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DRESS Syndrome Caused by Cross-reactivity Between Vancomycin and Subsequent Teicoplanin Administration: A Case Report

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Patient: Male, 79
Final Diagnosis: DRESS
Symptoms: Eosinophilia • fever • interstitial pneumonitis • skin rash
Medication: Teicoplanin • vancomycin
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Adverse events of drug therapy

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening syndrome comprising severe skin eruption, fever, eosinophilia, lymphadenopathy, and involvement of internal organs. Here, we describe a case of DRESS syndrome caused by cross-reactivity between vancomycin and subsequent teicoplanin administration.

Case Report: A 79-year-old male was admitted to our hospital for the treatment of injuries incurred in a traffic accident. Eosinophilia and lung dysfunction appeared after vancomycin administration. These symptoms were improved temporarily by withdrawal of vancomycin and administration of corticosteroid, but exacerbated by subsequent teicoplanin administration. These symptoms disappeared after discontinuation of teicoplanin. Based on comprehensive assessment of the overall clinical course, we judged that DRESS syndrome was induced by cross-reactivity between vancomycin and subsequent teicoplanin administration. Using the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, we categorized DRESS syndrome related to vancomycin and teicoplanin as "probable." We describe, for the first time, DRESS syndrome (defined using the RegiSCAR scoring system) caused by cross-reactivity between vancomycin and subsequent teicoplanin administration.

Conclusions: Clinicians should be aware that DRESS syndrome can be induced by cross-reactivity between vancomycin and teicoplanin.

MeSH Keywords: Drug Hypersensitivity Syndrome • Lung Diseases, Interstitial • Teicoplanin • Vancomycin

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/899149

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Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening syndrome comprising severe skin eruption, fever, eosinophilia, lymphadenopathy, and involvement of internal organs [1–3].

Vancomycin and teicoplanin are glycopeptides currently used for the treatment of infections caused by invasive beta-lactam-resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). Teicoplanin is not inferior to vancomycin with regard to efficacy and is associated with fewer adverse events than vancomycin, including events requiring the discontinuation of treatment, nephrotoxicity, and red man syndrome [4].

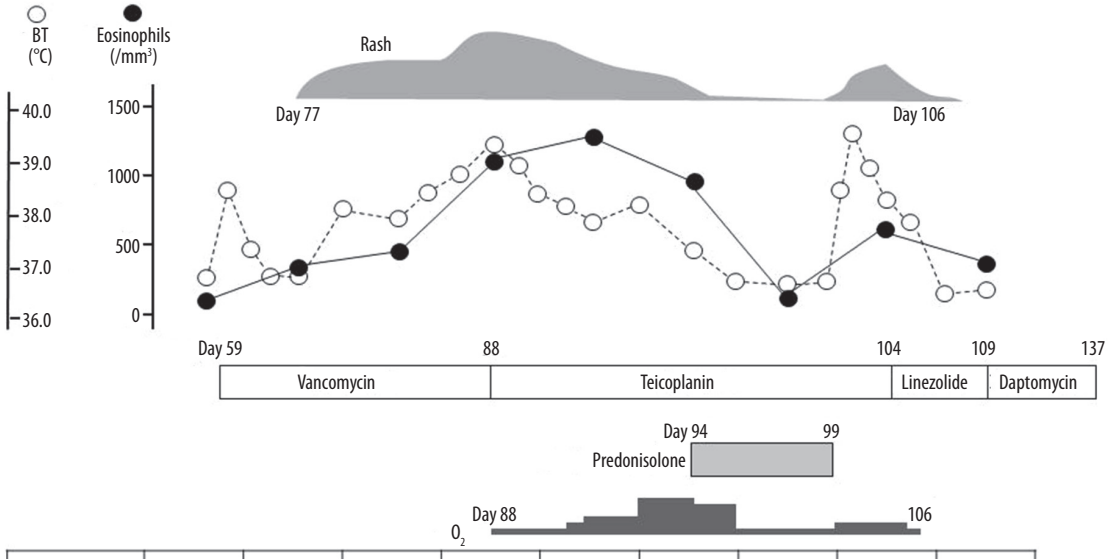
Herein, we describe a case of DRESS syndrome caused by cross-reactivity between vancomycin and subsequent teicoplanin administration. In the diagnosis of adverse drug reactions that developed in our patient, we applied 2 scoring systems: the Naranjo Probability Scale (NPS) [5] and the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system [6,7].

