DRESS syndrome presents as leukoencephalopathy

Seyed Hasan Tonekaboni[1], Narjes Jafari[1], Zahra Chavoshzadeh[2], Bibi Shahin Shamsian[3], Nima Rezaei[4,5,6]

[1] Pediatric Neurology Research Center, [2] Pediatric Infection Research Center, [3] Pediatric Hematology Research Center, Shahid Beheshti University of Medical Sciences, [4] Research Center for Immunodeficiencies, Children's Medical Center, [5] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, [6] Universal Scientific Education and Research Network (USERN), Tehran, Iran. Email: zahra_chavoshzadeh@yahoo.com
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DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a potentially life-threatening syndrome, which reflects a serious hypersensitivity reaction to drugs, presenting by generalized skin rash, fever, eosinophilia, atypical lymphocytosis, and internal organ involvement. Herein a 21-month old male infant with DRESS and Encephalopathy syndrome is presented who complicated after phenobarbital usage that persisted due to phenytoin cream usage. The case received phenobarbital after a seizure disorder presented as "status epilepticus". He developed drug eruption, fever, hepatosplenomegaly, increased liver enzymes, encephalopathy and progressive loss of consciousness with extensive hyperintense white matter lesions in brain MRI. After discontinuation of phenobarbital and phenytoin, all symptoms were resolved, while brain MRI became normal after two months. To our best knowledge, this is the first reported case that developed leukoencephalopathy along with DRESS syndrome.

Key words: antiepileptic drug, adverse drug reaction, DRESS, hypersensitivity, loss of consciousness.

The Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction[1]. Diagnosing of DRESS is challenging due to the diversity of cutaneous eruption and multiple organs involvement. It seems that the liver is the most frequently affected internal organ, while other organs such as kidney and brain are rarely involved[1]. Clinical manifestations of adverse drug reactions (ADRs) are highly variable and must therefore be suspected in any patient who develops any unusual manifestation after taking antiepileptic drugs (AED). Early recognition of DRESS and withholding or changing the medication are necessary to prevent potentially fatal outcomes[1,2].

Herein, a case with DRESS syndrome and leukoencephalopathy is presented for the first time, to our best knowledge.

Case Report

A 21-month old boy was referred to our center with history of febrile status seizure in the context of gastroenteritis. He had received phenobarbital and phenytoin to control seizures and discharged with phenobarbital with 5 mg per kg/day; however, he developed fever, maculopapular rash and edema in extremities (Fig. 1), hepatomegaly, encephalopathy with progressive loss of consciousness, and progressive disturbances in motor and speech skills after three weeks. No lymphadenopathy was detected. Routine laboratory tests showed leukocytosis with hypereosinophilia, increased ESR and liver enzymes (Table 1), but brain MRI showed diffuse symmetrical hyper intense lesions in white matter (Fig. 2) which was compatible with leukoencephalopathy. Abdominal sonography showed hepatosplenomegaly. EEG showed generalized epileptic discharges. Muscle electrophysiological studies (EMG and NCV) were normal. Phenobarbital was discontinued, as the primary suspect of hypersensitivity was reaction to drug. Despite supportive care, rash,

Table 1. The Results of Some Laboratory Tests That Were Requested For the Patient.

Test	Results	Normal range
Leukocytes Polymorphonuclear cells (PMN) Lymphocytes Eosinophils	19,000 60% (11,4000/mm^3) 23% (4,370/mm^3) 15% (2,850/mm^3)	4000-10000/mm^3
Hb	9.7	11-13 mg/dl
PLT	169,000	150,000-400,000/mm^3
AST	89	Up to 35
ALT	97	Up to 35
ESR	45	
CRP	+	-
VBG	PH:7.34 (HCO3: 22, CO2: 39)	PH: 7.35-7.45
Biochemistry	Na:136, K:3.8 BUN:7, Cr:0.8, Ca:9, P:4,2	Na:135-145, K:3.5-5
PT	13	11-13
PTT	34	32-35
Wright	Negative	-
2ME	Negative	-
Ammonia	37	Up to70 mg/dl
Lactate	16	Up to20 mg/dl
Metabolic screening	Normal	

