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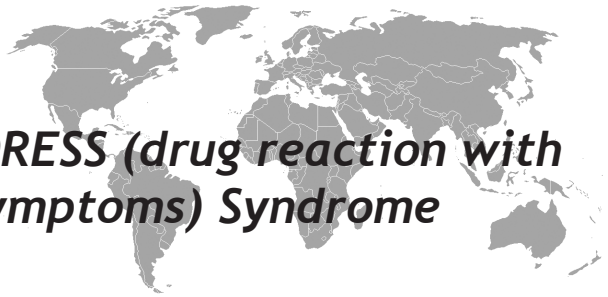
Case Report



Cefuroxime Axetil Related DRESS (drug reaction with eosinophilia and systemic symptoms) Syndrome

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ABSTRACT

DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome is a rare, potentially life-threatening, drug induced hypersensitivity reaction manifested by fever, rash, eosinophilia, lymphadenopathy, and organ involvement especially liver and kidney. The disease is characterized by a long latency period (at least two weeks) between the drug exposure and disease onset. The most commonly reported drugs associated with DRESS syndrome in the literature are allopurinol, and anticonvulsants. We describe a patient presented with eosinophilia, fever, diffuse maculopapular rash, hepatomegaly, and multiple intra-abdominal lymphadenopathies just ten days after initiation of cefuroxime axetil. In our case, we aim to announce the first case report of cefuroxime axetil related DRESS syndrome, and also speculate on the possible association between cephalosporin and DRESS syndrome.

Key words: *Cefuroxime axetil, DRESS, steroids*

Sefuroksim Aksetil İlişkili DRESS (drug reaction with eosinophilia and systemic symptoms) Sendromu

ÖZET

DRESS (Drug reaction with eosinophilia and systemic symptoms) sendromu nadir görülen, potansiyel olarak ölümcül, özellikle karaciğer ve böbrek gibi organ tutulumu ve ateş, döküntü, eosinofili ve lenfadenopati ile karakterize bir sendromdur. İlaç maruziyeti ile hastalığın başlangıcı arasında uzun bir latent periyod (en az iki hafta) ile karakterizedir. Literatürde DRESS sendromu ile ilişkili olduğu en sık rapor edilen ilaçlar allopurinol ve antikonvülzanlardır. Sefuroksim aksetil başlandıktan 10 gün sonra ateş, diffüz makülopapüler döküntü, hepatomegali ve multipl intra-abdominal lenfadenopatilerle prezente olan bir hastayı sunduk. Bu vakada, sefuroksim aksetile bağlı gelişen DRESS sendromunun ilk vaka bildirimini sunmayı ve sefalosporinlerle DRESS sendromu arasındaki muhtemel ilişkiyi tartışmayı amaçladık.

Anahtar kelimeler: *sefuroksim aksetil, DRESS, steroidler*

INTRODUCTION

Dress syndrome is an idiosyncratic drug reaction often occurring after drug use and characterized by multiple internal organ involvement. Clinical findings are eosinophilia, skin rash, hematological abnormalities and lymphadenopathy (1,2). Signs and symptoms are revealed after 2-8 weeks of taking suspected drug. Dress syndrome has been described firstly after the use of anti-epileptic drugs. Therefore, it has been named as hypersensitivity syndrome associated with anticonvulsant drug or drug associated pseudolymphoma (3,4). Anti-epileptics and sulfonamides are the most common drugs that cause DRESS syndrome although many drugs can cause it. However, there is no history of drug usage in some cases although they have the diagnostic criteria of dress syndrome (5). Dress syndrome is more common in adulthood independent of gender however its incidence is not known exactly (6). In the treatment, stopping the drug that causes it is essential. Also, systemic corticosteroids and intravenous immunoglobulins may be used if necessary. The disease mortality varies between 10-40% despite these treatments.

Cefuroxime axetil is a semisynthetic antibiotic in the cephalosporin group. It has a bactericidal effect by disrupting cell wall synthesis. It is a good choice for the treatment of infections of respiratory and urogenital sys-

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tems. It has side effects such as nausea, vomiting, diarrhea, abdominal pain, headache, anemia and skin rashes. In the literature, there is no dress syndrome due to cefuroxime axetil.