Case Report

A 79-year-old male was admitted to our hospital for the treatment of injuries incurred in a traffic accident. He had no significant history of tuberculosis, HIV infection, diabetes mellitus, hypertension, hyperlipidemia, hepatitis, or disease in any major organ. He had not been taking any medication and had not experienced allergies to drugs or food previously.

Osteosynthesis for femur fracture and debridement for thigh-skin necrosis were undertaken on day 13 and day 21 of hospital admission (i.e., hospital day (HD)13 and HD21), respectively). Then, MRSA was detected from a wound in a skin defect on HD52.

Figure 1 shows his clinical manifestations, laboratory data, and medication history. On HD54, serum level of C-reactive protein was 14.63 mg/dL. On HD59, vancomycin treatment (1.0 g every 12 h, i.v.) was initiated. On HD60, MRSA was cultured from blood. He developed upper-limb erythema and persistent fever (≥38°C) on HD77 (day 18 of vancomycin therapy) and on HD79 (day 20 of vancomycin therapy), respectively. Renal and liver function remained within normal limits. However,



Hospital day	54	77	81	88	92	94	96	104	109
WBC (/mm³)	9920	7210	5480	11010	6420	6930	5830	5980	4570
EOS (/mm³)	99	360	438	1101	1155	831	116	538	365
CRP (mg/dL)	14.63	4.80	4.94	7.62	5.46	6.66	2.13	8.58	1.89

Figure 1. Clinical manifestations, laboratory data, and medication history. WBC – white blood cell; EOS – eosinophils; BT – body temperature; CRP – C-reactive protein.

