Vancomycin-induced drug reactions with eosinophilia and systemic symptoms syndrome in a patient with positive family history

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Keywords: anticonvulsant, drug reaction with eosinophilia systemic symptoms, hypersensitivity syndrome, vancomycin

To the Editor:

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a serious but uncommon condition, with an estimated occurrence rate ranging between one in 1,000 to one in 10,000 drug exposures. DRESS has a heterogeneous presentation that manifests two to eight weeks after drug administration [1]. The variable presentation and delayed onset create difficulty in diagnosis and data for DRESS syndrome is fairly limited [2]. Many different drugs have been reported to cause DRESS syndrome, though it is commonly associated with antiepileptic agents, allopurinol, and sulfonamides [3]. Improved patient risk stratification in the development of this condition could advance patient safety.

Our patient is a 50-year-old woman who presented to an outside hospital with a one-day history of fever, widespread rash, and acute kidney injury. Four weeks prior to the onset of symptoms, she had started vancomycin and ertapenem for bilateral septic prosthetic knee joint infection. Her family history was notable for vancomycin induced DRESS syndrome in her adult daughter. The patient was diagnosed with DRESS syndrome and was treated with a prednisone taper starting at 50mg/day, tapering by 10mg every three days, for a planned 15-day course. Vancomycin and ertapenem were discontinued and she was started on doxycycline. Three days after discharge, she woke up with shortness of breath, tongue swelling, fever, and a widespread rash. She presented to our emergency department where she was febrile to 39.2°C and hypotensive to 87/56 mmHg. She had a pruritic diffuse morbilliform eruption on the trunk (**Figure 1A**) and proximal extremities (**Figure 1B**), as well as edema of the face, lips, and eyelids (**Figure 2**). The remainder of her physical examination was unremarkable. Laboratory evaluation revealed an elevated white blood cell count of 14,890 (normal range 4,800-10,080) with eosinophilia at 22.6%, elevated creatinine to 1.4mg/dL (baseline 0.6mg/dL, maximum 2.5 mg/dL at the outside hospital), and a low EGFR at 44mL/min/1.73m^2 (down from baseline of >59mL/min/1.73m^2). Liver function tests were normal and the patient tested negative for COVID-19.

During first night of her admission, the patient's facial and neck edema worsened and she complained of severe body stiffness and pruritis unrelieved by diphenhydramine. She was given intramuscular epinephrine and intravenous solumedrol. There was no airway compromise and her edema had improved some by the next morning. The morbilliform rash continued to progress to involve her hands, feet, and scalp. Serial complete blood counts during the first 24 hours showed a downward trend of eosinophils from 22.6% to 15.6%

