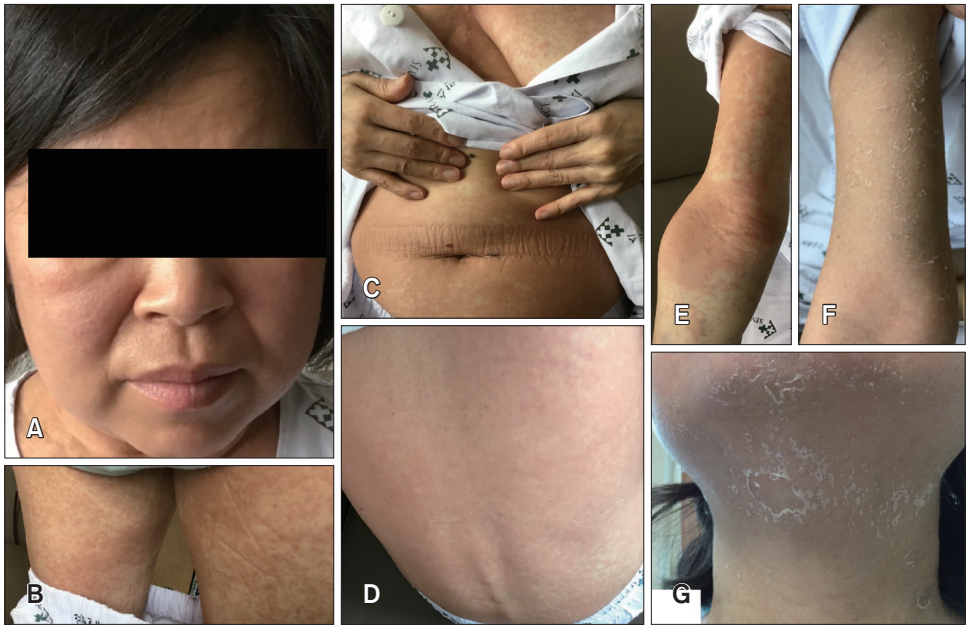

Fig. 1. Clinical presentation of the patient with facial edema (A) and generalized morbilliform eruption (B~E) following desquamation (F, G). We received the patient's consent form about publishing all photographic materials.

DRESS (a score of 8 points) with renal, liver, lung, and possible cardiac involvement (Table 1)[7]. All suspicious antibiotics were discontinued, and she was treated with high-dose systemic corticosteroids (1.0~2.5 mg/kg), sulfamethoxazole, and trimethoprim for the prophylaxis of *Pneumocystis jirovecii* pneumonia, which subsided fever and rash and normalized laboratory results after 34 days of treatment.

However, the combined use of multiple antibiotics hindered the identification of culprit drugs, and provocation tests were contraindicated in DiHS/DRESS. Therefore, LTT was at-