CASE

A 58-year-old white, caucasian male presented to the emergency department with a two day history of diffuse rash, fever and malaise. He was otherwise asymptomatic reporting no headache, shortness of breath, hemoptysis, and abdominal pain, blood in the stool, weight loss and arthralgia. Medical history of the patient revealed that he was currently taking no medications other than cefuroxime axetil using for 10 days for upper respiratory tract infection. His past surgical history was only an appendectomy of fourteen years ago. His family history was remarkable only for colon adenocarcinoma in his elderly brother. He did not use alcohol, or illicit drugs but use tobacco. On physical examination, the patient had fever (temperature, 39.2 o C), tachycardia (heart rate, 108/min), and normal blood pressure. No lymphadenopathy was palpated. His cardiovascular examination was normal and his lungs were clear on auscultation bilaterally. Abdominal examination revealed a soft, non-tender, non-distended abdomen with normal and active bowel sounds and hepatomegaly. His skin examination revealed diffuse morbiliform rash including the whole body accompanied with facial edema (Figure 1). Laboratory studies revealed the following (reference ranges shown parenthetically): creatinine, 0.86 mg/dL (0.5-1.4 mg/dL), urea, 46 mg/dL (10-45 mg/dL), alkaline phosphatase, 357 U/L (40-150U/L), gamma glutamyle transferase, 274U/L (5-55 U/L), aspartate aminotransferase, 109 U/L (10-40 U/L), alanine aminotransferase, 110 U/L (10-40 U/L), lactate dehydrogenase, 679 U/L (125-243 U/L), total bilirubin, 0.6 mg/dL (0.2-1.0 mg/dL), albumin, 2.83 (3.5-5.0 mg/dL), erythrocyte sedimentation rate, 43 (1-7), c-reactive protein, 2.59 mg/dL (0-0.8 mg/dL), INR, 1.09 (0.88-1.2). His leukocyte count was 17.300 K/uL (4.60-10.200 K/uL)

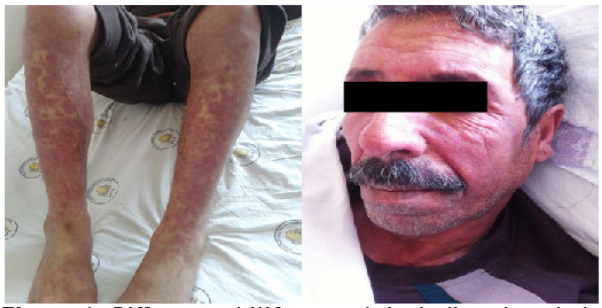

***Figure 1**. Diffuse morbiliform rash including the whole body of the patient accompanied with facial edema*

with neutrophil count of 13.800 and eosinophil count of 1380 (table 1 and table 2). The increase in the eosinophil count was consistent with the DRESS syndrome (7).

On peripheral blood smear examination (figure 2), predominancy of neutrophil and eosinophil, with rates of 70% and 14%, adequate platelet counts, normochromic normocytic red cells, and no toxic granulation of neutrophils were documented.

Electrocardiography revealed sinus tachycardia and no pathologic findings were noted on chest radiography. Urine evaluation was remarkable for protein levels, 500 mg/dL (normal range: negative), and leukocyte levels, 25 uL (reference range: negative). The urinary sediment was notable for red blood cell casts. Dress syndrome may be associated with drug induced viral activation (8). Therefore, HSV, EBV, CMV, anti HIV, hepatitis A, B and C serologies were studied and the results were negative. Throat cultures were also negative. On abdominal ultrasonography, multiple lymphadenopathies in the periportal and paraaortic region, hepatomegaly and renal parenchymal involvement or change were detected.

DISCUSSION

Patient was admitted to the emergency service with the complaints of high fever, morbiliform skin rashes and

Table 1. Complete blood count results of the patient

	15/11/13	*16/11/13*	*18/11/13*	*25/11/13*	*29/11/13*	*14/12/13*	*05/1/14*
WBC	*17.600*	*22.300*	*15.700*	*16.100*	*7.700*	*8100*	*9250*
NEU	*13.800*	*19.600*	*11.300*	*10.500*	*6300*	*5100*	*6250*
EOS	*1380*	*2230*	*0.304*	*0.536*	*0.050*	*0.035*	*0.003*
HGB	*11.9*	*12.6*	*10.5*	*12.1*	*13.1*	*11.8*	*12.8*

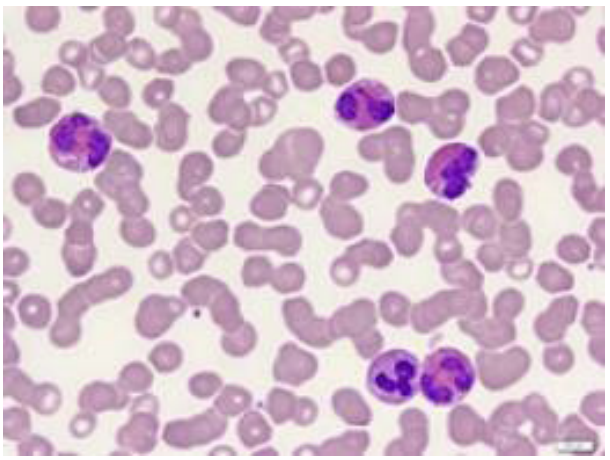

***Figure 2**. Peripheral blood smear of the patient*

hematuria and thereafter he was hospitalized with the preliminary diagnosis of acute tubulointerstitial nephritis, sepsis and vasculitis. On the physical examination of the patient; there were facial edema, generalized maculopapular skin rash and hepatosplenomegaly. Abdominal ultrasonography of the patient revealed generalized intraabdominal lymphadenopathy without peripheral lymphadenopathy (many lymphadenopathies in periportal and para-aortic area, the largest of them had a size of 18x10 mm), hepatomegaly (170 mm) and splenomegaly (138 mm). In the laboratory findings of the patient; there were deterioration of the liver function tests and increase in the levels of CRP and ESR. However, there were no toxic granulation and shift to the left in the peripheral blood smear of the patient but eosinophilia was detected. Results of the blood cultures which taken for the differential diagnosis of sepsis were negative. Findings specific to vasculitis such as mononeuritis multiplex and livedo reticularis were not found in our patient, also results of the p-ANCA and c-ANCA were negative. Serum complement levels were normal. The urine samples of patient revealed erythrocytes but there were no dysmorphic erythrocytes and red blood cell casts.

