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Phenytoin-associated DRESS syndrome: A Case Report

Fenitoine Bağlı DRESS Sendromu: Olgu Sunumu

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Abstract

Introduction: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a rare, life-threatening, delayed type drug reaction characterized by fever, skin rash, hematologic changes (eosinophilia, atypical lymphocytes), lymphadenopathy and involvement of the internal organs (liver, kidney, heart). It was first described associated with phenytoin but aromatic anticonvulsants and sulfonamides are the most common ones. The diagnosis of DRESS syndrome is made according to the clinician's decision with the scoring systems (Bocquet, J-SCAR, RegiSCAR) consisting of certain clinical and laboratory findings. The main criterias for these scores are fever, skin rash, eosinophilia and internal organ involvement.

Case: A 7-year-old male patient with ongoing investigations in our pediatric neurology outpatient clinic due to Lennox-Gastaut syndrome, mental-motor retardation and syndromic appearance was admitted with 39°C fever and rash on his body for 2 days. Our patient diagnosed with epilepsy had received antiepileptic treatment since he was one year old and it was learned that phenytoin was added to his current treatment because he had generalized tonic-clonic seizures 11 days before the admission. In the history of our case, there was a second-degree consanguinity between the mother and father. In physical examination; body weight was 16.5kg (<3p), height was 100 cm (<3p), head circumference was 48 cm (<3p). He had a syndromic facial appearance (retro-micrognathia, flat nasal bridge), leukocoria, small hands and foots, and a simian line in the right hand. There were diffuse millimetric maculopapular rashes on the body and a left cervical lymph node (1 x 1 cm). In laboratory examinations; hemoglobin was 13.1 gr/dL, leukocyte was 9710/mm³, platelet was 266000/mm³, total eosinophil count was 880/mm³, AST was 82 IU/L, and ALT was 45 IU/L. Phenytoin of our case, who was considered to have phenytoin-induced DRESS syndrome according to the RegiSCAR diagnostic criteria, was discontinued and the rash, eosinophilia and transaminase values were decreased within 3 days after starting antihistaminic and steroid treatment.

Conclusion: DRESS syndrome is a rare but life-threatening progressive condition and early diagnosis and timely treatment are life-saving. We present our case to emphasize the importance of questioning the history of drug use in patients presenting with fever and rash, and the necessity of keeping in mind the diagnosis, triggers and treatment of DRESS syndrome.

***Key words**: Phenytoin, DRESS syndrome, child*

Özet

Giriş: DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) sendromu; ateş, cilt döküntüsü, hematolojik değişiklikler (eozinofili, atipik lenfositler), lenfadenopati ve iç organ (karaciğer, böbrek, kalp) tutulumu ile karakterize, nadir görülen, hayatı tehdit edebilen, gecikmiş tip bir ilaç reaksiyonudur. İlk olarak fenitoin ilişkili olarak tanımlanmış olmakla beraber, en çok neden olan ilaçlar aromatik antikonvülzanlar ve sülfonamidlerdir. DRESS sendromu tanısı klinisyen kararına göre belirli klinik ve laboratuvar bulgularından oluşan puanlama sistemleriyle (Bocquet, J-SCAR, RegiSCAR) konulmaktadır. Bu skorlamalarda ana kriterler; ateş, cilt döküntüsü, eozinofili ve iç organ tutulumudur.

