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CASE REPORT

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Association Between HLA-A*32:01 and Vancomycin-Induced DRESS Syndrome in Two Pediatric Cases Using Multiple Antibiotics

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but life-threatening drug hypersensitivity reaction. It has recently been shown that those carrying some human leukocyte antigen (HLA) haplotypes are at high risk for the development of DRESS syndrome with some drugs. There is a strong association with HLA-A*32:01 positivity and vancomycin-induced DRESS syndrome. Here, we present two pediatric cases, one Turkish and the other Syrian, both of whom developed DRESS syndrome during the use of multiple antibiotics included vancomycin, and were shown to have HLA-A*32:01 positivity. To determine the causative drug in patients with DRESS syndrome, patch testing can be administered at least six months after the reaction while the lymphocyte transformation test can only be performed in reference centers. Therefore, delays may occur in identifying the causative drug, especially in patients using multiple drugs. As in our patients, it is important to note that screening for HLA-A*32:01 may enable earlier detection of the responsible drug, which is vancomycin.

Keywords: DRESS syndrome, human leukocyte antigen, pediatric, vancomycin

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but life-threatening drug hypersensitivity reaction. It is characterized by fever, widespread rash, lymphadenopathy, hematological abnormalities, and visceral involvement (1-3). In the presence of symptoms and signs suggestive of DRESS syndrome, the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring (<2: excluded; 2-3: possible; 4-5; probable; >5 definite) can be used for the diagnosis (1,4). The most common drug group causing DRESS syndrome is antibiotics and vancomycin is the most common cause among them (5). The drug provocation test is contraindicated in identifying the responsible drug, and patch testing and/or the lymphocyte transformation test (LTT) is recommended with suspected drug/drugs (4). On the other hand, the patch test's sensitivity is low and the application is risky. In addition, since it can be administered at least six months after the reaction, it causes a delay

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in the determination of the responsible drug. Moreover, LTT is often a guide in the recovery period of DRESS syndrome but can only be performed in reference centers (5). It has recently been shown that those carrying some human leukocyte antigen (HLA) haplotypes are at high risk for the development of DRESS syndrome with some particular drugs (1,4). There is a strong association with HLA-A*32:01 positivity and vancomycin-induced DRESS syndrome (6). Here, two pediatric cases, Turkish and Syrian, who developed DRESS syndrome during the use of multiple antibiotics, were shown to have HLA-A*32:01 positivity, and where the responsible drug was thought to be vancomycin are presented.

Case-1

A 16-year-old Turkish girl who was followed up with the diagnosis of ulcerative colitis and underwent total colectomy was consulted for complaints of maculopapular rash, facial edema, and fever (Figure 1). It was learned from the patient's history that she had long-term multiple antibiotic use for the pelvic fluid that developed in the postoperative period at an external medical center. She had received the treatments of vancomycin (22 days), meropenem (15 days), amikacin (19 days), fluconazole (15 days), metronidazole (22 days), and colistin (10 days) in the last eight weeks. The patient had been discharged after the completion of these treatments, and her symptoms had started on the third day after discharge. In addition, she had been given pantoprazole for the last six months. The patient was hospitalized with the diagnosis of possible DRESS syndrome and 60 mg/day methylprednisolone treatment was started at the same day (Table I). Pantoprazole was replaced with esomeprazole treatment. She was diagnosed with definite DRESS syndrome on the fifth day of hospitalization (Table I). Methylprednisolone treatment was increased to 120 mg/day. On the 10th day of the treatment, the rash almost completely faded. The eosinophilia and liver function tests improved. The rash completely disappeared within three weeks and systemic steroid treatment was tapered off within eight weeks. The patient's haplotype analysis showed the HLA-A*32:01 allele and it was thought that vancomycin could be the responsible drug. Due to the fistula tract infection after discharge, she was treated with meropenem in an external center without any problems. A patch test with vancomycin, amikacin, fluconazole, metronidazole, colistin, and pantoprazole was planned for the patient; however, it could not be done because her family did not accept it.