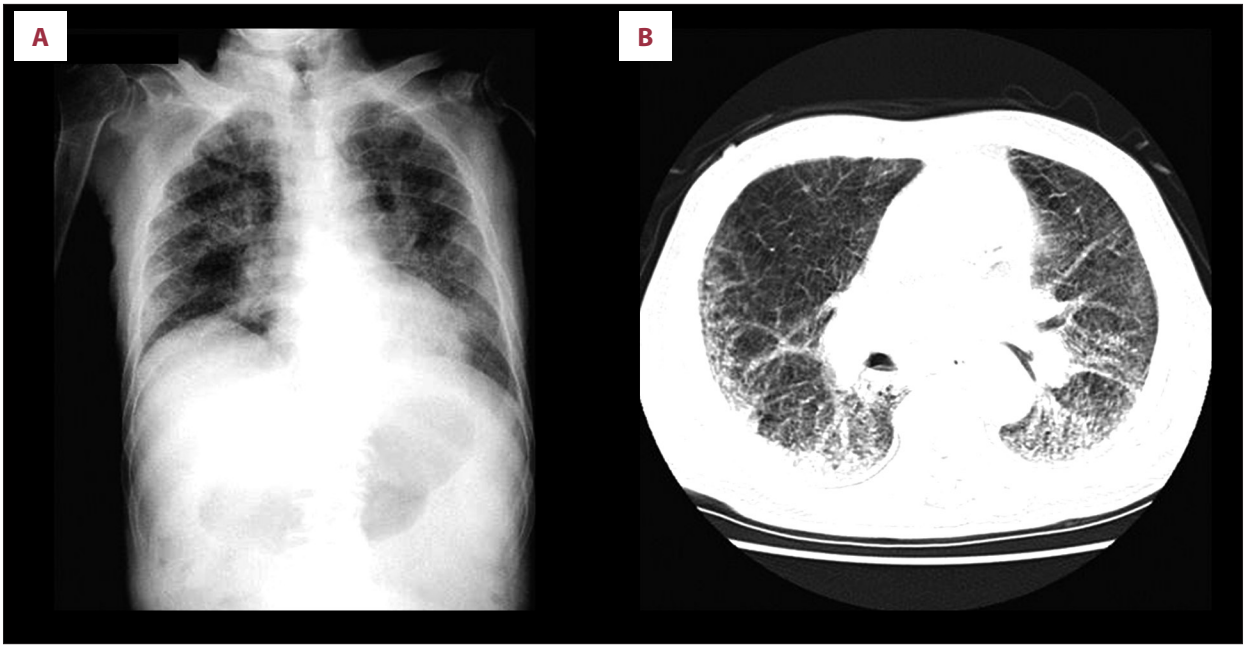


Figure 2. Radiography of the chest showing diffuse ground glass shadow (**A**) and computed tomography scan of the lungs showing diffuse pneumonic infiltration (**B**).

Table 1. Classification of adverse reactions according to the Naranjo Probability Scale. Bold cells are positive finding in our case. Total scores in our case for vancomycin and teicoplanin were 5 and 7, respectively.

Number	The Naranjo adverse drug reaction probability scale	Vancomycin			Teicoplanin		
		Yes	No	Do not know	Yes	No	Do not know
1	Are there previous conclusive reports of this reaction?	**+1**	0	0	**+1**	0	0
2	Did the adverse event appear after the drug was given?	**+2**	–1	0	**+2**	–1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	**0**	**+1**	0	0
4	Did the adverse reaction reappear upon re-administering the drug?	+2	–1	**0**	+2	–1	**0**
5	Were there other possible causes for the reaction?	–1	**+2**	0	–1	**+2**	0
6	Did the adverse reaction reappear upon administration of placebo?	–1	+1	**0**	–1	+1	**0**
7	Was the drug detected in the blood or other fluids in toxic concentrations?	+1	**0**	0	+1	**0**	0
8	Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1	**0**	0	+1	**0**	0
9	Did the patient have a similar reaction to the drug or a related agent in the past?	+1	0	**0**	**+1**	0	0
10	Was the adverse event confirmed by any other objective evidence?	+1	**0**	0	+1	**0**	0
	Total		**5**			**7**	

Final scores 1–4 = Possible, 5–8 = Probable, and >9 = Definite case.

Table 2. RegiSCAR scoring system for classification of DRESS syndrome. Bold cells are positive findings in our case. Total scores in our case for vancomycin and teicoplanin were 4 and 4, respectively.

Score	Vancomycin				Teicoplanin			
	–1	0	1	2	–1	0	1	2
Fever ≥38.5°C	No/U	**Yes**	–	–	No/U	**Yes**	–	–
Enlarged lymph nodes	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Eosinophilia		No/U				No/U		
Eosinophils	–	–	**0.7–1.49 ×10⁹ L⁻¹**	>1.5 ×10⁹ L⁻¹	–	–	**0.7–1.49 ×10⁹ L⁻¹**	>1.5 ×10⁹ L⁻¹
Eosinophils, if leukocytes <4.0×10⁹ L⁻¹	–	–	10–19.9%	≥20%	–	–	10–19.9%	**≥20%**
Atypical lymphocytes	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Skin involvement								
Skin rash extent (% body surface area)		No/U	**>50%**	–	–	No/U	**>50%**	–
Skin rash suggesting DRESS	No	U	**Yes**	–	No	U	**Yes**	–
Biopsy suggesting DRESS	No	**Yes/U**	–	–	No	**Yes/U**	–	–
Organ involvement*								
Liver	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Kidney	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Muscle/heart	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Pancreas	–	**No/U**	Yes	–	–	**No/U**	Yes	–
Other organ	–	No/U	**Yes**	–	–	No/U	**Yes**	–
Resolution ≥15 days	No/U	**Yes**	–	–	No/U	**Yes**	–	–
Evaluation of other potential causes								
Antinuclear antibody								
Blood culture								
Serology for HAV/HBV/HCV	–	–	–	–	–	–	–	–
Chlamydia/mycoplasma			Yes				Yes	
If none positive and ≥3 of above negative								
Total Score		**4**				**4**		

U – unknown/unclassifiable; HAV – hepatitis A virus; HBV – hepatitis B virus; HCV – hepatitis C virus. *After exclusion of other explanations: 1 – one organ; 2 – two or more organs. Final scores <2 = No, 2–3 = Possible, 4–5 = Probable, and >5 = Definite case.

eosinophilia (grade 1:>700/mm^3) developed on day 29 of vancomycin therapy. On HD88, the patient required supplemental oxygen and developed an extensive skin rash with eyelid edema. According to the NPS, we categorized these adverse reactions related to vancomycin as "probable," with a score of 5.

