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Febuxostat hypersensitivity: another cause of DRESS syndrome in chronic kidney disease?

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Summary
Febuxostat is a xanthine oxidase inhibitor that during the last years has successfully replaced allopurinol treatment in patients with chronic kidney disease (CKD) and hyperuricemia. Several adverse events have been observed during therapy with febuxostat. DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome induced by febuxostat has been poorly described, mainly in patient with CKD who previously developed allopurinol hypersensitivity syndrome. DRESS syndrome is characterized by manifold cutaneous reactions and systemic disorders with potential devastating consequences. The underlying pathogenetic mechanisms remain unidentified, though immune responses are often complicated. P-i concept can partially explain the phenomenon. The role of renal insufficiency appears to be crucial and further investigation is required. The present article describes the case of a CKD patient that developed febuxostat-related DRESS syndrome.

Introduction

Febuxostat is a selective inhibitor of xanthine oxidase and it is recommended as urate-lowering therapy in patients with chronic kidney disease. Among post-market adverse events of febuxostat, the most deleterious are hypersensitivity type cutaneous vasculitis (1), interstitial granulomatous reaction (2), rhabdomyolysis (3, 4), hepatitis (5) and severe neutropenia (6).

Herein we aim to report the case of a patient under febuxostat treatment that presented with fever, impaired liver function and hypersensitivity reaction with eosinophilia. According to the European RegiSCAR scale (7) the case was characterized as a "definite" Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, while the Naranjo Adverse Drug Reaction Probability Scale (8) illustrated febuxostat as the "probable" cause of the syndrome.

Case Report

A 62-years-old Caucasian male presented to our Emergency Department complaining of fever and a three-day history of generalized, erythematous, maculopapular rash without erosive lesions, accompanied with pruritus. No mucosal involvement was observed. The patient had a medical history of hyperuricemia, complicated with several gout episodes and deregulated hypertension, that had led to chronic kidney disease (GFR 52 ml/ min/ 1.73 m^2) due to hypertensive nephrosclerosis. He was under regular follow-up every three months. His medication included furosemide (40 mg/day), diltiazem hydrochloride (180 mg/day), clopidogrel (75 mg/day), ranitidine hydrochloride (150 mg/day) and moxonidine (0.4 mg/day). The patient received urate-lowering therapy with allopurinol (100 mg/day) that had been interrupted two months ago due to exfoliative dermatitis with eosinophilia and

poor uric acid control. After allopurinol discontinuation, the hematological profile had been normalized and dermatitis had resolved. Due to severe hyperuricemia (uric acid 12.6 mg/dL), allopurinol had been switched to febuxostat (80 mg/day) two weeks before symptoms arose.

On admittance, patient's vital signs were: blood pressure 110/80 mmHg, temperature up to 38.6 °C, pulse 105 beats per minute. The ECG showed sinus tachycardia. During physical examination neither lymphadenopathy nor other pathological findings were observed apart from a generalized, pruritic skin rush. Hematological examination revealed normochromic normocytic anemia (Hct 31.2% and Hb 9.7 mg/dL) and leucocytosis ($16.22 \times 10^9 L^{-1}$) with eosinophilia (41.8%, total count $6.8 \times 10^9 L^{-1}$). Further laboratory tests showed moderate acute liver injury (AST 148 mg/dL, ALT 107 mg/dL, γGT 830 mg/dL) with normal values of bilirubin, renal insufficiency (serum creatinine 1.78 mg/ dL, urea 86 mg/dL) without electrolyte disturbances (serum potassium 3.8 mg/dL, sodium 137 mg/dL and calcium 9.75 mg/dL), increase of C-reactive protein levels (5.38 mg/ dL, normal ranges 0-0.5 mg/dL) and Erythrocyte Sedimentation Rate of 98 during the first hour. The chest radiography and urine examination were normal. Thyroid hormones were within normal ranges too.

In order to exclude possible causes of eosinophilia and transaminasemia, several examinations were carried out. Immunological parameters such as ANA, c-ANCA, p-ANCA, ASMA, AMA, C3 and C4 levels, tumor markers, virological immune tests for EBV, CMV, HAV, HBV, HCV and HIV as well as Brucella melithensis, Toxoplasma Gondii and Echinococcus granulosus serological tests were negative. Furthermore, blood and urine cultures were collected but they were also negative. Stool microscopy had no evidence of parasitic infection and cultures were negative as well.

Liver or biliary tract diseases were also excluded since an abdominal ultrasound, computed tomography and magnetic resonance image scan revealed no pathological entities. The peripheral blood smear and bone marrow aspiration were negative for hypereosinophilic syndromes or other hematologic malignancies (**figure 1**).

