DRESS Syndrome Due to Ciprofloxacin Use: Case Report

Siprofloksasine Bağlı DRESS Sendromu

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ABSTRACT Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a life-threatening drug reaction usually caused by aromatic anticonvulsants, and manifests itself by skin rash, fever, hematological abnormalities sometimes accompanied by internal organ involvement such as hepatitis and nephritis. Although cases of toxic epidermal necrolysis (TEN) have been reported due to ciprofloxacin use, the development of DRESS is very scarce in the literature. Herein a 20-year-old female patient who developed DRESS with TEN and internal organ involvement after using oral ciprofloxacin for her complaints of nasal discharge, diarrhea and vomiting is presented. She was treated successfully with the hyperbaric oxygen and intravenous immunoglobulin administration.

Key Words: Ciprofloxacin; epidermal necrolysis, toxic; drug eruptions

ÖZET Eozinofili ve DRESS sendromu genellikle aromatik antikonvülzanların neden olduğu deri döküntüleri, ateş, ve hematolojik bozukluklarla kendini gösteren ve bazen hepatit, nefrit, gibi iç organ tutulumlarının da eşlik ettiği hayatı tehdit eden bir ilaç reaksiyonudur. Siprofloksasine bağlı gelişen toksik epidermal nekroliz (TEN) olguları bildirilmiş olmasına rağmen literatürde DRESS gelişimi çok nadirdir. Burada burun akıntısı, ishal, kusma şikayetleri nedeniyle oral siprofloksasin kullanması sonucu TEN ve iç organ tutulumuyla birlikte DRESS gelişen 20 yaşında bir kadın hasta sunulmaktadır. Olgumuz hiperbarik oksijen ve intravenöz immünglobulin tedavileri sonucunda iyileşmiştir.

Anahtar Kelimeler: Siprofloksasin; epidermal nekroliz, toksik; ilaç erüpsiyonları

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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, is a life-threatening drug reaction with a mortality of up to 10-20% usually caused by aromatic anticonvulsants, and manifests itself by skin rash, fever, hematological abnormalities sometimes accompanied by internal organ involvement such as hepatitis, nephritis.[1-3]

It may present itself with cutaneous manifestations in forms of erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[4]

Although the exact incidence is not clear, DRESS occurrence is estimated to be one out of 1000 to 10.000 new drug exposures. Development of TEN due to the use of oral ciprofloxacin is reported in current literature;

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however, only two cases of DRESS have been reported due to the use of ciprofloxacin.[1,5,6] Here, a young woman who used oral ciprofloxacin for nasal discharge, diarrhoea, vomiting, and developed TEN and consequently DRESS with the addition of systemic symptoms is presented.

CASE REPORT

A twenty-year-old female patient admitted to our emergency department with complaints of fever, coughing and redness and blisters presenting all over the body but especially on the arms and legs. Three days ago, she had taken ciprofloxacin tablets for complaints of nasal discharge, diarrhoea and vomiting. On physical examination she was confused. Body tempreture was 39.5° C, cardiac pulse rate of 110/min, blood pressure of 110/50 mmHg and her respiratory rate was 16/min.

Dermatological examination revealed that there were Nikolsky sign positive bullous lesions on an erythematous skin extending on the arms, legs, dorsal and ventral trunk, palms and soles of the feet and occupying approximately 80% of the of the body (Figure 1). There were bullae residues and white membranes on oral and anogenital mucosa. There was some conjunctival purulent discharge (Figure 2). Cardio-vasculary and respiratory system examination was normal. There were three lymphadenopathies in the axillary region and four lymphadenopathies localized bilaterally in the cervical region which were about 1-1.2 cm dimensions. The upper right quadrant of the abdomen was sensitive to palpation, but neither organomegaly nor rebound tenderness and defense were found.

The laboratory parameters of the patient are shown in (Table 1). Repeated complete blood counts showed atypical lymphocytosis and eosinophilia at 15%. The urinalysis and urine sediment showed 5-6 erythrocytes, ketonuria (80.45 g/day) and proteinuria. Grubel Widal, Brucella agglutination, EBV, herpes, toxoplasmosis, rubella, anti-HAV, anti-HIV, HBs-Ag, anti-HCV, HCV-RNA, CMV, parvovirus -19 antigen tests were all negative. Urine, throat, blood culture tests, ANA, anti-DNA, Coombs test were negative. The chest

FIGURE 1: Nikolsky sign positive bullae residue on the trunk during treatment.
(See color figure at http://www.turkiyeklinikleri.com/journal/dermatoloji-dergisi/1300-0330/)

FIGURE 2: Yellow pigmentation of conjunctiva, bullae residue on face, neck during treatment.
(See color figure at http://www.turkiyeklinikleri.com/journal/dermatoloji-dergisi/1300-0330/)

TABLE 1: Laboratory parameters.