Hb: Hemoglobin (Hb), PLT: Platelets (PLT), AST: Aspartate aminotransferase (AST) ALT: Alanine aminotransferase (ALT), ESR: Erythrocyte sedimentation rate (ESR), CRP: C- reactive protein (CRP), VBG: Venous blood gas (VBG), PT: Prothrombin time (PT), PTT: Partial thromboplastin time (PTT), 2ME: 2-Mercaptoethanol

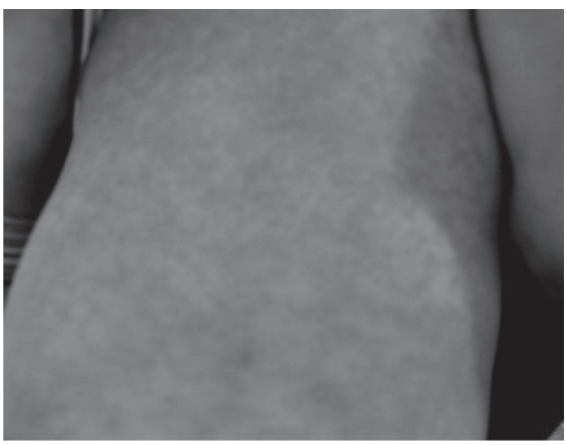

Fig. 1. Maculopapular skin rash in patient.

hepatomegaly and encephalopathy persisted. The patient with this history was referred to our center with probable diagnosis of histiocytosis. Bone marrow aspiration was performed which was normal. After precise history taking, it was detected that the patient used phenytoin cream for bedsores, because of prolonged hospital stay. Phenytoin cream was discontinued. After few days, rash, hepatomegaly and encephalopathy were fully recovered. Liver function test became normal. In subsequent brain MRI, lesions in white matter had completely disappeared after two months (Fig. 3).

It should be mentioned that on the biases of RegiSCAR scoring system[3], the patient had a score of 5 as followed which is compatible with probable diagnosis of DRESS: 1 score for eosinophila, 1 score for skin rash extent >50% body surface area, 1 score for skin rash suggesting DRESS, 1 score for liver involvement, and 1 score for brain involvement. He was discharged from the hospital in a general good condition and he has remained seizure free on follow-up.

Discussion

The DRESS is a severe ADR, with estimated incidence of ranging from 1 in 1,000 to 1 in

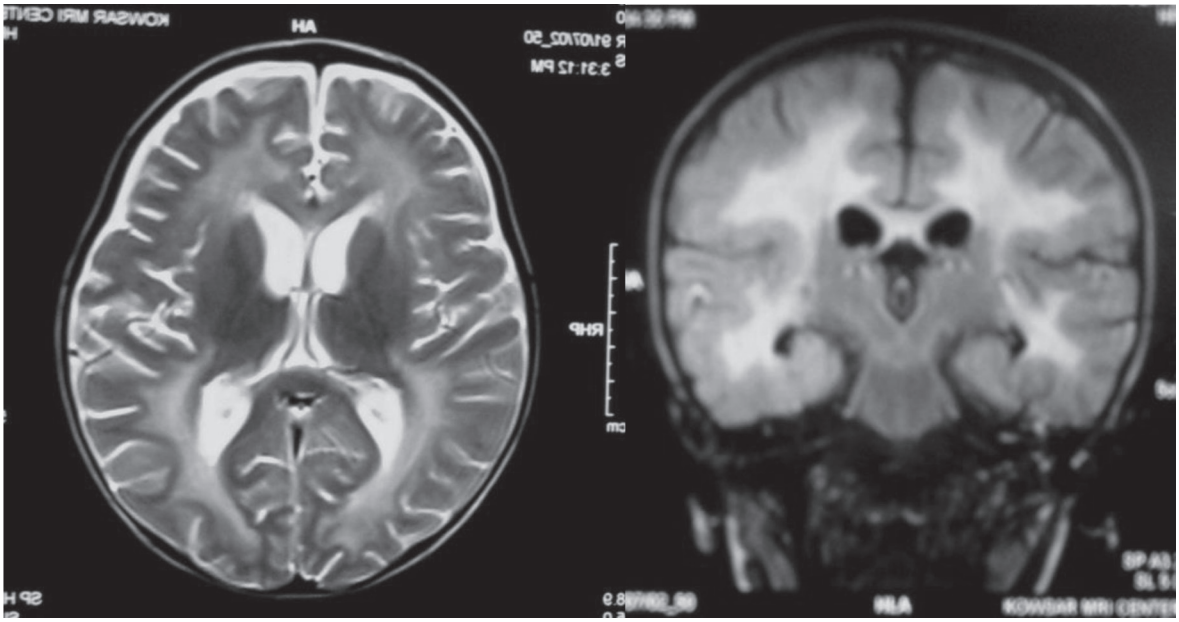

Fig. 2. Extensive hyperintense lesions in white matter in brain imaging at acute phase disease.