Vancomycin-induced hypersensitivity syndrome was suspected, so vancomycin therapy was discontinued and teicoplanin treatment (400 mg every 12 h, i.v.) was initiated on HD88. On HD94, radiography of the chest showed a diffuse "ground glass" shadow (Figure 2A). Computed tomography of the lungs revealed diffuse pneumonic infiltrates (Figure 2B). Oxygen and prednisolone (50 mg/day, p.o.) for hypersensitivity syndrome with lung dysfunction (interstitial pneumonitis) were administrated on HD88–106 and on HD94–99, respectively. As a result, hypersensitivity syndrome with interstitial pneumonitis was improved temporarily. However, the patient again developed fever (≥38°C) and upper-limb erythema on day 12 and day 15 of

Table 3. Clinical characteristics of teicoplanin-induced DRESS syndrome or DIHS by cross-reactivity between vancomycin and teicoplanin described in the literature.

Author	Age/Sex	Prior vancomycin (days)	Onset after teicoplanin therapy (days)	Clinical manifestation	Hematologic abnormalities	Internal organ involvement
David Lye et al. [8]*	26/M	17	5	Fever, pruritic erythematous, maculopapular rash, rigors, sweats, lethargy, chills, headache, abdominal pain, myalgia	Leucopenia, neutropenia, eosinophilia	NA
	49/F	15	11			
	26/M	8	10			
	63/M	5	10			
	54/F	4	11			
	24/F	9	11			
	58/F	10	11			
	79/F	6	6			
Hsiao et al. [9]	57/F[2]	24	11		Leucopenia, neutropenia	
Hsiao et al. [10]	47/F[3]	17	11	Fever, bilateral lymphadenopathy, wheezing, myalgia	Leucopenia, neutropenia, thrombocytopenia	Liver (hepatitis)
Hsiao et al. [11]	53/M	24	10		Leucopenia, neutropenia, thrombocytopenia	NA
	42/M	10	11	Fever, rash	Leucopenia, neutropenia	NA
	68/M	16	8		Leucopenia, neutropenia	NA
	38/M	7	10	Rash	Eosinophilia	NA
Kwon et al. [12]	50/M	18	3	Rash, cough, dyspnea, wheezing, abdominal pain, nausea, vomiting	Eosinophilia	Lung (pneumonitis), kidney (nephritis)
Tamagawa et al. [13]**	52/F	–	14	Fever, skin eruption, lymphadenopathy, facial edema	Eosinophilia, atypical lymphocyte	Liver (hepatic dysfunction), kidney (renal dysfunction)
Our case	79/M	28	16	Fever, rash, eyelid edema	Eosinophilia	Lung (pneumonitis)

* The detailed data on hematologic abnormalities and clinical manifestation in an individual case were not reported. ** This case was changed from teicoplanin to vancomycin. NA – not available

teicoplanin therapy, respectively. On HD92 (day 4 of teicoplanin therapy) and on HD104 (day 16 of teicoplanin therapy), the eosinophil count increased to 1,155/mm^3 and 538/mm^3, respectively. According to the NPS, we categorized these adverse reactions related to teicoplanin as "probable," with a score of 7. Teicoplanin-induced hypersensitivity syndrome was suspected, so teicoplanin therapy was discontinued and linezolid treatment (600 mg every 12 h, i.v.) was initiated on HD104. After withdrawal of teicoplanin therapy, fever and rash disappeared on HD106.

After reviewing the time span between medication administration and symptom onset, we strongly suspected cross-reactivity between these 2 glycopeptide antibiotics, although we could not completely exclude the possibility of reappearance of DRESS with vancomycin use. When using the RegiSCAR scoring, we categorized DRESS syndrome related to vancomycin and teicoplanin as "probable," with a score of 4. Tables 1 and 2 show the detailed application of the NPS and RegiSCAR scoring systems for our patient, respectively.