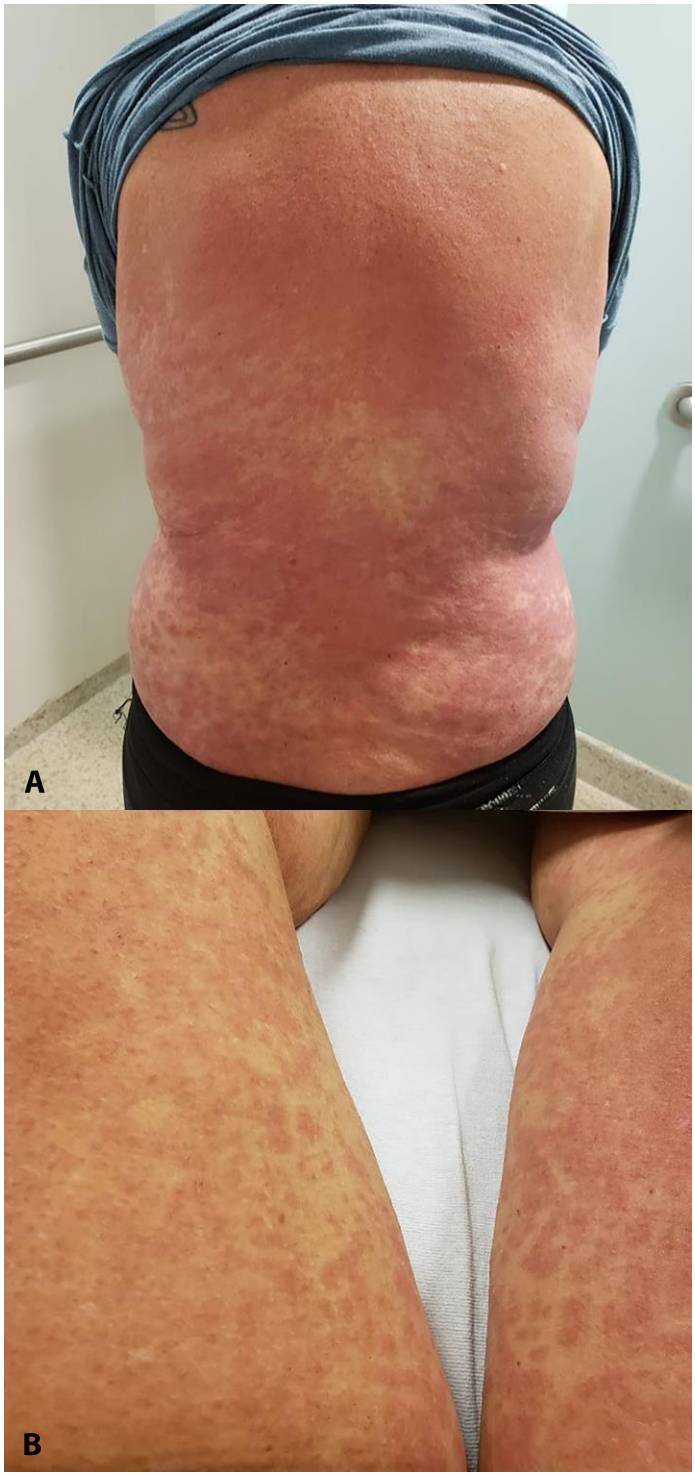

Figure 1. *Morbilliform rash involving **A)** the patient's back and **B)** medial thighs.*

to 6.0% to 5.3%. On the second day of admission, she required additional diphenhydramine and intravenous solumedrol for discomfort and by the third day of admission her facial edema and flushing had improved. She was discharged on a prednisone taper. By the time of her outpatient follow up (17 days later), her cutaneous symptoms had resolved, and her laboratory abnormalities had normalized.

