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A Case of DIHSS/DRESS Syndrome-Related Acute Hepatic Failure

Akut Hepatik Yetmezliğin Eşlik Ettiği DiHSS/ DRESS Sendromu Olgusu

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ABSTRACT

'Drug Induced Hypersensitivity Syndrome' (DiHS) or 'Drug Rash with Eosinophilia and Systemic Symptoms' (DRESS) syndrome is a life threatening, delayed type drug hypersensitivity reaction. This syndrome is characterized by fever, skin rash, lymphadenopathy, hematological abnormalities and visceral involvement and liver is the most frequently involved visceral organ. Liver involvement is mostly presented as acute anicteric hepatitis with elevated liver enzymes. Rarely, it can be presented as cholestasis which indicates a worse prognosis. In this article, a case of valproic acid induced-DRESS syndrome who presented with acute hepatic failure is presented. Diagnosis of DRESS syndrome may delay due to the long interval between drug intake and the onset of symptoms. The variety of symptoms can also be challenging. Early diagnosis is important in terms of reducing morbidity and mortality.

Key Words: Drug Induced Hypersensitivity Syndrome, DRESS, Drug allergy, Hepatic failure

ÖZ

"Drug Induced Hypersensitivity Syndrome" (DIHS) ya da diğer adı ile "Drug Rash with Eosinophilia and Systemic Symptoms" (DRESS) sendromu, yaşamı tehdit edebilen gecikmiş tip ilaç hipersensitivite reaksiyonudur. Ateş, deri döküntüsü, lenfadenopati, hematolojik anormallikler ve çoklu organ tutulumu ile karakterizedir. Karaciğer en sık tutulan organ olup, çoğunlukla karaciğer enzim yüksekliği ve akut anikterik hepatit şeklinde karşımıza çıkmaktadır. Çok daha nadir olarak kolestaz eşlik edebilir ve bu durum kötü prognoza işaret etmektedir. Bu yazıda valproik asit ilişkili hepatik yetmezlik ve ağır kolestazın görüldüğü DRESS sendromlu bir olgu sunulmuştur. İlaç kullanımı ile semptomların başlangıcı arasındaki sürenin uzun olması ve semptomların çeşitliliği nedeniyle DRESS sendromunun tanısında gecikmeler olabilmektedir. Hastalığın erken tanınması, morbidite ve mortaliteyi azaltmak açısından oldukça önem taşımaktadır.

Anahtar Sözcükler: Drug Induced Hypersensitivity Syndrome, DRESS, İlaç alerjisi, Hepatik yetmezlik

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INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS), also known as drug rash with Eosinophilia and Systemic Symptoms (DRESS), is a delayed type of drug-sensitive reaction that may be life-threatening, first identified by Bocquet et al. (1) in 1996. Diagnostic criteria were then determined by the Japanese drug study group and the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) respectively (2,3). Total score according to the RegiSCAR scoring system <2 points: not DRESS, 2-3 points: likely DRESS; 4-5 points: possible DRESS and >5 points as certain DRESS (3).

The incidence of this picture, characterized by fever, skin rash, lymphadenopathy, hematological abnormalities (eosinophilia, atypical lymphocytes), multi-organ involvement is estimated to be between 1/1000 and 1/10.000, although the exact incidence is unknown (4). It is more rare in childhood than in the adult age group. In etiology, aromatic anticonvulsants such as phenitoin, phenobarbital, carbamazepine and lamotrigin, sulfonamides, allopurinol, dapson, gold salts, and minocycline are among the most commonly considered drugs responsible (4,5). Although the pathogenesis is not fully understood, the deficiency of the epoxy hydroxylase enzyme, which eliminates the toxins that are the destruction products of aromatic anticonvulsants, is one of the most commonly considered mechanisms responsible (6). The genetic predisposition to some HLA alleles has been suggested, and studies are ongoing. In addition, the reactivation of especially the human herpes virus (HHV) 6, Ebstein Barr Virus (EBV), cytomegalovirus (CMV), and Herpesviruses like HHV 7 is also thought to play a role in DRESS syndrome (6,7)

The most frequently accompanying organ involvement in DRESS is liver, with most patients experiencing anicteric hepatitis with elevated serum alanine aminotransferase (ALT) enzyme (4). Much more rarely, it can become icteric and accompany cholestasis, and this often indicates a worse prognosis(4). A DRESS syndrome case is presented who with acute hepatic insufficiency and has been successfully treated, a very heavy picture to raise awareness about this severe drug reaction, which is thought to have been less diagnosed because it did not come to mind.