Discussion

DRESS syndrome is an acute drug-induced hypersensitivity reaction. Estimated incidence of DRESS syndrome ranges from 1 in 1000 to 1 in 10 000 drug exposures [3]. Recognition of DRESS syndrome is important because mortality can occur in ≤10% of patients. Teicoplanin-associated DRESS syndrome or drug-induced hypersensitivity syndrome (DIHS) has rarely been reported in the literature [8–13]. Table 3 shows the clinical characteristics of our patient and other reported cases of teicoplanin-induced DRESS/DIHS by cross-reaction between vancomycin and teicoplanin. In our patient, rash, eosinophilia, and lung dysfunction (interstitial pneumonitis) appeared after vancomycin administration. These symptoms were improved temporarily by withdrawal of vancomycin and administration of corticosteroid, but exacerbated by teicoplanin administration. The symptoms disappeared after discontinuation of teicoplanin. Based on comprehensive assessment of the overall clinical course, we judged that DRESS syndrome with rash, eosinophilia, and interstitial pneumonitis was induced by cross-reactivity between vancomycin and subsequent teicoplanin administration. To define DRESS syndrome more accurately, the RegiSCAR scoring system has been recently developed [6,7]. By using the RegiSCAR scoring system, we categorized DRESS syndrome related to vancomycin and teicoplanin in our patient as probable (score=4). We report, for the first time, a case of DRESS syndrome defined using the RegiSCAR scoring system caused by cross-reactivity between vancomycin and subsequent teicoplanin administration.

Pulmonary involvement was reported in 2 of the 8 patients listed in Table 3. This symptom is of particular interest because it was reported only in 5% of 172 cases of DRESS syndrome [3]. In addition, neutropenia was reported in 4 of the 11 patients listed in Table 3. Based on a retrospective review by Hung and colleagues, 12 of 109 patients with vancomycin-induced fever and/or rash were reported to subsequently develop teicoplanin-induced fever or rash after switching to teicoplanin. However, 4 of the 8 patients with vancomycin-induced neutropenia subsequently developed neutropenia after switching to teicoplanin [14]. Vancomycin-induced neutropenia should therefore be considered as a contraindication for switching from vancomycin to teicoplanin.

The pathogenesis of DRESS syndrome remains obscure, with a number of mechanisms implicated in its development [3]. First, DRESS is associated with the reactivation of HHV-6 and other herpes viruses. The serology of these viruses should be determined in DRESS patients (although virus reactivation was not found in our case). Second, the formation of reactive metabolites is hypothesized to play a role in the pathogenesis of DRESS syndrome. Because neither vancomycin nor teicoplanin is metabolized in the liver, reactive metabolites could not have contributed to the pathogenesis of DRESS in our case. New options for the treatment of severe DRESS have to be considered for sequential pathogenetic mechanisms. N-acetylcysteine potentially neutralizes drug-derived reactive metabolites responsible for protein adduct formation and specific T cell stimulation, and replenishes the glutathione stores to counterbalance oxidative stress. Prednisone may inhibit lymphoproliferation, while valganciclovir can prevent complications related to HHV-6 reactivation. Therefore, combination therapy using N-acetylcysteine, prednisone, and valganciclovir as a treatment option for DRESS has been proposed [15]. Finally, it seems clear that genetic background plays a role in susceptibility to rare diseases or drug reactions. More than 50% of HLA-B5701-positive individuals develop hypersensitivity to abacavir. Because the HLA systems are a component of the acquired immune response, HLA testing should be performed in every case of DRESS to collect data indicative of possible associations.

Conclusions

Clinicians should be aware that DRESS syndrome can be induced by cross-reactivity between vancomycin and teicoplanin. The management of DRESS syndrome is immediate withdrawal of the suspected offending medication and administration of a corticosteroid. Moling et al. recently suggested adding N-acetylcysteine and valganciclovir for a better management of DRESS syndrome and its complications (e.g., CMV infection) to [15].

Conflict of interest

None declared.

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