Case-2

A two-year-old Syrian girl who was operated due to a perforating eye injury was consulted for fever, maculopapular rash, and facial edema on the 21st day of vancomycin and ceftazidime treatments in the postoperative period (Figure 2). It was learned that the patient had also been given amoxicillin-clavulanate and metronidazole treat-

Table I: Case-1 initial and following RegiSCAR[a] criteria

	Initial	Following
Body temperature (^{0}C)	39	38.5
Skin rash extent (BSA)[b]	>50%	>50%
Desquamation	No	Yes
Facial edema	Yes	Yes
Lymphadenopathy	No	No
Eosinophil count (x10^9/L)	1100	4300
Atypical lymphocytes	No	No
ALT (U/L)	16	80
AST (U/L)	21	70
Rash resolution time (days)	-	21
Excluding other causes	No	Yes
RegiSCAR score	2	6

aRegiSCAR: European Registry of Severe Cutaneous Adverse Reactions, **bBSA:** Body surface area

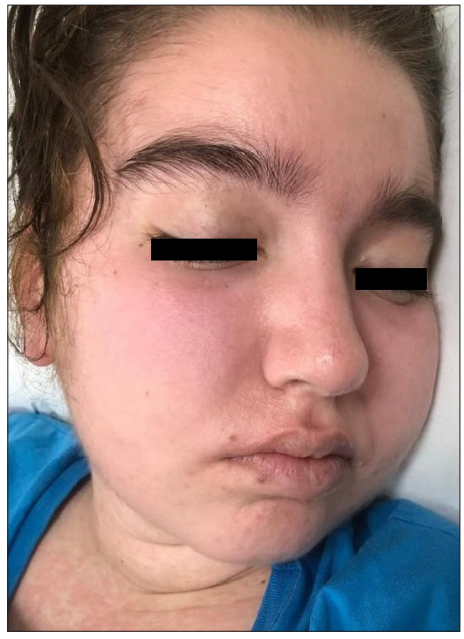

Figure 1: Midfacial edema and erythematous macules and papules on case-one's neck.

ments for five days at an external center in the last eight weeks. With the diagnosis of possible DRESS syndrome, 2 mg/kg/day methylprednisolone treatment was started (Table II). On the fourth day, she was diagnosed with definite DRESS syndrome (Table II). On the fifth day of the treatment, the rash and eosinophilia improved. The rash completely disappeared within two weeks and systemic steroid treatment was tapered off within eight weeks. The patient's haplotype analysis showed the HLA-A*32:01 and HLA-A*03:01 alleles, and it was thought that vancomycin could be the responsible drug. The patient was scheduled for patch testing with vancomycin, ceftazidime, amoxicillin-clavulanate, and metronidazole; however, it could not be done due to the return of the patient to Syria.

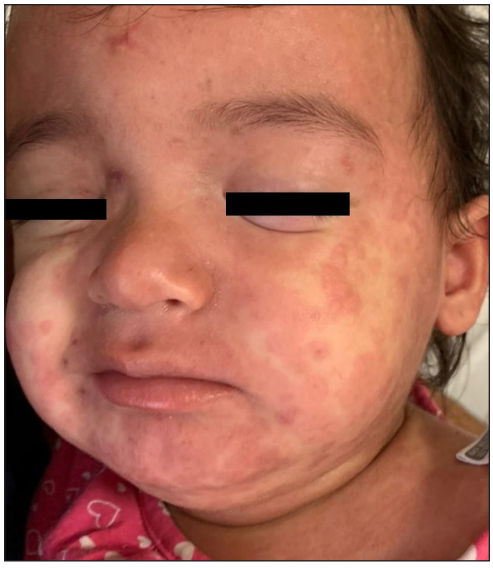

Figure 2: Midfacial edema and erythematous macules and papules on case-two's face and neck.