When we deepen the patient's history, we detected that patient used cefuroxime axetil two weeks ago due to the upper respiratory tract infection. The patient began using cefuroxime axetil 10 days ago and stopped treatment 3 days ago. Dress syndrome was considered with the available data. Dermatology consultation was requested. They also considered dress syndrome as a preliminary diagnosis and they wanted skin biopsy. Skin biopsies were taken from lower extremities which had generalized morbiliform rash. Dermal biopsy specimens were evaluated by pathology and they were reported as dermal edema and generalized perivascular lymphocytic and eosinophilic infiltration. This biopsy result was compatible with skin findings of the dress syndrome (9).

The current clinical and laboratory findings of patients were announced as dress syndrome although there was no data in the literature about the dress syndrome after cefuroxime axetil usage. Dress syndrome is almost always with the internal organ involvement. Less frequently, multi organ involvement may also be seen (10). In the

Table 2. Biochemistry results of the patient

	15/11/13	16/11/13	18/11/13	25/11/13	29/11/13	14/12/13	05/01/14
Glucose (mg/dl)	110	138	192	80	181	96	105
Urea (mg/dl)	46	42	40	33	46	39	26
Creatine (mg/dl)	0.86	0.83	0.69	0.64	0.74	0.46	0.60
Na (mmol/l)	128	127	133	138	133	141	139
K (mmol/l)	4.3	3.7	3.7	3.8	4.1	4.6	3.9
AST (u/l)	109	184	268	127	106	82	41
ALT (u/l)	110	110	270	290	256	113	44
ALP (u/l)	357	287	438	359	286	211	231
GGT (u/l)	274	266	556	304	288	111	65
LDH (u/l)	679	743	841	456	307	245	210
Albumin (g/dl)	2.83	2.42	2.40	2.61	3.3	3.6	3.8
ESR (mm/h)	43	47	38	30	25	20	19
CRP (mg/dl)	2.59	2.55	1.95	0.65	0.25	0.20	0.25

clinical follow-up, high transaminase levels, hematuria and lymphadenopathies were detected and we associated them with the internal organ involvement of the dress syndrome. Acute tubulointerstitial glomerulonephritis which was one of our preliminary diagnoses is the typical renal involvement form of the dress syndrome (11). Hematuria and 500 mg/day of proteinuria which were detected in our patient were consistent with ATI. We did not receive patient's approval for the kidney biopsy although we scheduled it. Increase in the serum levels of ALP and GGT were consistent with the liver involvement. Respiratory disease consultation was also requested for the evaluation of the respiratory system and there was no pathological finding in the evaluation.

One mg/kg/day methyl prednisolone therapy was started because of severe clinical symptoms although cefuroxime axetil was discontinued 3 days ago. Liver function test of the patient were improved after the steroid treatment. Serum LDH and GGT levels were decreased. A good fever response was observed in the follow-up with the treatment. Skin rashes were decreased significantly with the treatment. CRP, ESR and serum albumin levels were improved but hematuria was still going on. Patient was discharged on the 7th day of methyl prednisolone therapy (dose of the methyl prednisolone reduced to 0.5 mg/kg/day) with recommendation of the absolute bed rest. In the first month of outpatient visit; liver and renal functions of the patient were become in the normal limits. Hematuria was positive in spot urine test. Reactive lymph nodes were seen in abdominal ultrasonography. Steroid treatment was tapered slowly within the 4 weeks.

In the treatment of dress syndrome; supportive therapy and the discontinuation of the causative drug were essential. Patients may improve with the discontinuation of the suspected drug but this approach may be inadequate in the several internal organ involvements. Steroid therapy seems reasonable and is chosen by many clinicians in the treatment of severe internal organ involvement while there is no consensus on the use of steroids (12,13). Our patients did not continue cefuroxime axetil therapy in the time admission. Supportive treatment was initiated firstly and thereafter steroid treatment was started. Patient responded well to the steroid treatment. Clinically and laboratory improvement were observed in the patient. Steroid dose was tapered slowly and treatment was stopped in 6 weeks.

There are numerous publications in the literature about the relationship between Dress syndrome and usage of aromatic anti-convulsants and sulfonamides (14). However, there was no case in the literature about the dress syndrome after usage of cefuroxime axetil which has a wider field of use. Dress syndrome may develop after the use cefuroxime axetil and therefore should be considered in the differential diagnosis.

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