CASE REPORT

An 11-year-old male patient applied to our hospitals emergency clinic with fever lasting for 3 days and with a widespread rash all over the body. In the patient's history, he was diagnosed with epilepsy 36 days ago and started valproic acid therapy, and a week ago he was again medical exam and examined in the centre for fever complaints, levatirecetam was replaced with the valproate acid treatment due to elevated aspartate aminotransferase (AST) and alanine aminotránsferaze (ALT) values.

In the physical examination that took place at our hospital, the overall condition was good, he was conscious, his body temperature was 38.7°C, his breathing rate was 23/min, his heart rate was 108/min and his blood pressure was 100/60 mmHg. In the physical examination, there were maculopapular rashes that were to be visible on both sides of cheeks, widespread throughout the body, some with a tendency to merge, including icteric sclerosis. the liver was about two centimeters below the costa (Figure 1A). Other system inspections are normal.

In laboratory studies; haemoglobin 10.8 g/dL, leukocyte count 11.4x103/µL (peripheral proliferation; 60% partial, 30% lymphocytes, 9% monocytes and 1% eosinophilic), thrombocyt count 143x103/µL, AST 1372 U/L (<51) ALT 782 U/ L (<37), lactate dehydrogenase (LDH) 785 IU/ L(<332), gamma glutamil transferase (GGT) 224 U/ l(<61), total bilirubin 4.46 mg/ dL(<1.2), direct bilirubine 4.3 mg/dl(<0.3), INR 1.28 (0.8-1.2) alkaline phosphatase (ALP) 417 U/l (129-417), fibrinogen 78 mg/dl (180-350), C-reactive protein (CRP) 3 mg/L(<5) were found. The serologies of EBV, CMV, Parvovirus, Rubella, Toxoplasma, anti-HIV, Hepatitis A, B and C were negative. Reproduction was not detected in blood and urine cultures taken under sterile conditions. In the patient's abdomen ultrasound examination, the liver's craniocodular length was estimated to be 139 mm above the upper limit of normal for age, while the dorsal craniocaudal length increased by 141 mm for age. The lumen of the gallbladder was observed in contractual appearance, its thickness increased, and an effusion of 4.5 cm was detected in the pelvis.

The patient was initiated intravenous fluid therapy, sefotaxim, pantoprozole, and continued oral levetiracetam therapy. Due to high liver function tests, intravenous infusion of n-acetylsysteine (NAC) was initiated to benefit from its cytoprotective effect. In patients with hyperbilirubinemia dominated by direct bilirubin and elevated GGT, oral ursodeoxycholic acid (UDKA) was initiated due to cholestasis. Treatment with 2 mg/kg methyl prednisolone was initiated after a skin biopsy with DRESS pre-diagnosis. After three days of systemic steroid therapy, the patient with fever and rashes decreased in AST, ALT, GGT and bilirubin, but received 5 mg of vitamin K for 2 days because of INR: 1. 52. On the 7th day of service recovery, a patient with recurrent fever, developing consciousness fainting and elevated liver enzymes (AST: 866 U/L, ALT: 694 U/l, total bilirubin:16.06 mg/ dL, direct bilirubine: 14.04 mg/dL, INR: 1.8) was monitored in pediatric intensive care unit for acute hepatic insufficiency. In addition to intravenous therapy with 2 mg/kg/day of methyl prednisolone, 2 g/day intravenous immunglobulin (IVIG) (with a duration of 2 days) and once fresh frozen plasma of 15 cc/ kg/dose were given. After two days of intensive care follow-up, the patient's overall condition improved, fever decreased, rashes reduced, and liver enzymes gradually declined, and the INR returned to normal. For cardiovascular involvement troponin T (tropT) was 0.006 ng/mL (<0.014), and creatine kinase (CKMB) was 23 U/l (<247). No pathology was detected

