DRESS syndrome associated with allopurinol

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ABSTRACT

Introduction: DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a severe drug reaction with an estimated mortality of up to 10% largely due to multi-organ dysfunction. Diagnosis is challenging because the extent of skin involvement does not always correlate with the extent of internal organ involvement and therefore early recognition of symptoms is vital to minimize morbidity and mortality. Management involves prompt cessation of the culprit drug, administration of corticosteroids and supportive treatment.

Case Report: We report a case of an 87-year-old female with medical history significant for stage five chronic kidney disease, recently started on allopurinol for gout presented with dizziness, skin rash and eosinophilia which rapidly progressed to shock state followed by altered mentation, worsening renal failure, severe metabolic acidosis, deranged liver enzymes and gastrointestinal bleed requiring blood transfusion.

Conclusion: Allopurinol is commonly used in clinical practice for the treatment of symptomatic hyperuricemia and gout. It has been associated with DRESS syndrome especially when used indiscriminately.
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Introduction: DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a severe drug reaction with an estimated mortality of up to 10% largely due to multi-organ dysfunction. Diagnosis is challenging because the extent of skin involvement does not always correlate with the extent of internal organ involvement and therefore early recognition of symptoms is vital to minimize morbidity and mortality. Management involves prompt cessation of the culprit drug, administration of corticosteroids and supportive treatment. Case report: We report a case of an 87-year-old female with medical history significant for stage five chronic kidney disease, recently started on allopurinol for gout presented with dizziness, skin rash and eosinophilia which rapidly progressed to shock state followed by altered mentation, worsening renal failure, severe metabolic acidosis, deranged liver enzymes and gastrointestinal bleed requiring blood transfusion. Conclusion: Allopurinol is commonly used in clinical practice for the treatment of symptomatic hyperuricemia and gout. It has been associated with DRESS syndrome especially when used indiscriminately.

Keywords: DRESS syndrome, Allopurinol, Multi-organ failure

INTRODUCTION

The drug rash with eosinophilia and systemic symptom (DRESS) is a severe adverse drug reaction characterized by fever, rash, lymphadenopathy, hematologic abnormalities (including eosinophilia and atypical lymphocytosis) and multi-organ dysfunction. Allopurinol, a commonly used drug for the treatment of gout and other complications of hyperuricemia is documented as one of the drugs associated with DRESS syndrome. In this report, we present a patient with recent exposure to allopurinol and multi-organ failure typical of DRESS syndrome.

CASE REPORT

An 87-year-old African-American female with past medical history of hypertension, gout, chronic kidney disease stage five, coronary artery disease, and ischemic stroke with no residual neurological deficit presented with dizziness of one day duration and skin rash (Figure 1) for 1 week. There was no history of allergy or sick contacts. The patient’s medications included aspirin, allopurinol 300 mg/day started about five weeks ago for gout treatment, colchicine, and metoprolol. Her family and social history were noncontributory. Vitals signs were as follows: temperature 96.9 °F, pulse rate 96/min, respiratory rate 18/min, blood pressure 104/57 mmHg, SaO2 97%. Physical examination was remarkable for
diffuse pruritic erythematous papular rash on trunk, bilateral 2+ pitting edema and morbid obesity. The rest of the physical examination including heart, lung, abdomen, nervous system, and rectal examinations were unremarkable. Laboratory examinations were remarkable for (normal range is given in brackets) white blood cell count 7.7x10³/μL (4.5x10³–1.1x10⁴/μL), 23.6% eosinophils (0–7.5%), hematocrit 33.7 (36–46%), platelet count of 106x10³/μL (130x10³–400x10³/μL), blood urea nitrogen (BUN) 74 mg/dL (8–20 mg/dL), creatinine 7.4 mg/dL (0.4–1.3 mg/dL), serum bicarbonate 18 mmol/L (22–32 mmol/L) and an anion gap of 8. Liver function tests and coagulation profile were normal at presentation. Urinalysis was also normal. Immunological test results were negative for anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies (cANCA and pANCA). Rapid plasma reagin (RPR), hepatitis B surface antigen, and hepatitis C antibody were negative. Complement (C3) level was low at 37 mg/dL (79–152 mg/dL). X-ray of chest was normal and computed tomography (CT) scan of head revealed remote right cerebellar and right parietal infarcts along with ischemic white matter and intracranial atherosclerosis. Electrocardiography showed normal sinus rhythm at 92 bpm, echocardiogram showed normal left ventricular function with ejection fraction of 55–60%, aortic valve calcification. Carotid Doppler was negative.