	Day 1	Day 15	Day 60
WBC (mm^3)	2000	10200	5500
Hgb (mg/dl)	13	9	11.7
Platelets (mm^3)	106.000	746.000	176.000
Eosinophils	15%	8%	3%
CRP (0-0,800 mg/dl)	9.6	1.2	0.3
ALT (IU/L)	405	596	109
AST (IU/L)	797	228	49
GGT (IU/L)	214	760	230
T. Bilirubin (mg/dl)	3.93	29.86	3.04
D. Bilirubin (mg/dl)	2.89	28.68	3
ALP (IU/L)	95	200	120
LDH (IU/L)	2031	680	230
CK (IU/L)	197	29	12
Amylase (IU/L)	1575	138	85

X-ray, abdominal ultrasonography was normal. Magnetic resonance cholangiopancreatography

(MRCP) revealed the pancreas, intra-and extrahepatic bile ducts to be normal. A sinus tachycardia was present on the ECG.

On histopathological examination, in addition to full-thickness necrosis of the epidermis, diffuse necrosis of keratinocytes, basal layer separation and sub-epidermal vesicle formation, perivascular lymphocytic infiltration were determined (Figure 3). Based on clinical, laboratory and histopathological findings the patient is considered to have DRESS. Table 2 shows that our patient meets all the inclusion criteria for a potential case of DRESS in RegiSCAR. An overview of the RegiSCAR scoring system and our patient's results are given in Table 3.

All the drugs taken by the patient was stopped and saline wet dressings and a topical antibiotic creams were applied. Along with fluid and electrolyte replacement, the patient was given total parenteral nutrition since she could not be fed orally.

A proton pump inhibitor, oral nystatin, and intravenous 1 mg/kg/day methylprednisolone were started. Upon gradual worsening of the symptoms and the start of purulent sputum on the 2nd day of treatment, sputum culture antibiogram was repeated and amikacin 1 g/day, tigecycline 100 mg/day were initiated and then methylprednisolone was stopped and IVIG therapy was started at a dose of 2 g/kg/day for 3 days adding up to a total of 300 grams. Epidermal detachment stopped on the 5th day of the IVIG therapy.

On the 5th day of treatment a total of six sessions of hyperbaric oxygen therapy (HBOT) with an absolute atmospheric pressure of 5.2 for 90 min/day was performed. On the 10th day epithelization started and skin lesions began to heal. She was discharged on 30th day since her general condition improved and had stable vital signs. After one month on the follow-up visit, some mild postinflammatory hyperpigmentation were observed on the affected areas (Figure 4). Her written consent was obtained for publication purposes prior to discharge from the hospital.

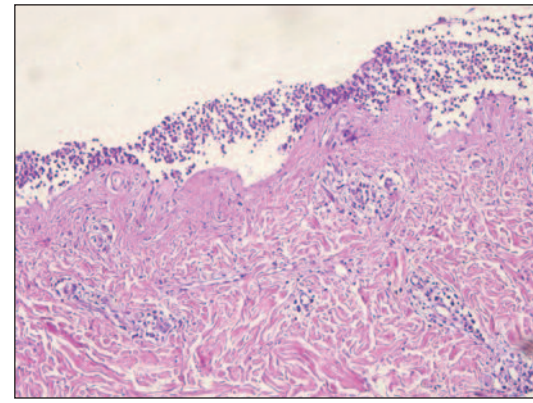

FIGURE 3: Full-thickness necrosis of the epidermis, diffuse necrosis of keratinocytes, basal layer separation and subepidermal vesicle formation, perivascular lymphocytic infiltration (HE, 20x10).
(See color figure at http://www.turkiyeklinikleri.com/journal/dermatoloji-dergisi/1300-0330/)

TABLE 2: Inclusion criteria for potential case of DRESS according toRegiSCAR in our patient.

Hospitalization	+
Reaction suspected to be drug related	+
Acute skin rash	+
Fever above 38 ˚C	+
Enlarged lymph nodes at at least two sites	+
Involvement of at least one internal organ	+
Blood count abnormalities	+
Lymphocytes above or below the laboratory limits	+
Eosinophils above the laboratory limits (in percentage or absolute count)	+
Platelets below the laboratory limits	+

DISCUSSION

The pathogenesis of DRESS is thought to be an abnormal immune response induced by the formation of reactive metabolites in a genetically susceptible individual.[7] The formation of reactive metabolites in the development of hypersensitivity reactions and enzymatic detoxification of metabolites has been implicated in the defects that lead to accumulation of bioproducts. Various groups of drugs including anticonvulsants, non-steroidal anti-inflammatory drugs, allopurinol and antibiotics may cause TEN. In several publications, antibiotics such as amoxicillin, cephalosporins, and recently ciprofloxacin have been accused in TEN patients.

TABLE 3: Scoring system for classifying DRESS cases applied to our patient.

