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CASE REPORT OPEN ACCESS

DRESS Syndrome Associated with Elevated Liver Enzyme and Acute Kidney Injury after Allopurinol Use

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia and atypical lymphocytosis), lymphadenopathy, and internal organ involvement (liver, kidney, and lung). Moreover, retrospective studies have reported a mortality rate between 5% and 10%. In this paper, a case of DRESS with renal and hepatic organ involvement developing 2 weeks after the use of allopurinol which is among the most common drugs for DRESS will be presented.

Keywords: Allopurinol, DRESS, elevated liver enzyme, acute kidney injury

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a very rare, potentially life-threatening, drug-induced hypersensitivity reaction including skin eruption, hematologic abnormalities (eosinophilia and atypical lympho cytosis), lymphadenopathy, and internal organ involvement (liver, kidney, and lung)(1-3). DRESS is characterized by a long latency (2-8 weeks) between drug exposure and disease onset, a prolonged course with frequent relapses despite the discontinuation of the culprit drug, and a frequent association with the reactivation of latent human herpesvirus infections (4-6). The most frequently reported causes are anti-epileptics (e.g. carbamazepine, lamotrigine, phenytoin, and phenobarbital) and allopurinol (7). The incidence of DRESS is unknown. A 7-year prospective study in the West Indian general population estimated the incidence as 0.9/100.000 annually (8). In this case report, a case of DRESS syndrome after allopurinol use was presented.

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Case Presentation

A 63-year-old patient with chronic renal disease applied to emergency service with the spill completed in all bodies after allopurinol and calcitriol used in 2 weeks. In physical examination of the patient, body temperature is measured as 39°C, and a combined maculo papular rash of head, neck, thorax, abdomen and extremities has been determined. In the laboratory review of the first application to the hospital, urea: 98 mg/dl (n:19-49), CRE:2.5 mg/dl (base CRE:1.9), AST: 318 u/l (n<35), ALT: 340 u/l (n<50), ALP: 243 u/l (n:53–141), GGT: 132 u/l (n<38), amylase: 52 u/l (n:30–118), lipase: 42 u/l (n:12–53), LDH: 642u/l (120–246), total/direct bilirubin:1/0.4mg/dl, albumin:40g/l, WBC: 11.000 (n:4,300–10,300), neutrophil: 10.130 (n: 1,500–7,700), lymphocyte: 1,220 (n:1,100–4,500), eosinophil: 30 (n:50–550), Hb: 12g/dl, PLT: 207.000 (n: 150.000–350.000), INR: 1 (n), and normal electrolyte level were detected.

Serological tests (Cytomegalovirus, Epstein–Barr, human immunodeficiency virus, hepatitis a, b, and c, toxoplasma, HSV, and rubella) and autoimmune hepatitis markers (antinuclear antibody, "liver-kidney" microsomal antibody type-1, "anti-smooth muscle" antibody, "anti-soluble liver" antibody, and "anti-double strain" DNA) that have performed to make the differential diagnosis of liver enzyme elevation were found negative. Leukocytosis, neutrophil dominance, neutrophil hypersegmentation, anisocytosis, and poikilocytosis were detected in the peripheral spread. Serum ceruloplasmin, IG G-A-M, and serum copper levels were normal. There was no reproduction in blood, urine, and throat cultures. Except for grade 1 hepatosteatosis and a decrease in kidney dimensions, no pathological findings were determined in abdominal imaging. Reactive lymph nodes were seen in two different regions in the cutaneous USG. A skin punch biopsy was



Figure-1. Facial edema and extensive maculopapular rash

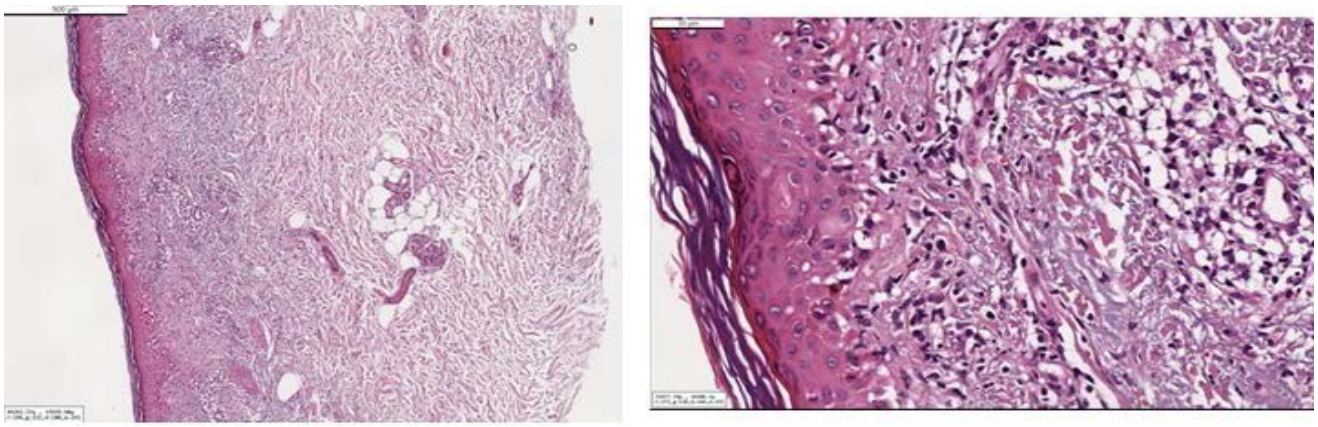


Figure-2. Microscopically, the presence of inflammatory cells containing eosinophil leukocytes in the dermis, superficial dermis in the perivascular area, compatible with a drug reaction

performed from the patient's maculopapular rash. The pathology result was interpreted as a drug reaction (Figure-1 and 2).