Due to great suspicion of DRESS syndrome, febuxostat was discontinued and the patient received intravenous therapy with dimethindene maleate and methylprednisolone in an initial dose of 125 mg/dL twice daily followed by 40 mg/dL three times daily for a total period of ten days. Within four days, body temperature became normal. Meanwhile, skin rush became exfoliative (**figure 2**) and transaminase levels decreased gradually. The patient was released on the tenth day of hospitalization. After three months in total, transaminase and eosinophil levels were normalized.

Figure 1

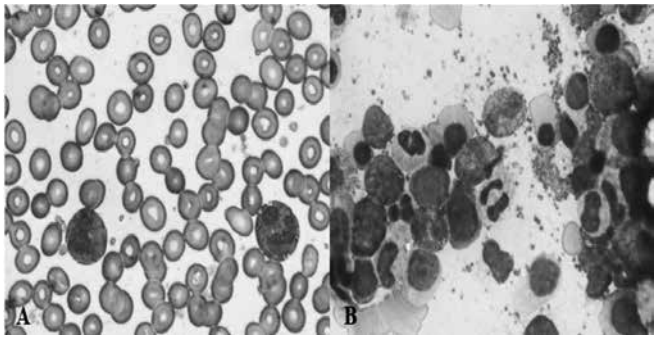
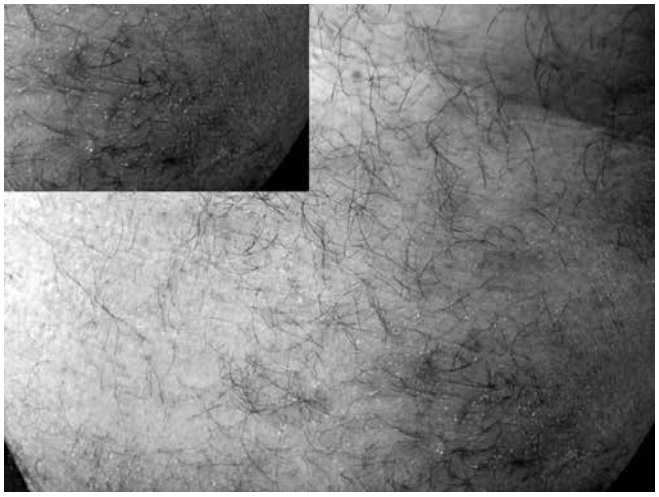


Figure 2



Discussion

Drug Rash (or Reaction) with Eosinophilia and Systemic Symptoms (DRESS) syndrome was first described in the 1950's by Chaiken et al (9), while in 1996 received its name by Bocquet et al (10) in an effort to clarify the vagueness of the terminology used to describe cutaneous drug reactions. Other similar nomenclature used for such reactions are drug-induced hypersensitivity syndrome, drug hypersensitivity syndrome or severe cutaneous adverse drug reactions (SCAR).

This syndrome represents a severe, potentially fatal, drug-induced hypersensitivity reaction. The estimated incidence ranges from 1 in 1,000 to 1 in 10,000 drug exposures without sex predilection (11), while adults are more affected than children (12). Its mortality has been calculated to 10 - 12% (13). The most frequent causative agents seem to be anticonvulsants, allopurinol (14) and sulfonamides (14). Other medication related to DRESS syndrome less frequently are dapsone (15), linezolide (16) and micocycline

(17). Cross-sensitivity among aromatic anticonvulsants in Chinese population has been referred to be almost 75% (18).

Apart from skin rash DRESS syndrome is characterized by fever, lymph node enlargement, hematologic disorders (eosinophilia, atypical lymphocytes, thrombocytopenia and lymphocytosis) and internal organ involvement, mainly liver but also kidneys, lungs, heart and pancreas (19). Systemic disorders partially come up as a result to eosinophilia. Eosinophils enter tissues and cause further damage by releasing toxic granule products or cytokines that may be involved in tissue remodeling and fibrosis (20). The reaction occurs within two to six weeks after drug initiation and may persist or even worsen upon drug discontinuation (21).

A plethora of pathogenetic mechanisms regarding DRESS syndrome have been proposed. Among them, the most important suggests an immunologically driven pathway. It seems that hypersensitivity induced by allopurinol is strongly associated with HLA-B*58:01 (22). In 2014, Yun J et al generated T cell lines that react to allopurinol (ALP) or oxypurinol (OXP) from HLA-B*58:01(+) and HLA-B*58:01(-) donors, and observed that ALP/OXP-specific T cells reacted immediately to the addition of the drugs and bypassed intracellular Ag processing, which is consistent with the "pharmacological interaction with immune receptors" (p-i) concept. They concluded that the drug-specific T cells are activated by OXP bound to HLA-B*58:01 through the p-i mechanism (23). Moreover, asymptomatic reactivation of chronically persistent viruses, such as Human Herpesvirus -6 and -7 (HHV-6/7), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), has been incriminated as possible pathogenetic mechanism. This reactivation leads to expansion of activated T lymphocytes in the blood, including both CD8+ and CD4 cells (22). Alternatively, it has also been suggested that predisposition to auto-immune disease may contribute to the development of a drug hypersensitivity syndrome (24).