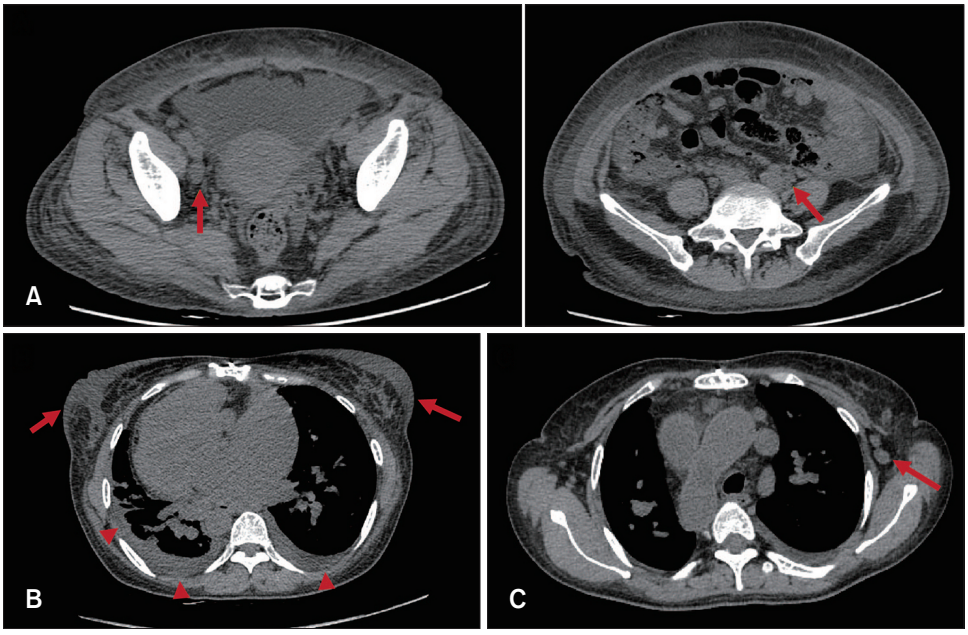

Fig. 2. Lymphadenopathy and pulmonary involvement based on chest computed tomography. (A) Increased size of multiple lymph nodes (arrows) in the retroperitoneum, both iliac chains, and inguinal area. (B) Diffuse body wall edema and skin thickening of both breasts (arrows) with pulmonary edema and bilateral pleural effusion (arrowheads). (C) Multiple enlarged lymph nodes (arrow) in the axillae.

Table 1. Assessment of clinical features based on RegiSCAR criteria

Item	Score			Comment
	–1	0	1	
Fever ≥38.5℃	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≥2 different areas
Eosinophilia ≥ 0.7×10^9/L or ≥10% if WBC <4.0×10^9/L		N/Y	Y	Score 2, when ≥1.5×10^9/L or ≥20% if WBC <4.0×10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS:
Extent >50% of BSA	N	N/U	Y	≥2 symptoms
Rash suggesting DRESS		U	Y	Purpuric lesions (other than legs), infiltration, facial edema, psoriasiform, and desquamation
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≥15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if tested negative for any three of the following: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, and blood culture

The patient fulfilled the diagnostic criteria for DRESS by a score of 8 points in the International Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria scoring system. N: no, U: unknown, Y: yes, WBC: white blood cell, BSA: body surface area, DRESS: drug reaction with eosinophilia and systemic symptoms, HAV: hepatitis A virus, HBV: hepatitis B virus, HCV: hepatitis C virus, ANA: antinuclear antibody.