Olgu: Lennox-Gastaut sendromu, mental-motor retardasyon ve sendromik görünüm nedeniyle çocuk nöroloji polikliniğimizde tetkikleri devam eden, 7 yaş erkek olgu; 2 gündür 39°C ateş ve tüm vücutta döküntü şikayetleri ile başvurdu. Bir yaşından beri epilepsi tanısı ile birçok antiepileptik tedavi alan olgumuzun başvurudan 11 gün önce jeneralize tonik-klonik nöbetleri olduğu için mevcut tedavisine fenitoin eklendiği öğrenildi. Olgunun soygeçmişinde anne ve baba arasında 2. dereceden akrabalık mevcuttu. Fizik muayenesinde; vücut ağırlığı; 16,5 kg (<3p), boy; 100 cm (<3p), baş çevresi; 48 cm (<3p), sendromik yüz görünümü (retro-mikrognati, burun kökü basıklığı), lökokori, sağ elde simian çizgisi, küçük el ve ayak mevcuttu. Vücutta yaygın milimetrik makülopapüler döküntüler ve sol servikalde 1x1 cm lenfadenopatisi vardı. Laboratuvar incelemelerinde; hemoglobin: 13.1 gr/dL, lökosit: 9710/mm³, trombosit: 266000/mm³, total eozinofil sayısı: 880/mm³, AST: 82 IU/L, ALT: 45 IU/L saptandı. RegiSCAR tanı kriterlerine göre feniton ilişkili DRESS sendromu düşünülen olgunun fenitoini kesildi, antihistaminik ve steroid tedavisi başlandıktan 3 gün sonra döküntüleri, eozinofili ve transaminaz değerleri geriledi.

Sonuç: DRESS sendromu nadir rastlanan ancak hayatı tehdit edebilen progresif bir durum olup erken teşhis ve zamanında tedavi hayat kurtarıcıdır. Ateş ve döküntüyle başvuran olgularda ilaç kullanım hikayesinin sorgulanmasının önemini ve DRESS sendromunun tanısı, tetikleyicileri ve tedavisinin akılda tutulmasının gerekliliğini vurgulamak amacıyla olgumuzu sunuyoruz.

***Anahtar kelimeler**: Fenitoin, DRESS sendromu, çocuk*

Introduction

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a rare, life-threatening, delayed-type drug reaction characterized by fever, skin rash, hematological disturbances (eosinophilia, atypical lymphocytes), lymphadenopathy and internal organ involvement (liver, kidney, heart). Anticonvulsants and sulphonamides are the most common causative drugs.[1] In this report, a case of DRESS syndrome that developed due to phenytoin therapy for epilepsy is presented.

Case Report

A 7 year-old male case who has been followed-up in our pediatric neurology clinic due to Lennox-Gastaut syndrome, mental-motor retardation and syndromic appearance presented with a temperature of 39°C and skin rash on whole body which began before 2 days. It was learned that our patient, who has received various antiepileptic treatment for the diagnosis of epilepsy since the age of 1, had a generalized tonic-clonic seizures 11 days before his admission and that phenytoin was added to his current sodium valproate treatment. In family history of the case; his parents were second-degree relatives. On the physical examination; his weight was 16.5 kg (<3p), height was 100 cm (<3p), head circumference was 48 cm (<3p) and he had a syndromic facial appearance (retro-micrognathia, flat nasal bridge), leucocoria and simian line in the right hand, as well as small hands and feet. He had a widespread millimetric maculopapular rash on his body and a lymphadenopathy of 1x1 cm in size in the left cervical chain (Figure 1A).

Laboratory results were as follows: hemoglobin: 13.1 gr/dL, leukocyte: 9710/mm³, platelet: 266.000/mm³, total eosinophil count: 880/mm³, AST: 82 IU/L and ALT: 45 IU/L, and in peripheral blood smear; 56% PMNs, 28% lymphocytes, 7% monocytes and 9% eosinophils were observed. Of the case which was considered to have phenytoin-associated DRESS syndrome in accordance with RegiSCAR diagnostic criteria; his phenytoin treatment was discontinued; and the laboratory results following antihistamine and steroid treatments were as follows: hemoglobin: 14.2 gr/dL, leukocyte: 5990/mm³, platelet: 221.000/mm³, total eosinophil count: 90/mm³, AST: 48 IU/L and ALT: 38 IU/L, as well as the skin rashes regressed (Figure 1B).