Our patient presented with generalized rash, fever and systemic disorders such as severe eosinophilia and liver impairment. Several tests ruled out potential diseases: idiopathic eosinophilic syndrome, eosinophilic leukemia or other malignancies, parasitic infection or infection of hepatotropic viruses, Addison's disease or connective tissue disorders. As a result, DRESS syndrome due to febuxostat was considered probable.

In order to test our hypothesis, the RegiSCAR scoring system was used. This scale was designed to grade suspected cases of DRESS as "no" (score < 2), "possible" (score 2-3), "probable" (score 4-5), or "definite" (score > 5). DRESS is considered as "definite" in our case, given that other causes of febrile eruption with eosinophilia and liver involvement were excluded. Thus, our patient was classified as a "definite" case because of the presence of fever > 38 ^{o}C (0 points), eosinophils ≥ 1.5×10^{9} L^{-1} (2 points), skin involvement > 50% of body surface area (1 point), resolution past 15 days (0 points), internal organ involvement of liver (1 point) and exclusion of other possible causes (1 point). Furthermore, our patient's skin involvement, composed of maculopapular erythematous lesions, was consistent with the RegiSCAR description. According to Naranjo Adverse Drug Reaction Probability Scale (8), febuxostat was illustrated as the "probable" cause of the syndrome (score 5), even if alternative causes such as secondary allopurinol hypersensitivity reaction could have caused the events.

To our knowledge, there are only four possible cases of hypersensitivity syndrome due to febuxostat. All patients had previously experienced cutaneous reactions due to allopurinol hypersensitivity. In 2010, Mauck et al reported cross-sensitivity of allopurinol and febuxostat in a 44 years-old woman with chronic kidney disease (25). In 2012, Abeles AM described hypersensitivity due to febuxostat in a patient with moderate renal insufficiency that had previously developed allopurinol hypersensitivity syndrome (AHS) (26). Dore et al reported the case of an immunosuppressed patient with myopathy developing hypersensitivity syndrome in both combination of azathioprine-allopurinol and azathioprine-febuxostat (27). Recently, Lien and Logan referred another case of severe febuxostat - allopurinol cross reaction leading to DRESS syndrome in a 76-year-old woman with chronic kidney disease. The authors suggested a non-immunological mechanism related to the common pharmacological action of the drugs, inhibition of xanthine oxidase, as the possible cause of the syndrome (28). In a case series of thirteen patients with a history of allopurinol hypersensitivity syndrome who received febuxostat, one experienced a hypersensitivity type of cutaneous vasculitis (leukocytoclastic vasculitis) (1). The authors suggested careful dose escalation and close monitoring when febuxostat is prescribed in allopurinol-intolerant patients. Thus, there are indications that allopurinol and febuxostat share relative pathophysiological mechanisms leading to hypersensitivity syndromes. The fact that patients with history of AHS were excluded from phase III studies of febuxostat (26) suggests that further investigation needs to be conducted.

It is noteworthy that most patients experiencing cross-sensitivity of allopurinol and febuxostat suffered from chronic kidney disease. It is known that renal insufficiency represents an important risk factor of AHS since renal clearance of oxypurinol, the major metabolite of allopurinol, is directly correlated with glomerular filtration rate. As a result, serum half-life time of oxypurinol is prolonged leading to accumulation of oxypurinol in the serum of those patients (26). On the other hand, febuxostat is primarily metabolized in the liver while its metabolites are partially excreted to urine (29). Thus, in patients with chronic kidney disease, accumulation of febuxostat metabolites in serum could be a potential explanation of allopurinol-febuxostat cross sensitivity.

Conclusions

In April 2008, febuxostat obtained marketing approval from the European Medicines Agency as a new, promising urate-lowering therapy. It is widely used, particularly in patients with chronic kidney disease and pure uremic control. In these patients, hypersensitivity induced by febuxostat does exist, although it appears less frequently than allopurinol hypersensitivity syndrome. The precise mechanism remains unidentified. Cross-sensitivity between allopurinol and febuxostat may occur. We suggest that patients with renal insufficiency treated with febuxostat should be closely monitored especially when allopurinol intolerance pre-exists. Clinicians' awareness during febuxostat administration is necessary in order to identify systemic disorders of DRESS syndrome leading to potentially life-threatening consequences.

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