Table II: Case-2 initial and following RegiSCAR[a] criteria

	Initial	Following
Body temperature (^{0}C)	38.5	38.5
Skin rash extent (BSA)[b]	>50%	>50%
Desquamation	No	Yes
Facial edema	Yes	Yes
Lymphadenopathy	No	Yes
Eosinophil count (x10^9/L)	860	2130
Atypical lymphocytes	No	No
ALT (U/L)	56	47
AST (U/L)	31	55
Rash resolution time (days)	-	15
Excluding other causes	No	Yes
RegiSCAR score	2	6

aRegiSCAR: European Registry of Severe Cutaneous Adverse Reactions, **bBSA:** Body surface area

DISCUSSION

In the study conducted for the first time by Konvinse et al., the HLA-A*32:01 allele was shown in 82.6% of 23 European patients diagnosed with vancomycin-induced DRESS syndrome. In this study, HLA-A*32:01 positivity was not demonstrated in any of the 46 patients who were given vancomycin treatment and did not develop DRESS syndrome (6). In another study, which included 14 patients who developed vancomycin-induced DRESS syndrome, HLA-A*32:01 positivity was shown in five patients (7). When this group was compared with the group that received vancomycin treatment and did not develop DRESS syndrome, HLA-A*32:01 positivity was again found to be significantly higher (6,7). Therefore, we think that we detected the responsible drug early by showing the HLA-A*32:01 allele in our cases, even though they were non-European cases.

It is known that DRESS syndrome is a T cell-mediated hypersensitivity reaction. Drug antigens cause reaction by stimulating T cells directly and/or through HLA molecules through various mechanisms such as the hapten/prohapten model, pharmacological interaction and altered peptide repertoire model (1). In the study of Konvinse et al., it was predicted that vancomycin atoms contact D-Ala D-Ala in the central region of the antigen-binding cleft of HLA-A*32:01 (6). Ogese et al. have demonstrated by in vitro methods that naive T cells from healthy donors expressing HLA-A*32:01 are stimulated by vancomycin towards CD4+ and CD8+ T cells (8).

In the study of Konvinse et al., the risk of developing DRESS syndrome was found to be approximately 20% with four weeks of vancomycin treatment in HLA-A*32:01 positive patients. It has been estimated that the prevalence of HLA-A*32:01 in the European ancestry is approximately 6.8%; therefore 75 patients should be screened in order to prevent vancomycin-induced DRESS syndrome that may develop in a patient with HLA-A*32:01 analysis (6). Thus, HLA-A*32:01 screening before treatment in patients who will be given vancomycin will benefit from rational drug use.

However, in patients who develop DRESS syndrome with vancomycin, there are different HLA alleles other than HLA-A*32:01. In an adult case series reported from Australia, it was shown that three patients had the HLA-A*24,32; HLA-A*03,68 and HLA-A*24,32 alleles (9). The HLA-A*03,02 allele was shown in an adolescent patient with vancomycin-induced DRESS syndrome reported in our country (10). In our second case, the HLA-A*03:01 allele was also shown in addition to HLA-A*32:01. However, it is not yet known whether alleles other than HLA-A*32:01 are risk factors for the vancomycin-induced DRESS syndrome.

Although patch tests are helpful in determining the drugs that cause the DRESS syndrome, their sensitivity is low and application is risky. In addition, since they can be administered at least six months after the reaction, this causes a delay in the determination of the triggering drug. On the other hand, LTT is often a guide in the recovery period of DRESS syndrome but its application is difficult and can only be performed in reference centers (5). As in our patients, it was thought that screening for HLA-A*32:01 will guide the process until patch tests are performed in the determination of the responsible drug in patients using multiple antibiotics together with vancomycin. We recommended that vancomycin not be used in both patients. However, we planned to do patch tests with five antibiotics, including vancomycin, and pantoprazole in the first patient, and with four antibiotics, including vancomycin, in the other.

The use of the suspected drug in the following period in patients who develop DRESS syndrome is an absolute contraindication. For this reason, alternative treatments are sought in these patients, which are more toxic, more expensive, ineffective and lead to antibiotic resistance. Therefore, the responsible drug should be well defined in DRESS syndrome. HLA-A*32:01 screening may enable earlier detection of the responsible drug, especially in European ancestry DRESS syndrome patients who used multiple drugs together with vancomycin.

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Authorship Contributions

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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