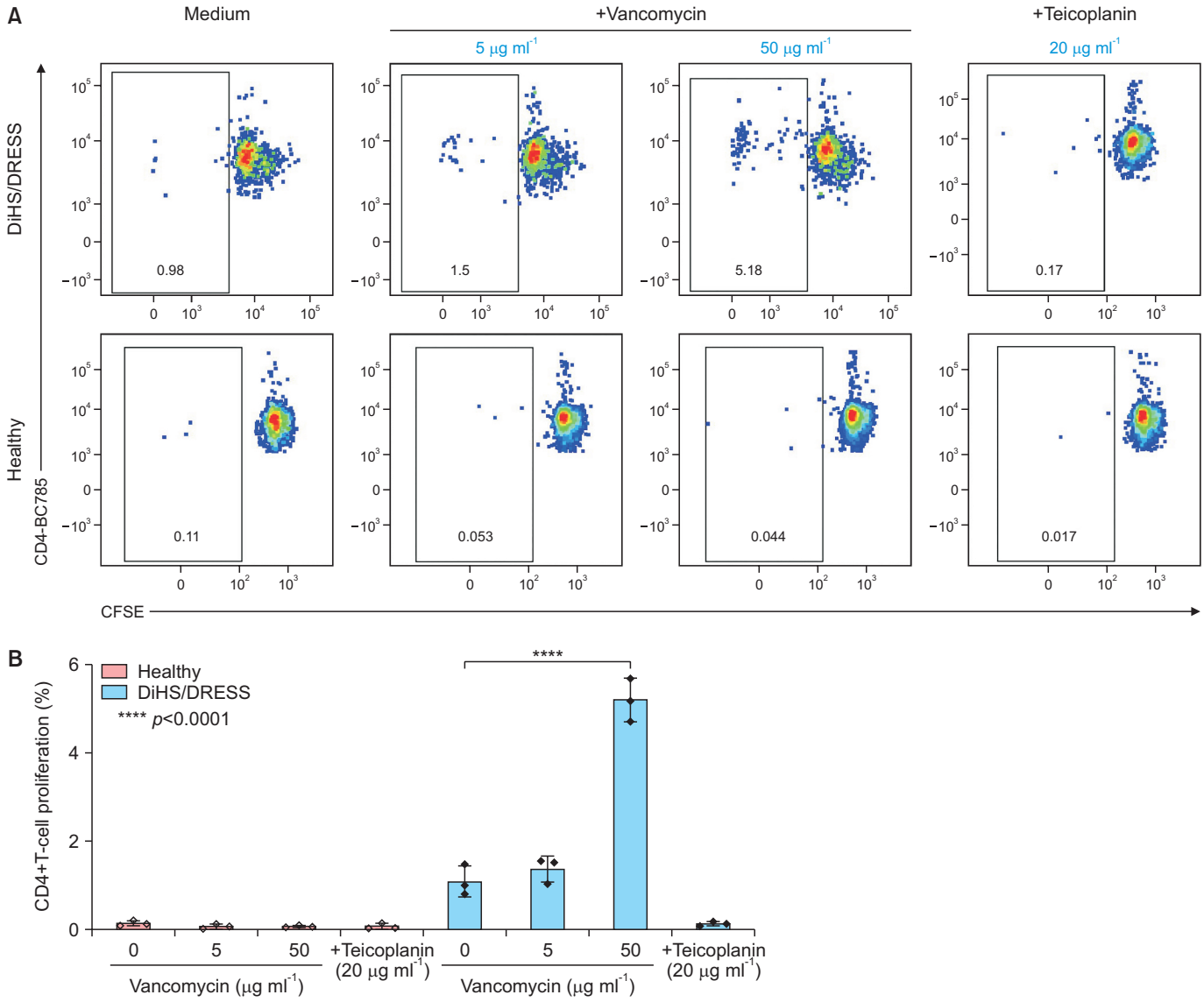

Fig. 3. Lymphocyte transformation test confirmed a causative medication of DiHS/DRESS. Peripheral blood mononuclear monocytes (PBMCs) were isolated from freshly isolated whole blood using a Ficoll-Paque gradient method. Carboxyfluorescein diacetate succinimidyl ester (CFSE)-labeled PBMCs were cultured with or without 0, 5, and 50 μg/ml of vancomycin or 20 μg/ml of teicoplanin for 7 days. Zombie-aqua^{-}CD3^{+}CD4^{+} T cells were gated using flow cytometry. (A) Representative flow cytometry plots and (B) quantified results of CFSE-diluted fraction as a measure of cell proliferation with or without vancomycin or teicoplanin (the percentage of CFSE-diluted cells among Zombie-aqua^{-}CD3^{+}CD4^{+} cells, n=3, a representative data from more than two independent experiments with similar results). Statistics based on multiple comparison to healthy volunteer (0 μg/ml) and DiHS/DRESS (0 μg/ml) by one-way ANOVA, ****p<0.001, post-hoc comparison between the negative control and 50 μg/ml vancomycin. DiHS: drug-induced hypersensitivity syndrome, DRESS: drug reaction with eosinophilia and systemic symptoms.

