Oxcarbazepine에 의한 DRESS증후군 환자에서 확인한 HLA DRB1*04:03 1예

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HLA DRB1*04:03 and Drug Reaction with Eosinophilia and Systemic Symptoms Induced by Oxcarbazepine: A Case Report

Drug reaction with eosinophilia and systemic symptoms(DRESS), which occurs 2-8 weeks after taking a medication is a rare and potentially life-threatening drug-induced hypersensitivity reaction, which includes skin eruption, hematologic abnormalities, lymphadenopathy, and internal organ such as liver, lung, kidney involvement. Antiepileptic agents (e.g., carbamazepine, lamotrigine, phenytoin, and phenobarbital) and allopurinol are the most commonly reported causes. However, new antiepileptic agents, such as oxcarbazepine, rarely cause drug reaction with eosinophilia and systemic symptoms. A 11-year-old boy who was administered oxcarbazepine for 34 days developed widespread rashes, facial edema, fever, cough, nasal stuffiness, tonsillitis, and cervical lymphadenopathy. Laboratory test results showed leukocytosis, eosinophilia, thrombocytosis, elevated c-reactive protein, and elevated liver transaminase levels. As we suspected drug reaction with eosinophilia and systemic symptoms, we immediately withdrew oxcarbazepine and commenced corticosteroid therapy. The patient's skin lesions and abnormal laboratory results slowly improved. Before change the antiepileptic agents, we performed human leukocyte antigen (HLA) typing to assess the genetic risk factors of the drug reaction and the result was positive for *HLA DRB1*04:03* known to cause severe acute drug hypersensitivity, such as Stevens-Johnson syndrome by oxcarbazepine in Koreans. We have presented the first report of drug reaction with eosinophilia and systemic symptoms associated with oxcarbazepine in a patient with *HLA DRB1*04:03*. Although DRESS by oxcarbazepine is extremely rare and unpredictable, when suspected clinical symptoms occur, it is necessary to interrupt the causative drug rapidly and confirming the patient's HLA typing may help to select a safer alternative drug.

Key Words: Drug hypersensitivity syndrome, Oxcarbazepine, Drug eruptions, Eosinophilia

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug-induced hypersensitivity reaction that includes skin eruption, hematologic

abnormalities including eosinophilia or atypical lymphocytosis, lymphadenopathy, and the involvement of internal organs, such as the liver, kidney, and lung. It is part of the triad of life-threatening drug hypersensitivity syndromes, along with acute generalized exanthematous pustulosis (AGEP) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)¹⁾. DRESS is diagnosed primarily based on the following European Registry of Severe Cutaneous Adverse Reactions to Drugs (RegiSCAR) criteria: acute onset of rash, fever above 38°C, lymphadenopathy at two sites, the involvement of at least one internal organ, and abnormalities in lymphocyte and eosinophil count²⁾. The incidence of DRESS is unknown. A prospective 7-year study in a general West Indian population estimated an annual incidence of 0.9/100,000 children, but most cases occur without sex predilection in adults³⁾. Antiepileptic agents (e.g., carbamazepine, lamotrigine, phenytoin, and phenobarbital) and allopurinol are the most commonly reported causes. There is evidence for genetic predisposition to DRESS in relation to allopurinol (*HLA-B*58:01*), carbamazepine (*HLA-A*31:01*), or dapsone (*HLA-B*13:01*)^{4,5)}. However, oxcarbazepine-induced DRESS is rare, especially in children.

Here, we report a case of DRESS syndrome, which presented as exfoliative dermatitis after the administration of oxcarbazepine for 34 days in a 11-year-old boy with HLA DRB1*04:03.

Case report

A 11-year-old boy visited our emergency room because of five seizures, with or without fever, within 1 day. Electroencephalography (EEG) and brain magnetic resonance imaging revealed no remarkable abnormal findings. One month later, he

experienced another afebrile seizure. The EEG was repeated and showed focal slowing over the right occipital area. Owing to his repetitive seizures and abnormal EEG, we diagnosed epilepsy and prescribed oxcarbazepine (11 mg/kg/day per oral, divided twice).

On the 34th day after oxcarbazepine was commenced, the patient returned with widespread skin rashes with itching sensation, facial edema, fever, cough, and nasal stuffiness. His body temperature was 38°C and other vital signs were normal. Erythematous maculopapular eruptions appeared on his face first and spread to his neck, trunk, and extremities simultaneously and appeared scattered and coalescent. Red to brown scaling with erythema was present on whole body surface (Fig. 1). Upon physical examination, the patient had tonsillar enlargement, enlarged multiple cervical lymph nodes of approximately 2×2 cm without tenderness, and erythematous maculopapular rashes covering the whole body. Because we suspected a drug hypersensitivity reaction, we ceased all medications, including oxcarbazepine, chlorpheniramine and acetylcysteine. He had never suffered from drug allergy before and he took the two drugs latter only one day. However, the skin eruption, itching sensation, and facial edema intensified and fever persisted. Based on the clinical findings, we suspected DRESS and admitted the patient to hospital.