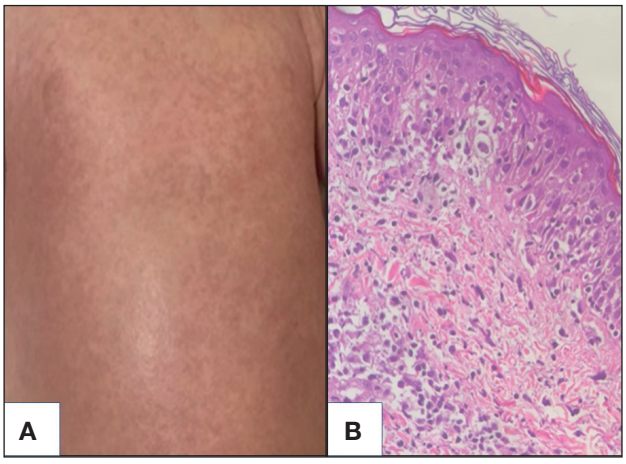

Figure 1: (A) Maculopapular rashes, commonly found in the patient's body, with a tendency to merge. **(B)** The hematoxylene-eosin-painted section of the skin punch biopsy shows focal spongiosis, lymphocyte exocytosis and basal vacuoleal changes in the epidermis.

in echocardiography. The differential diagnosis of alpha-1 antitripsin, alphafetoprotein, hepatic autoimmune antibodies, seruloplasmine was examined and the results showed no pathology. Microscopic examinations of the punch biopsy sample of the hematoxylene-eosin-painted cuts from the inguinal rash region showed focal spongiosis in the epidermis, lymphocyte exocytosis, and basal vacuoleal changes. Perivascular mononuclear inflammation infiltration observed in superficial and medium dermis (Figure 1B). The lymphocytes subgroups were CD45 %95, CD3+CD4+ %36.2, CD3 +CD8+ %48.6, CD3-CD16/56+ %1.4, CD19+ %11.2 and CD4/CD8 ratio 0.7. The number of CD8+ cytotoxic T lymphocytes was also increased. The patient's RegiSCAR score was 4 (possible DRESS) with fever, rash, biopsy DRESS-compatible findings, liver involvement more than 15 days of rash and excluding other findings.

The patient with a decrease in liver enzymes and a return to normal INR was discontinued with NAC infusion after 6 days On the 15th day of hospitalization, the patient, who was generally in good condition, with no fever and acute phase reagents negative, was discontinued from the current antibiotics, with AST: 69 U/L ALT: 116 I/L GGT:264 IU/L INR:0.84 on the 20th day, and with direct bilirubin reduced to 3.7 mg/dL The patient was discharged with a plan to discontinue systemic steroid therapy at 6 weeks by reducing the dosage from 2 mg/kg/day. The patient's skin appearances began to decrease from the 12th day of hospitalization, and was completely recovered in control a month later. It was not done because the patient's provocation test with the drug was contraindicated. Skin patch tests and intradermal tests could not be done because the family didn't approve because of the severity of the clinical picture.

The patient's ursodeoxycholic acid treatment was discontinued in the second month of follow-up, when liver enzymes returned to normal. The patient, who had been monitored with intermittent poliklinical controls for a year, had no recurrence of rash, and liver enzymes were observed within the normal range, with anti-nuclear antibodies (ANA), celiac and autoantibodies of the thyroid negative for autoimmune diseases.