tempted using peripheral blood sampled during the recovery period. The acquisition of blood samples was approved by the Institutional Review Board (No. 4-2020-0056) of Severance Hospital, and written informed consent was obtained from the patient before sampling. Since the vancomycin trough and peak concentrations of the patient were approximately 12.78~16.46 μg/ml and 27.78~35.16 μg/ml, respectively, LTT was performed with 5 μg/ml (low dose) and 50 μg/ml (high dose) of vancomycin. The history of previous exposures to rifampicin and gentamicin favored vancomycin as a potential culprit. Teicoplanin, another glycopeptide antimicrobial against MRSA, was tested together for future use. To quantify

lymphocyte proliferation, isolated peripheral blood monocytes (PBMCs) were labeled with carboxyfluorescein diacetate succinimidyl ester (CFSE) (CellTrace™ CFSE Cell Proliferation Kit; ThermoFisher Scientific), and 2×10^5 PBMCs per well were incubated with or without antibiotics in 96-well plates for 7 days. The cultured PBMCs were harvested and stained with mouse anti-human CD3 (clone OKT3; BioLegend), CD4 (clone RPA-T4; BioLegend), and CD8 (clone RPA-T8; BioLegend) antibodies and Zombie Aqua Fixable Viability Kit (BioLegend), and then analyzed by flow cytometry (BD LSR Fortessa). The proliferating fraction of CD4 T cells was defined as the CFSE-diluted ratio among viable $CD3^+CD4^+$ cells. Flow cytometry identified a mild increase in the proliferation of CD4 T cells after incubation with 5 μg/ml (mean 1.5%, standard deviation=0.29%; p=0.86), suggesting that this patient's offending agent was vancomycin. CD4 T cells showed a high increase in proliferation at 50 μg/ml (mean 5.18%, standard deviation=0.50%; p<0.0001) of vancomycin, which confirmed that DRESS was induced by vancomycin in this patient. Moreover, the results did not show an increase in teicoplanin (20 μg/ml) (Fig. 3). Collectively, these results confirmed that vancomycin is a culprit medication for DiHS/DRESS in patients without cross-reaction with teicoplanin[8,9].

DISCUSSION

Herein, we report a case of vancomycin-induced DiHS/DRESS with renal, hepatic, pulmonary, and cardiac involvement, where the causal relationship was confirmed with LTT[10-12]. Without LTT, the confirmation of the offending drug was challenging due to concurrent administration of multiple antibiotics of different classes. Although vancomycin-induced DRESS is associated with a high renal predilection, multi-organ involvement in this case hindered us from predicting a causative drug[13-15]. Although HLA-A*32:01 has been reported as a pharmaco-genetic marker for the development of vancomycin-induced drug hypersensitivity in European populations, the reported high-risk HLA phenotype was not found in this case[16].

Currently, a complete allergy workup, including skin testing followed by a provocation test, is required to identify the culprit drug in drug eruptions. Since *in vivo* testing may accompany the risk for re-eliciting symptoms, applications of *in vitro* tests may be a safer approach in SCARs[17,18]. In this regard, various methodologies for *in vitro* tests have been applied in DiHS/DRESS[16]. Notably, LTT, a method to detect and quantify drug-activated T cells, is currently the most commonly used *in vitro* test[19]. In our study, the lymphocyte proliferative response was evaluated using flow cytometry-based methods using CFSE staining, an alternative method that enables the calculation of the fraction of proliferation and the specific characterization of cellular proliferation[20].

Collectively, this case highlights the usefulness of LTT, particularly in vancomycin-induced DiHS/DRESS. LTT can overcome the challenges associated with identifying the causative medication of DiHS/DRESS, such as the lack of predictive pharmacogenetic information in the Asian population and the frequent concomitant use of multiple medications. Furthermore, this technique may enable the selection of alternative antibiotics for future use in patients vulnerable to drug hypersensitivity. From this perspective, we anticipate this laboratory test can contribute to pharmacovigilance system by generating firm evidences for the causal relationship.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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ORCID

Kyung Bae Chung, https://orcid.org/0000-0002-2121-3553
Ji-Hye Hwang, https://orcid.org/0000-0002-9924-5723
Doyoung Kim, https://orcid.org/0000-0002-0194-9854

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