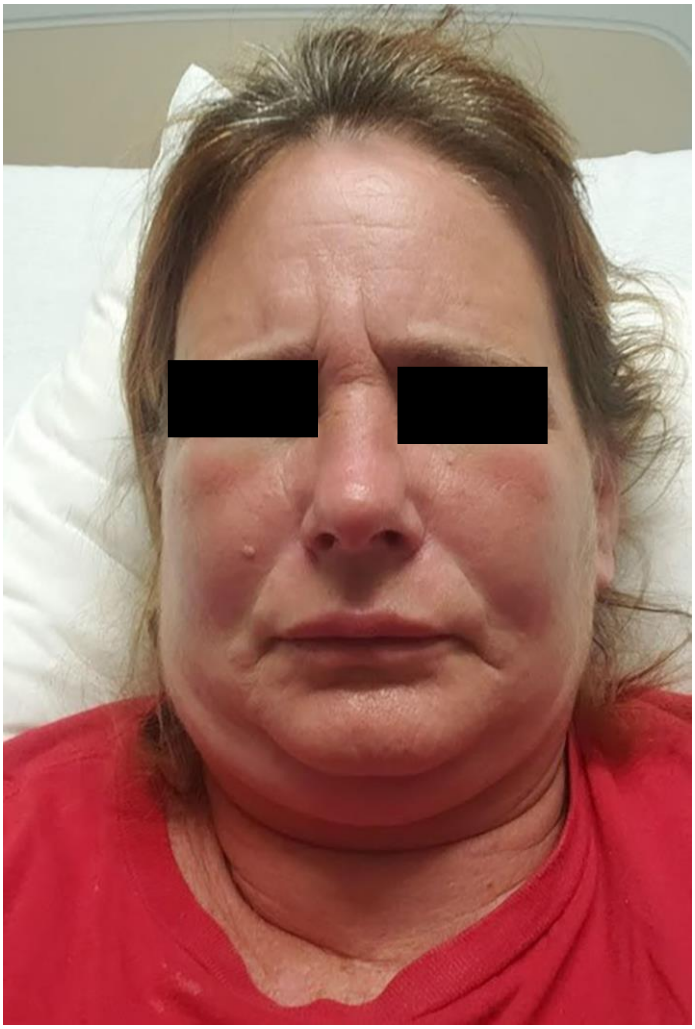

Figure 2. *Erythema and edema of the patient's lips, eyelids, and face.*

Accurately diagnosing DRESS syndrome is critical given the potential morbidity and mortality [4]. Our patient developed DRESS syndrome while on antibiotics for a prosthetic joint infection. Both vancomycin and carbapenem antibiotics have been cited as inducing agents of DRESS syndrome, though in the case of this patient vancomycin is the favored causative agent. Notably, her daughter also developed DRESS syndrome while on vancomycin for septic arthritis of her right hip joint in 2018. Although ertapenem induced DRESS syndrome cannot be ruled out in this patient, based on her family history, the rarity of carbapenem induced DRESS syndrome, and the renal involvement characteristically seen in vancomycin induced DRESS

syndrome, the authors favor vancomycin as the causative agent in this case [5,6]. Although many medications have well-documented associations with DRESS syndrome, the connection between DRESS syndrome and vancomycin, the most commonly used antimicrobial drug in acute care hospital settings, has not been well-reported [7]. Published reviews on vancomycin associated DRESS syndrome cover a small sample size [5,8]. Notably, a higher incidence of renal dysfunction has been observed in cases of vancomycin-associated DRESS syndrome compared to other medications [5]. Similarly, our patient presented with an acute kidney injury.

Having a family history of DRESS syndrome is known to increase the risk of developing DRESS syndrome [9,10]. Associations between human leukocyte antigen (HLA) genotypes and the development of DRESS have been identified, such as an association between allopurinol with *HLA-B*5801* and carbamazepine with *HLA-B*1502* [11,12]. Although data on vancomycin associated DRESS syndrome is still somewhat sparse, *HLA-A*32:01* has been linked to vancomycin induced cases. One retrospective study looking at 23 cases of vancomycin induced DRESS syndrome found that 19 of the 23 studied patient cases carried the *HLA-A*32:01* allele, compared to none of the matched controls [13]. Though more research into genetic susceptibility to DRESS syndrome is needed, this study provides convincing evidence that genetic susceptibility is common in vancomycin induced DRESS syndrome. Additionally, as none of the vancomycin tolerant controls possessed the *HLA-A*32:01* allele, this further supports a high penetrance for genetic susceptibility to vancomycin induced DRESS syndrome. This case report documents a novel example of vancomycin-induced DRESS syndrome in first-degree relatives.

Given the increasing number of medications found to have HLA associated linkages to DRESS syndrome, clinicians should consider preemptive preventative HLA screening in patients with a positive family history of DRESS syndrome. Since vancomycin is often used on an urgent if not emergent basis, waiting on the result of genetic testing before starting vancomycin therapy may not always be a feasible option. Obtaining this information ahead of time in patients with a positive family history of vancomycin DRESS syndrome would improve the risk benefit analysis for both physicians and patients and allow them to make more informed decisions regarding patient safety. When the HLA genotype of a patient with a positive family history of vancomycin induced DRESS syndrome is not known, use of alternative antibiotic therapy may be appropriate, which would have benefited the patient in this case. A more comprehensive understanding of genetic susceptibility to DRESS syndrome could improve patient safety and antibiotic choice, ultimately decreasing the incidence of DRESS syndrome.

Potential conflicts of interest

The authors declare no conflicts of interest.

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