Score	-1	0	1	2	Min.	Max.	Our patient's score
Fever ≥38.5°C	no/U	**yes**			-1	0	0
Enlarged lymph nodes		no/U	**yes**		0	1	1
Eosinophilia		no/U			0	2	
Eosinophils			0.7-1.499x109 L^{-1}	**≥1.5x109 L^{-1}**			1
Eosinophils, if leucocytes <4.0x109 L^{-1}			**10-19.9%**	≥20%			1
Atypical lymphocytes		no/U	**yes**		0	1	1
Skin involvement		no/U	**>50%**		-2	2	2
• Skin rash extent (% body surface area)							
• Skin rash suggesting DRESS	no	U	**yes**				
• Biopsy suggesting DRESS	no	**yes/U**					
Organ involvement					0	2	2
• Liver		no/U	**yes**				
• Kidney		no/U	**yes**				
• Lung		no/U	yes				
• Muscle/heart		no/U	yes				
• Pancreas		no/U	**yes**				
• Other organ		**no/U**					
Resolution ≥15 days	**no/U**	yes			-1	0	-1
Evaluation of other potential causes							
• Antinuclear antibody							
• Blood culture							
• Serology for HAV/HBV/HCV			**yes**		0	1	1
• Chlamydia/mycoplasma							
•I f none positive and ≥3 of above negative							
Total score					-4	9	8

U:unknown/unclassifiable. 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5,definite case.

To our knowledge there are only two cases that developed DRESS after ciprofloxacin treatment, published in 2010 and 2011.[5,6] In DRESS the spectrum of skin lesions may vary from maculopapular eruptions to TEN.[4]

In our case, DRESS developed on the 3rd day of the ciprofloxacin treatment and we evaluated the skin lesions as TEN for both histopathological and clinical features.

The variations in cutaneous eruptions and the type of organ involvements make the diagnosis of DRESS a challenging process. High fever, the exanthematous and maculopapular character of the rash, usually misleads the diagnosis towards infectious diseases. Generalized lymphadenopathy, hematologic disorders, high liver function tests, lactic dehydrogenase levels, gastrointestinal bleeding, acute tubular necrosis, pneumonia, bacterial conjunctivitis are considered as the indicators of internal organ involvement.[8] Cholestatic hepatitis accompanying TEN is rare in the literature.[9]

In our case, the presence of high fever, maculopapular rash in the beginning and consequently the rise in hepatic enzymes can be assumed as infectious causes. The laboratory parameters of our patient shows that complete blood counts were normal, agglutination, serological and ELISA tests were all negative, urine, throat, blood culture tests, ANA, anti-DNA and Coombs test were negative. The chest X-ray, abdominal US were normal. Therefore, we excluded the infectious causes.

The RegiSCAR scoring system has been developed to delineate each of these SCARs as distinct entities and to grade DRESS cases as "no", "possible", "probable" or "definite".[10-12]

FIGURE 4: Postinflammatory hyperpigmentation, one month after treatment. (See color figure at http://www.turkiyeklinikleri.com/journal/dermatoloji-dergisi/1300-0330/)

Our patient fulfills the inclusion criteria for a potential case of DRESS according to RegiSCAR and our patient's results are concluded as a "definite" case of DRESS with a score of eight.

TEN patients are under risk of sepsis due to widespread necrosis of the epidermis therefore these patients should be treated under sterile conditions, as in intensive care or burn centers.[13,14] However, as it has been emphasized in the literature that scarce number of burn units, we had to treat our patient in our clinic after preparing a sterile environment because of unavailability of burn unit.

Patients who cannot eat food due to severe oral mucosal involvement, need fluid and electrolyte replacement, as well as, total parenteral nutrition support.

Our patient was given parenteral fluid replacement and nutrition support therapy. Although the use of short-term methylprednisolone, 1-2 mg/kg/day, in the early period of TEN is reported to have no negative effects on mortality and morbidity, there have not been any large controlled trials carried out with this regard.

In addition, the use of high-dose IVIG and plasmapheresis treatments were reported to give positive results in a few case series. In the literature only three studies, two retrospective and one prospective, have been reported about the use of IVIG.[15] First study reports a recovery rate of 88%, and the second reports 83% of reduction in mortality rate while the third study reported no effect of IVIG therapy.[16,17]

In our case, upon the development of clinical sepsis in two days and no response to treatment with methylprednisolone, we started IVIG therapy, at a dose of 2 g/kg/day starting on the second day, for 3 days adding up to a total of 300 grams. Epidermal detachment stopped on the fifth day of the IVIG therapy.

Ruocco et al. reported that HBOT gave promising results in the treatment of TEN in 3 cases and has a very positive effect on wound healing, enhancing proliferation fibroblasts, collagen synthesis, maturation and angiogenesis.[18]

We continued HBOT until her lesions were epithelialized. As a result, randomized, controlled trials are needed in order to determine the effect of combined therapy of IVIG and HBOT in patients with severe TEN and internal organ involvement.

DRESS most commonly occurs secondary to the use of aromatic anticonvulsants according to literature. Although many cases of TEN developed due to the use of ciprofloxacin, only two DRESS cases have been reported in the literature previously.

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