Within 48 hours, the patient developed hypotension (89/59 mmHg) tachycardia (105 beats per minute) and tachypnea (26 breaths per minute), drug hypersensitivity was suspected, allopurinol was discontinued, corticosteroids administered (hydrocortisone 50 mg IV every 8 hr) and IV fluids (normal saline) given to stabilize blood pressure. The patient later developed confusion and unresponsiveness (repeat CT scan of head showed no new changes and lumbar puncture was unremarkable). There was worsening of pre-existing renal failure with severe metabolic acidosis (BUN 84 mg/dL (8–20 mg/dL), creatinine 9 mg/dL (0.4–1.3 mg/dL), arterial pH 7.06 (7.35–7.45) and serum bicarbonate 6.5 mmol/L) and hemodialysis was started. Other laboratory abnormalities were as follows: aspartate aminotransferase (AST) 391 IU/L (15–41 IU/L), alanine aminotransferase (ALT) 328 IU/L (17–63 IU/L), serum amylase 244 U/L (28–100 U/L), serum lipase 215 U/L (22–51 U/L) and serum lactate 33 mg/dL (4.5–14 mg/dL). She later developed coffee ground vomitus with a drop in hematocrit to 18.7% (36–46%). Two units of packed red cells were transfused and hematocrit stabilized at about 24–25%. Septic work-up was done and was negative.

During the following week, her mental status improved, vitals stabilized, liver enzymes, amylase/lipase, lactate levels normalized and eosinophilia resolved. The skin rash became hyperpigmented and desquamated with clear, fluid-filled vesicles also noticed in some areas. Skin biopsy showed interface dermatitis with separation of the dermis-epidermal junction (Figure 2A–B). She was later discharged and continued on intermittent hemodialysis for end-stage renal failure.
DISCUSSION

DRESS syndrome a type-IV delayed hypersensitivity reaction is a severe and potentially life-threatening drug induced reaction characterized by severe skin rash, fever, lymph node enlargement, hematologic derangements (including eosinophilia or mononucleosis like atypical lymphocytes) and internal organ involvement—most commonly the liver and, to a lesser extent, the kidneys, lungs, and brain [1].

It typically has long latency period (1–8 weeks) after initiating the culprit drug and symptoms may persist or even worsen after discontinuing the drug as seen in our patient [1, 2]. The rash manifests as a diffuse erythematous eruption (morbilliform rash) on the face, upper trunk, and upper extremities, usually accompanied by fever, facial and periorbital edema. The extent of skin involvement does not always correlate with the severity of internal organ dysfunction. Lesions may later become vesicular or exfoliated [2]. Desquamation/scaling may occur with healing.

It has an estimated incidence of 1 in 1000 to 1 in 10,000 drug exposures and mortality rate of about 10% due to visceral organ compromise especially liver failure [3, 4]. Infectious complications have also been described especially in patients treated with corticosteroids.

Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulfonamides are the most common causes of DRESS syndrome but a number of other drugs including lamotrigine, allopurinol, non-steroidal anti-inflammatory drugs, captopril, calcium channel blockers, mexiletine, fluoxetine, dapsone, terbinafine, anti-inflammatory drugs, captopril, calcium channel blockers, mexiletine, fluoxetine, dapsone, terbinafine, metronidazole, minocycline and antiretroviral drugs have also been implicated [4].

