

A Rare Cause of Drug-Induced Skin Rash and Eosinophilia

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ABSTRACT

Allopurinol is a well-known drug to treat hyperuricemia in patients with chronic kidney disease, gout, or tumor lysis syndrome. The most common side effects are nausea, vomiting, elevated liver enzyme, pancreatitis, and skin rashes. Drug reaction with eosinophilic and systemic symptoms (DRESS) syndrome is a rare but life-threatening complication of allopurinol treatment. Here, we present a 60-year-old male patient admitted with skin rashes, stomatitis, dyspnea, jaundice, elevated liver enzymes, acute renal failure, and eosinophilia, who was diagnosed with allopurinol-related DRESS syndrome.

Keywords: Eosinophilia, allopurinol, nephritis, DRESS syndrome

ÖZ

İlacı bağılı cilt döküntüsü ve eozinofilinin nadir bir nedeni

Allopurinol kronik böbrek hastalığı, gut ya da tümör lizis sendromunda hiperürisimi tedavisinde kullanılan iyi bilinen bir ilaçtır. En yaygın yan etkileri olarak bulantı, kusma, karaciğer enzimlerinde yükselme, pankreatit ve deri döküntüsü görülmektedir. Allopurinol tedavisinin nadir görülen ancak yaşamı tehdit eden bir yan etkisi olarak eozinofili ve sistemik semptomların eşlik ettiği ilaç reaksiyonu (DRESS) sendromu görülebilir. Biz bu vaka takdiminde deri döküntüleri, stomatit, solunum güçlüğü, sarılık, yükselmiş karaciğer enzimleri, akut böbrek yetmezliği ve eozinofili belirtileriyle yatırılan allopurinol ile ilişkili DRESS sendromu tanısı konmuş 60 yaşında bir erkek hastayı sunacağız.

Anahtar kelimeler: Eozinofili, allopurinol, nefrit, DRESS sendromu

Introduction

Allopurinol acts by xanthine oxidase inhibition leading to decreased production of uric acid. It is commonly prescribed for gout or hyperuricemia related to different etiologies. During allopurinol therapy, patients may suffer from gastrointestinal symptoms including nausea, vomiting, diarrhea, and dyspepsia (1).

Less frequently, skin lesions like urticaria, Stevens-Johnson syndrome, and drug-related lupus erythematosus may be observed (2). Drug reaction with eosinophilic and systemic symptoms (DRESS) syndrome is an extremely infrequent skin disorder related to drug use. It is usually seen at 2-6 weeks of treatment; however, it may still occur in the 3rd month of therapy (3). Diagnostic criteria of DRESS syndrome are shown in Table 1. A 60-year-old male patient with allopurinol-induced DRESS syndrome is presented.

Case Report

A 60-year-old male with a history of hypertension and stage-3 chronic kidney disease admitted with maculopapular skin rash, dyspnea, jaundice, and fever after initiation of allopurinol therapy for gout arthritis 3 weeks previously. He admitted to the clinic with acute tubulointerstitial nephritis, toxic hepatitis, and acute pancreatitis, suggesting allopurinol-induced DRESS syndrome. On physical examination, he had scleral icterus, maculopapular rash, ulceration of the oropharynx and edema of the lip (Figure 1). No evident lymphadenomegaly was observed on physical examination.

Laboratory examination showed urea=210mg/dl, creatinine=6.7 mg/dl, AST=31 IU/L, ALT=156 IU/L, ALP=534 U/L, GGT=458 U/L, total bilirubin=8.3 mg/dl, direct bilirubin=7.7 mg/dl, total protein 4.5 g/dl, albumin=2.4 g/dl, Hgb=9.1 g/dl, Wbc=9300, eosinophils 2500,



Figure 1: Allopurinol related skin rashes (Dress syndrome)