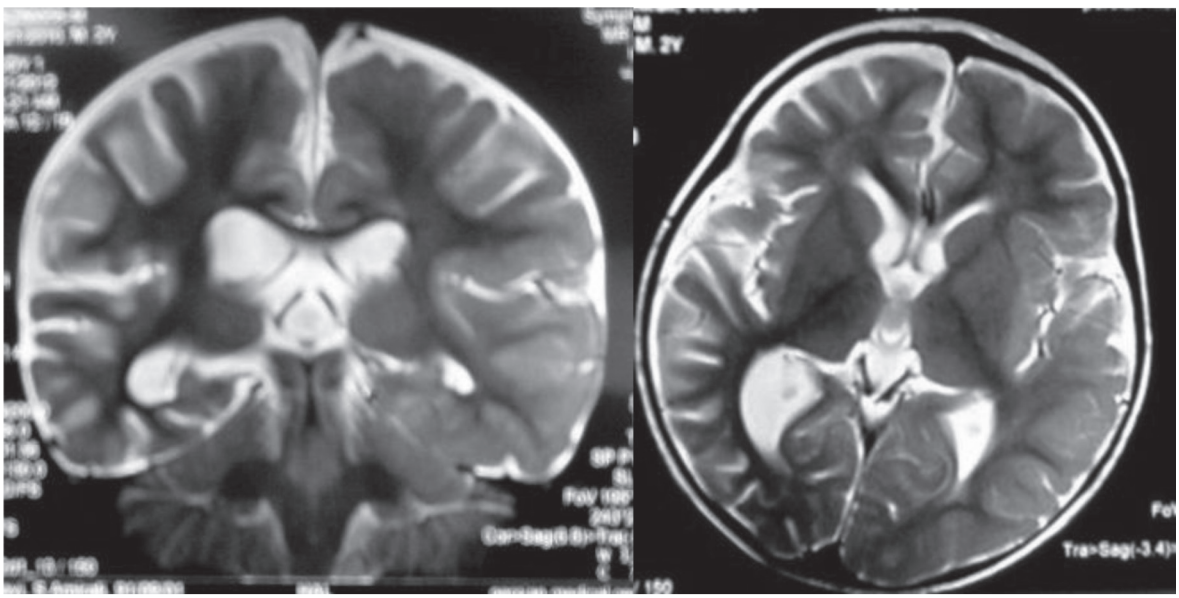

Fig. 3. Improvement of lesions in latter brain imaging after treatment.

10,000 drug exposures[1]. This is a potentially life-threatening syndrome, including a severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement. The liver is the most frequently affected internal organ, while other organs such as kidney or the central nervous system could rarely be involved[2]. However, recognizing this syndrome is of particular importance, as the mortality rate is up to 10%[1,2]. Carbamazepine, lamotrigine, allopurinol, sulfasalazine, phenobarbital, and nevirapine are the most common drugs causing DRESS[1]. The most common presentation seems to be persistent fever with skin rash: typically in the face, upper trunk, and extremities, with edema of the face being a hallmark of DRESS syndrome[1]. Other manifestations could be enlarged lymph nodes, arthritis, or arthralgia. The most dangerous aspect of DRESS syndrome is visceral involvement, with hepatitis being the most common (50% of all cases)[4,5]. Although

fulminant hepatitis is the main cause of death, myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis, and inflammation of the brain can also occur[6].

To the best of our knowledge, this is the first time that DRESS with leukoencephalopathy is reported in association with phenytoin cream. The main treatment for DRESS could be withdrawal of culprit drug and corticosteroid. Clinical presentations of ADR to AED are highly variable and involve various internal organs. Although they mainly involve liver and kidneys, other organs could be rarely involved. Therefore hypersensitivity could be considered in patients using AEDs, if they develop unusual manifestation. Early recognition of such complication and cessation of the suspect medications are required to prevent potentially fatal outcomes.

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