DISCUSSION

DIHSS/DRESS is a very serious and life-threatening late-type systemic drug hypersensitivity reaction. Clinical symptoms usually occur after 2-6 weeks of starting use of the drug, and the rash is usually in the form of maculopapular erythematosus skin rash, and sometimes the lesions can progress to vesicles, ulcers, atypical target lesions, purpura, sterile small pustules, and even exfoliative dermatitis or erythrodermia (3,5). In our patient, the widespread, fusion-prone maculopapular rash appeared one month after starting valproic acid therapy. Diagnostic criteria of the Japan Allergy Association or RegiSCAR are widely used in DIHSS/DRESS diagnosis (3,4). In laboratory evidence, leukocytosis and eosinophilia are often present in patients, while the absence of eosinophilia does not rule out the diagnosis. Literature reports eosinophilia rates ranging from 60-70% in various studies (8). Even some patients, especially in the early stages, may experience leukopenia or lymphopenia (8). One or both CD4+ and CD8+ T cells have increased together, and CD19+ B cells and CD16-56+ NK cells are decreased. CD4+ T cells are high in the early stages, gradually decreasing, returning to normal after about 2 months, and their numbers correlate with the severity of the clinical symptoms (9). Again, the detection of CD4+ and CD8+ T lymphocytes in skin lesions reveals the role of these cells in the pathogenesis of the disease. Our patient was not diagnosed with eosiofilia at the time of diagnosis, but the lymphocytes subgroup analysis showed that CD8+T cells were high and NK cells low.

Fever accompanying skin signs, lymphadenopathy, flu-like symptoms, eosinophilia, and internal organ involvement such as hepatitis, myocarditis, pericardiitis, nephritis and colitis being seen in DIHSS/DRESS and the prognosis is usually determined by internal organ involvement (5,10). The most commonly involvement organ is the liver and is mostly in the form of acute anicteric hepatitis. When the picture becomes icteric and accompanied by cholestasis, this usually indicates a worse prognosis (4). Coagulopathy and sepsis associated with hepatic necrosis, which is primarily responsible for mortality in DIHS/DRESS, with mortality ranging from 5 to 10% (3,5,11). In our patient in addition to steroid therapy, IVIG has been given, predicting high mortality due to severe cholestasis and acute hepatic insufficiency. In literature, the widely accepted treatment for DIHS/DRESS is the discontinuation of the drug responsible and systemic corticosteroid therapy. Treatment with a minimum dose of 1 mg/kg of prednisolone equivalent to a steroid is recommended to be discontinued and reduced at 6-8 weeks after clinical remission (6). High doses (1gr/

kg) of IVIG for 2-5 days are recommended for patients who do not respond to steroid therapy, and therapies such as valgansiclovir or plasmaferese are indicated for patients with herpes virus reactivation (12). There is evidence that NAC treatment also prevents the progression of liver damage (13). The NAC was initiated early in order to benefit our patient from its cytoprotective effect.

With the development of fever, lymphadenopathy or atypical lymphocytosis, DRESS syndrome can be confused with acute viral infections or hematological malignancies. Reactivation of human immunodeficiency virus (HIV), Epstein Barr virus (EBV) and HHV-6 can occur as mononucleosis-like diseases along with rash and systemic symptoms. When it comes to liver involvement, viral serological tests should be performed for hepatotropic viruses such as hepatitis viruses and influenza. Peripheral spread should be carefully examined for hematological malignancies, and bone marrow should be assessed if suspected. For the distinctive diagnosis, it is important to have drug use in the story that may be responsible for DRESS.

The risk of life-threatening reactions in the long-term follow-up of patients requires that drug use and drug provocation tests, such as drugs responsible for the drug or cross-reaction aromatic anticonvulsants, should be avoided, and patients and their relatives should be informed in detail. If necessary, skin patch tests may be used to detect a suspect drug or find a safe alternative drug. (14). The skin patch test could not be carried out because the family did not approve because of the weight of the clinical Picture.

11.5% of patients with DRESS syndrome can develop long-term symptoms such as organ failure and autoimmune diseases autoimmune thyroid disease is most frequently in adolescents and kidney failure in the elderly (4). Long-term monitoring of patients is important for autoimmune diseases. Our patient's liver enzymes and kidney function tests, which have been monitored for a year with periodic poliklinical controls, have been observed within the normal range, and no autoantibody positive has been detected.

Clinical characteristics DRESS syndrome may be diagnosed with delays due to its wide range and the length of time between drug use and the onset of symptoms (6). Early detection of the disease, immediate discontinuation of the relevant drug or drugs, and initiation of necessary supportive therapies are essential for reducing morbidity and mortality.

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