On the first hospital day, chest x-ray and laboratory studies were performed (Table 1). The initial laboratory results revealed leukocytosis and eosinophilia with the following parameters: white blood cells (WBC), 26,190/ μ L; hemoglobin, 12.8 g/dL; hematocrit, 38.0%; platelets, 406,000/ μ L; and eosinophil, 9.8% (2570/ μ L). Serum immunoglobulin E, aspartate/alanine transaminase (AST/ALT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were within normal ranges. DRESS is

Fig. 1. Diffuse maculopapular confluent rash over trunk (A) and the lower extremities (B).

Table 1. Progression of Clinical Manifestations and Laboratory Tests

Days after onset	Day 1	Day 3	Day 6	Day 10	Day 30
Clinical findings					
Fever	Yes	No	No	No	No
Rash	Yes	Yes, exfoliative	Yes, exfoliative	No	No
Facial edema	Yes	Yes	No	No	No
Cervical lymph nodes	2x2 cm, hard	2x2 cm, hard	1x1 cm, soft	Normal	Normal
Treatment	IV dexamethasone+Topical corticosteroid+antihistamine		Oral prednisolone+Topical corticosteroid+antihistamine		Topical corticosteroid only
Laboratory findings					
WBC(/ μ L)	26,190	25,500	36,060	19,960	8,590
Eosinophil (%/ μ L)	9.8 (2,570)	5.9 (1,504)	1.7 (613)	33 (6,590)	4.3 (370)
AST/ALT (IU/L)	23/36	105/155	23/139	32/67	28/44
CRP (mg/dL)	0.83	3.17	0.12	0.61	0.01
HLA typing	A*26:02, A*32:01, B*15:07(B62), B*40:06(B61), C*03:03(Cw9), C*08:01, DRB1*04:03, DRB1*09:01				

IV, intravenous; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; HLA, human leucocyte antigen.

diagnosed primarily based on the following European Registry of Severe Cutaneous Adverse Reactions to Drugs (RegiSCAR) criteria: acute rash, fever above 38°C, lymphadenopathy at two sites, involvement of at least one internal organ, and abnormalities in the lymphocyte and eosinophil counts. We administered intravenous dexamethasone 5 mg twice per day and topical desonide for 2 days. We also use antihistamine to relieve his itching sensation. Although his fever subsided, the skin rash, facial edema, and laboratory results deteriorated. On the third hospital day, AST, ALT, and CRP were elevated and eosinophilia persisted (WBC, 25,500/ μ L; eosinophil, 5.9%; AST/ALT, 105/155 IU/L; CRP, 3.17 mg/dL). We changed the treatment to oral prednisolone 1 mg/kg/day and topical methylprednisolone for 3 days. The skin lesions and cervical lymphadenopathy improved. Except for eosinophilia, the abnormal laboratory findings also improved. We stopped oral prednisolone, not tapering, and maintained topical methylprednisolone. We conducted several viral studies to find out whether virus infection triggered DRESS. The respiratory virus polymerase chain reaction (PCR), the Epstein-Barr virus (EBV) virus capsid antibody (VCA) IgM, hepatitis viral study, and the human herpes virus 6 (HHV6) PCR were negative. To assess the genetic risk factors of the drug reaction, the human leukocyte antigen (HLA)-ABC, DR, DQ DNA high resolution typing was performed and the result was positive for DRB1*04:03. The patient was discharged without any oral medication.

On the 30th day after the cessation of oxcarbazepine, the patient visited the emergency room after a seizure. His skin had improved and the laboratory findings were also within normal ranges. We prescribed levetiracetam to treat the seizures. He has not experienced any seizures or adverse reactions for 6 months.

Discussion

DRESS is a hypersensitivity reaction to a drug. It is potentially fatal because it leads to life-threatening organ failures. Liver failure is the main cause of death and may vary from hepatocellular and cholestatic damage to fulminant hepatic failure⁶.

The incidence of DRESS is unknown. A prospective seven-year study in a West Indian general population estimated an annual incidence of 0.9/100,000 children⁷. Oxcarbazepine-induced DRESS is even more rare, only a few cases have been reported in adults and children⁸⁻¹¹.

The pathogenesis of DRESS is multifactorial and uncertain. The reactivation of viruses, genetic predisposition, and defects in drug metabolism have been proposed as possible factors in the pathogenesis of DRESS⁶. DRESS is frequently associated with the reactivation of latent HHV infections¹². In a study of 40 patients with DRESS, evidence of Epstein-Barr virus (EBV), HHV-6, or HHV-7 reactivation was found in 29 patients¹³. The initial event in DRESS is a viral reactivation that induces the expansion of a T cell population that cross-reacts with the drug¹³. Several studies have revealed an association between HLA type and susceptibility to DRESS: *HLA-B*58:01* is strongly associated with allopurinol-induced severe cutaneous drug reactions, including DRESS⁴; a strong association between *HLA-A*31:01* and carbamazepine-induced DRESS was found in European and Han Chinese patients⁵; *HLA-B*38:02* was found to be a potential risk factor for oxcarbazepine-induced maculopapular eruption¹⁴; the *HLA-B*15:02* allele contributed to the genetic susceptibility of oxcarbazepine-induced maculopapular eruption in the Chinese Han population¹⁵; and a significant association of *HLA-B*40:02* and *HLA-DRB1*04:03* with oxcarbazepine-induced cutaneous adverse drug reactions ranging from maculopapular eruption to SJS/TEN has been

reported in Korean patients, but oxcarbazepine-induced DRESS associated with HLA-DRB1*04:03 has not yet been reported¹⁶⁾. This report is the first to identify an association between HLA-DRB1*04:03 and oxcarbazepine-induced DRESS.