Allopurinol, a hypoxanthine analog has been widely used in clinical practice over decades for the treatment of hyperuricemia and gout [5]. It is usually well-tolerated with no adverse effects in most cases, but is by no means a benign drug. About 2% of the treated patients develop a skin rash, and some may experience severe drug hypersensitivity reaction [5]. A multinational study (EuroSCAR) revealed that allopurinol is the drug most commonly associated with Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) in Europe and Israel [6]. In a Korean study involving 38 patients with DRESS syndrome, allopurinol was found to be responsible for 5.3% of the cases [7].

The pathogenesis of DRESS syndrome is not fully known but different factors have been postulated including immunological factors, genetic factors (risk as high as 25% if first degree relative had the syndrome) and drug detoxification pathways [8]. In a prospective study involving 40 DRESS patients, Epstein-Barr virus, human herpesvirus 6 and 7 reactivations were found in 76% of the cases. The culprit drugs are able to trigger these viral reactivations that in turn induce a pathogenic antiviral CD8 immune response [9].

A possible mechanism may be allopurinol or oxypurinol (major metabolite of allopurinol) hypersensitivity and immune complex formation resulting in vasculitis [10]. The accumulation of oxypurinol especially with reduced renal clearance leads to a greater risk of developing DRESS syndrome. Multiple studies have shown that advanced age, underlying renal impairment, higher doses, and concomitant use of thiazide diuretics are potential risk factors for developing allopurinol-induced DRESS syndrome [11].

Published data from the French pharmacovigilance center showed that allopurinol was associated with more severe forms of DRESS syndrome and mortality rate much higher than cases due to other drugs [12].

Diagnosis is based on clinical and laboratory findings and although skin biopsy may support diagnosis, it is usually non-specific. It may show a lymphocytic infiltrate in the papillary layer of the dermis, which may also contain eosinophils (generally denser than in other drug reactions) [2]. The main stay of therapy in DRESS syndrome involves the immediate cessation of the culprit drug. In cases where the culprit drug is not obvious, clinical judgment must be used to select which medication to discontinue. Patch testing or lymphocyte transformation tests used to detect delayed hypersensitivity may be helpful in identifying the drug [13].

Corticosteroids are currently being used with some success, but their role remains controversial due to lack of controlled clinical trials supporting their use [14].

At present, the only indications for allopurinol use are symptomatic hyperuricemia (i.e., gouty arthritis, urate nephropathy and nephrolithiasis) and prophylaxis of urate nephropathy during chemotherapy in neoplastic diseases. However, a Medline literature review of 101 reported cases of allopurinol hypersensitivity syndrome revealed that in 80% of cases allopurinol was administered primarily for asymptomatic hyperuricemia and most patients received excessive doses [14]. Therefore, it is imperative that allopurinol be administered only when indicated and in the appropriate dose.

The patient described in this case report is very old lady with multiple comorbidities started about five weeks prior to presentation for the treatment of gout and presented with rash, eosinophilia and multi-organ failure. Differential diagnoses included drug hypersensitivity reaction (DRESS syndrome), Churg–Strauss syndrome (CSS), idiopathic hypereosinophilic syndrome and eosinophilic leukemia [14]. Churg–Strauss syndrome was excluded as the patient had no history of asthma, allergic rhinitis, or sinus abnormalities and P-ANCA was negative. Idiopathic hypereosinophilic syndrome was ruled out as it is a diagnosis of exclusion, typically affects men aged 20–50 years, and requires persistence of eosinophilia for at least six months. Eosinophilic leukemia was also excluded with the absence of immature eosinophils in peripheral smear. Of all the medications taken by the patient, the only potential trigger documented...
in literature was allopurinol. This medication was immediately discontinued and IV corticosteroids started along with other supportive measures. The patient showed progressive improvement afterwards.

CONCLUSION

Allopurinol is a drug commonly used in medical practice but its indiscriminate use can lead to severe consequences. DRESS syndrome is a severe drug reaction that has been associated with allopurinol. Recent use of this drug coupled with the presence of skin rash, eosinophilia and multi-organ dysfunction should raise clinical suspicion of DRESS syndrome. Prompt cessation of the drug, use of corticosteroids and other supportive measures has shown to improve outcomes.

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