A scoring system was applied to the patient for the diagnosis of DRESS syndrome. In the scoring system, body temperature is higher than 38.5°C, lymphadenopathy greater than 1 cm in two different regions (inguinal and cervical), and a rash covering more than 50% of body surface area, facial edema+purpura, drug rash findings in skin biopsies, elimination of the liver and kidney dysfunction and other alternative causes. DRESS syndrome secondary to the use of allopurinol was diagnosed. Allopurinol treatment was discontinued. Methyl prednisolone treatment was started at 40 mg/day. The patient's liver and creatinine levels decreased after steroid. Regression was detected in the body rash. The decrease in serum aminotransferase and creatinine values is shown in Table-1. After creatinine returned to basal rates, normalization of aminotransferase enzymes and rash regression, the cortico steroid dose was decreased gradually and discontinued and the patient was discharged.

Table-1. Laboratory findings

Periods	ALT IU/L	AST IU/L	ALP IU/L	GGT IU/L	CRE mg/dl	UREA mg/dl
When hospitalized *(23.10.2019)*	340	325	243	132	2,5	98
7th day of treatment *(30.10.2019)*	467	190	213	368	1,5	100
14th day of treatment *(06.11.2019)*	142	46	116	347	1,5	77
16th day of treatment *(08.11.2019)*	19	20	63	55	1,1	21

Discussion

As in our case, DRESS diagnosis is suspected in a patient who received new drug treatment in the previous 2–6 weeks and presents symptoms and findings such as skin rash (morbilliform or diffuse, confluent and infiltrated), enlarged lymph nodes, fever [38°-40°C (100-104°F)]), and facial edema. High-risk drugs that cause this syndrome include lamotrigine, phenytoin, allopurinol, sulfasalazine, sulfamethoxazole, vancomycin, dapsone, carbamazepine, and minocycline. To help clinicians while diagnosing

Table-2. DRESS scoring system

Features		Yes		No
Fever ≥38.5°C (101.3°F)		0		–1
Enlarged lymph nodes (>1 cm, at least two sites)		1		0
Eosinophylia: >700 or >%10	(leucopenia)	1	2	0
Atypical lymphocytes		1		0
Skin rash extent >50% of body		1		0
Skin rash (at least two the following: edema, infiltration, purpura, and scaling)		1		0
Skin biopsy suggesting DRESS		–1		0
Internal organ involvement: 1	2 or more	1	2	0
Resolution in more than 15 days		0		–2
At least three biological investigations done and negative to exclude the alternative diagnosis (blood culture, ANA, hepatitis virus presence, mycoplasma, and chlamydia)		1		0

Final score <2: no, 2-3: possible, 4-5: probable, and >5: definite

DRESS or making differential diagnoses, the registry of severe cutaneous adverse reaction has developed a scoring system based on clinical characteristics, the extent of skin involvement, organ involvement, and clinical course (9). DRESS is classified as definite, probable, and possible (Table-2).

Rarely, DRESS could be diagnosed without "d" (no drug cause), without "r" (there was no rash in 2 of 176 cases in literature), without "e" (eosinophilia was not present in 10%–50% of the cases), and even without systemic symptoms (9).

Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN) which is considered in the differential diagnosis starts 4–28 days after exposure to the medicine. More than 90% of SJS/TEN cases include at least two sites: erosions and severe mucosal involvement with hemorrhage, whereas mucosal involvement is seen in 50% of patients with DRESS, generally includes one region (mostly the mouth or pharynx), and does not develop erosion. Eosinophilia and atypical lymphocytosis are not observed in SJS/TEN, whereas leukopenia is common and lymphopenia is almost constant.

With DRESS, fever, rash, lymphadenopathy, and abnormal liver enzymes, it can imitate adults still a disease, but generally, eosinophilia is not present in the still disease. Besides, DRESS typically is seen 2–6 weeks after exposure to suspected drugs that cause this syndrome, and atypical lymphocytosis is more likely to be seen than granulocytosis. For this patient, differential diagnosis was made by not presenting arthritis and arthralgia, symptoms occurring two weeks after drug use, rash different from STILL syndrome (salmon color and non-pruritic macular and maculopapular rash on body or extremities in fever periods). The pathology result of skin biopsy was interpreted as a drug reaction. For DRESS baseline treatment, cutting responsible drug is recommended. In addition, we recommend not to use new drugs to patients with ongoing DRESS and DRESS suspected patients.

Medium or high-dose corticosteroid treatment is recommended when the liver (three or more times higher values of transaminases) and kidney (1.5 times higher base creatinine levels, hematuria, proteinuria) involvement is present (e.g., 0.5–2 mg prednisolone or prednisolone equivalent). Systemic steroids are administered until normalization of laboratory parameters and patient's clinical wellness is provided and treatment is gradually reduced for 8–12 weeks. A faster reduction may cause recurrence. For the patient, normalization of the laboratory parameters and patient's clinical wellness is seen after steroid treatment. Cyclosporine could be a second step treatment for patients having DRESS and severe organ involvement, and there was no response to corticosteroids. There are several reports on the rapid response of patients with DRESS with organ involvement with oral cyclosporine treatment (10,11). Intra venous immunoglobulins (IVIGs) are useful for some patients and not for the others (12,13). IVIG treatment is not recommended while waiting for preferable evidence. In this case, DRESS syndrome secondary to exposure to allopurinol which is frequently used in first step health services is presented. DRESS is suspected when maculopapular rash developed, especially after the drug use, and forwarding patients to the upper center should be considered for systemic steroid treatment.

Conflict of Interest

The authors declare that they have no conflict of interests.

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