Discussion

DRESS syndrome is a rare, acute-onset, life-threatening drug reaction characterized by fever, skin rash, internal organ involvement and hematological abnormalities. The mortality rate of DRESS syndrome is approximately 10%.[2]

DRESS syndrome was initially described as a hypersensitivity syndrome to phenytoin. However, later on it was determined that other various medications also cause it. Patrice Cacoub et al. compiled case reports reported in PubMed-MEDLINE between 1997 and 2009; they reported that there was a total of 172 cases of DRESS syndrome associated with 44 different drugs and that these cases were most commonly associated with antiepileptic drugs and allopurinol.[3] In the study by Yang et al. which included cutaneous side effects of antiepileptic drugs, they reported that 43.6% of the cases had carbamazepine and phenytoin-associated DRESS syndrome.[4] In the another study, however, Botelho et al. demonstrated that the most common drug causing DRESS syndrome was phenytoin.[5] Our case has an importance as he has been considered to have phenytoin-associated DRESS syndrome.

Diagnosis of DRESS syndrome is made via scoring systems comprised of specific clinical and laboratory findings (Bocquet, J-SCAR, RegiSCAR) according to the decision made by the clinician.[1,6] In RegiSCAR scoring, there is a scoring system according to parameters including rash, fever, lymphadenopathy, internal organ involvement, presence of atypical lymphocytes and eosinophils, absence of other causes (negative viral serology, negative blood cultures, negative anti-nuclear antibody) and clinical manifestations persisting for more than 15 days.[6] Our case had fever (0 point), lymphadenopathy (1 points), eosinophilia (1 point), skin involvement (1 point) and liver involvement (1 point). He was diagnosed with possible DRESS syndrome after receiving 4 points according to RegiSCAR scoring.

In DRESS syndrome, the most common hematological disturbance is eosinophilia, where as the most common internal organ involvement is liver involvement.[7] In our case, total eosinophil count was 880/mm³, AST 82 IU/L and ALT 45 IU/L, which supported our diagnosis.

Duration between administration of the drug and development of DRESS syndrome may vary between 2 to 6 weeks. Recovery period after discontinuation of the drug may last 6 to 9 weeks.[8] In our case, he had complaints of fever and rash 11 days after he began to use phenytoin and complete regression of the rashes took approximately 4 weeks.

The most important step in treatment of DRESS syndrome is early diagnosis and abrupt discontinuation of the drug. Topical corticosteroids may be beneficial; however, systemic steroid or immunosuppressant treatment is usually required.[2,8] The drugs used by our case were checked; phenytoin, which was determined to be one of the most common causes after the literature review, was discontinued, steroid treatment was initiated and he was then followed-up. During follow-ups, rashes were relieved by the 3rd day and completely regressed within approximately 4 weeks. Response to discontinuation of the drug and steroid treatment also supports diagnosis of DRESS syndrome. In conclusion; DRESS syndrome is a progressive condition which is rare but can be life-threatening and early diagnosis and prompt treatment is

lifesaving. We would like to express the importance of investigation of history of drug use and that diagnosis, triggers and treatment of DRESS syndrome should be kept in mind in cases presenting with fever and rash.

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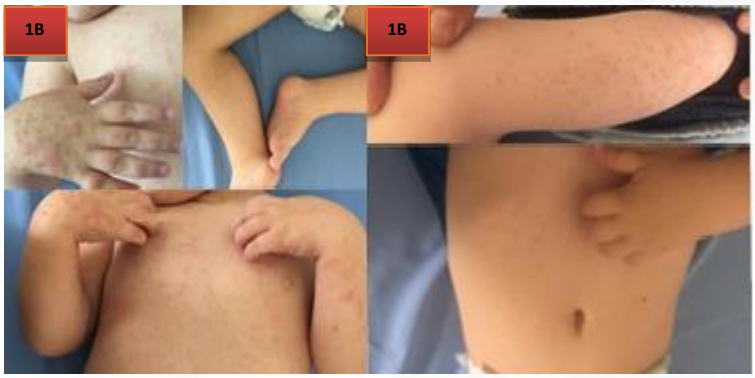

Figure 1A: A widespread milimetricmaculopapular rash on whole body, Figure 1B: Regression of rashes after treatment