The latent period between drug exposure and the onset of symptoms is considerably longer in DRESS than in most drug eruptions, such as SJS and TEN¹⁷⁾. In most patients, the reaction begins between 2 and 6 weeks after the initiation of the offending medication. Fever, malaise, lymphadenopathy, and skin eruption are the most common initial symptoms. The skin rash begins as an eruption on the trunk that progresses rapidly to a diffuse, confluent, and infiltrated erythema with follicular accentuation.

The diagnosis of DRESS is based on clinical features and laboratory tests. Patients with DRESS without life-threatening organ involvement and those with only modest elevation of liver transaminases can be treated symptomatically. Our patient showed maculopapular eruption, fever, lymphadenopathy, eosinophilia, and involvement of the liver with a slight elevation of AST/ALT.

There is no consensus regarding the medical treatment for DRESS. The discontinuation of the causative drug is the primary treatment. For the symptomatic relief of pruritus and skin inflammation, high- or super-high potency topical corticosteroids are recommended. Systemic corticosteroids are also used and other immunosuppressive agents can be added. Further investigation into the treatment of DRESS syndrome is needed. When doctors assess patients, who experienced DRESS induced by antiepileptic drugs, cross-reactivity with other antiepileptic drugs should be considered. Three different antiepileptic drugs, phenytoin, lamotrigine, and oxcarbazepine, which have an aromatic ring, all share a common risk allele. Carbamazepine-induced maculopapular eruption is strongly associated with HLA-B*1502 in the Han Chinese population. HLA-B*1502 carriers should avoid aromatic antiepileptic drugs¹⁸⁾. Levetiracetam-induced cutaneous adverse drug reactions were not associated with HLA genes in a small sample of Chinese patients with epilepsy and in North-Indian patients^{19,20)}. We prescribed levetiracetam because there were no reports of levetiracetam-induced adverse drug reactions associated with DRB1*04:03.

Because oxcarbazepine-induced DRESS is extremely rare, it is difficult to predict and recognize this condition. Early diagnosis and cessation of the causative drug is the most important treatment of DRESS. Additionally, if the patient's HLA type is known, the selection of a safer medication is easier. Patients who experienced oxcarbazepine-induced DRESS are likely to have

serious life-threatening drug reaction to other antiepileptic drugs, so identification of HLA type before change the antiepileptic drugs is important and may be essential.

요약

DRESS 증후군은 매우 드물지만 생명을 위협할 수 있는 약물 과민 반응으로 약물복용 2-8주 이후 발생하여 피부발진, 혈액학적 이상, 임파선염, 간/폐/신장 등 내부 장기 침범을 보인다. 유발 약물로는 항경련제(carbamazepine, lamotrigine, phenytoin, phenobarbital)와 allopurinol이 흔하며 oxcarbazepine과 같은 새로운 항경련제에서는 DRESS 증후군에 대한 보고가 거의 없다. 뇌전증으로 oxcarbazepine을 34일간 복용 중이던 11세 남아가 발열, 기침, 코막힘 등 가벼운 상기도 감염 증상과 전신 박탈성 피부 발진, 얼굴부종, 경부 임파선염으로 내원하였다. 혈액검사에서 백혈구 증가증, 특히 호산구 증가증이 관찰되었고 CRP와 간효소 수치가 상승하였다. DRESS 증후군을 의심하여 즉시 oxcarbazepine을 중단하고 corticosteroid 치료를 시작하였고, 피부병변과 혈액학적 이상은 서서히 호전되었다. 항경련제 변경 전 약물 과민 반응에 대한 환자의 유전적 소인을 평가하기 위해 HLA typing을 시행하였고 한국인에서 oxcarbazepine에 의한 Stevens-Johnson syndrome과 같은 심각한 급성 약물 과민 반응을 일으킨다고 알려진 *HLA DRB1*04:03*이 확인되었다. *HLA DRB1*04:03*에서 oxcarbazepine에 의한 아급성 약물 과민 반응인 DRESS 증후군은 본 증례가 첫 보고이다. Oxcarbazepine에 의한 DRESS 증후군은 매우 드물어 예측하기 힘들다. 의심되는 임상증상이 발생하였을 때 원인 약물을 신속히 중단할 필요가 있으며 환자의 HLA typing을 확인하는 것은 보다 안전하게 대체 약물을 선택하는데 도움이 될 것으로 생각된다.

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