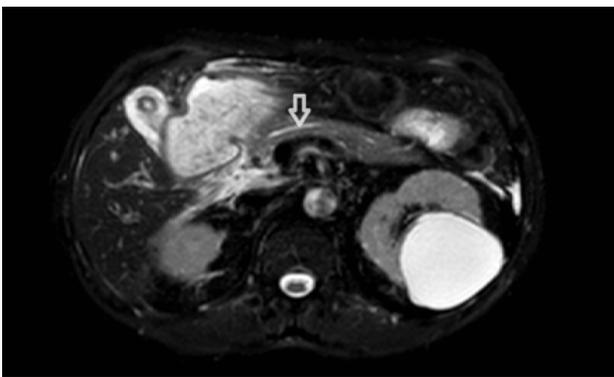


Figure 2: Abdoman MRI examination showing dilated pancreatic duct

amylase=400 U/L, lipase=600 U/L. He had no abnormal finding in ultrasonographic and MRI examination except a dilated pancreatic duct (Figure 2). Blood smear analysis indicated lymphocytosis. No remarkable findings were determined in urinalysis and posteroanterior lung graphy.

The diagnosis of DRESS syndrome based on medical history, laboratory analysis and physical examination findings is summarized in Table 1; steroid therapy was initiated. The

patient underwent hemodialysis for oligoanuric renal failure. Skin rash and intraoral lesions were responding well to steroid therapy on the 2nd day. On the 8th day of therapy, laboratory abnormalities including increased bilirubin, creatinine, ALT, amylase, and lipase levels had resolved.

Discussion

Allopurinol is not only a widely-used drug for hyperuricemia but also has beneficial effects on proteinuria and blood pressure levels (1). As the number of patients using allopurinol is increasing, side effects of the drug can be observed more frequently. DRESS syndrome is a rare drug hypersensitivity reaction characterized by a clinical picture and laboratory abnormalities defined by Bocquet et al. (4) (Table 1).

The most common drugs related to DRESS syndrome are anticonvulsants, including phenytoin, carbamazepine, and phenobarbital (5). Intolerance to allopurinol can be as high as 10%; however; it is rarely associated with DRESS syndrome with a frequency of less than 0.4% of all allopurinol users (6). Allopurinol-induced DRESS syndrome is a kind of delayed allergic reaction that is usually observed 4-6 weeks after treatment. Genetic and immunologic factors and infectious agents like Human Herpes Virus type 6 are implicated in DRESS syndrome (3). Oxypurinol, a metabolite of allopurinol, plays a key role in the pathogenesis of allopurinol-related DRESS syndrome due to the accumulation of this metabolite especially in patients with renal insufficiency (7).

The presenting feature of the syndrome is skin rash followed by eosinophilia, lymphadenopathy, and hepatic involvement (3). Compared to toxic epidermal necrolysis, which is characterized by hemorrhagic mucocutaneous involvement, DRESS syndrome presents with maculopapular rash accompanied by exfoliative dermatitis and edema in the upper extremities, abdomen, and face as seen in our case (1).

Table 1: Diagnostic criterias of Drug Rash with Eosinophilia and Systemic Symptoms

Cutaneous drug reaction	Usually 2 to 4 weeks of drug use
Hematologic abnormalities	Eosinophils $\geq 1.5 \times 10^9/L$ or presence of atypical lymphocytes
Systemic involvement	Adenopathies ≥ 2 cm in diameter hepatitis (liver transaminase ≥ 2 UL N) interstitial nephritis interstitial pneumonitis carditis

ULN: upper limit of normal

The discontinuation of drugs is of vital importance in the management of DRESS syndrome; however, patients who are unresponsive to the withdrawal of the drug may require steroid therapy, which leads to a gradual improvement of eosinophilia and skin rashes followed by recovery of other clinical conditions like hepatitis or nephritis (8). Hepatic involvement is considered as a major cause of morbidity in DRESS syndrome (1). In rare cases cardiovascular disorders including myocarditis, pericarditis, or arrhythmias may result in death. The mortality rate of this disorder may reach up to 10% (4).

DRESS is a rare but severe drug reaction with fatal consequences. Physicians should consider DRESS syndrome in patients with skin rash and eosinophilia with a short-term

history of allopurinol use. Understanding the exact frequency and pathogenic mechanism of the disease may help to establish preventive strategies and to increase physicians' awareness of DRESS syndrome.

Contribution Categories	Name of Author
Follow up of the case	H.M., E.S., C.H., N.G.
Literature review	O.S., F.P., E.G., H.S., A.E.A.
Manuscript writing	A.E.A., N.G., O.S., H.M., F.P.
Manuscript review and revision	N.G., A.E.A., H.S., E.S., C.H.

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