Pustular drug hypersensitivity syndrome due to allopurinol

Chaker Ben Salem, Wafa Saidi1, Sofiene Larif, Neila Fathallah, Raoudha Slim, Houssem Hmouda

Department of Pharmacology, Faculty of Medicine of Sousse, 1Department of Dermatology, Farhat Hached University Hospital, Tunisia

Received: 31-10-2014
Revised: 21-11-2014
Accepted: 22-12-2014

Correspondence to:
Dr. Chaker Ben Salem,
E-mail: bensalem.c@gmail.com

ABSTRACT

Allopurinol hypersensitivity syndrome (AHS) is a severe drug reaction. It is characterized by rash, fever, and internal organ involvement. It may present in different clinical forms. We present a case of acute generalized exanthematous pustulosis occurring as a manifestation of AHS.

KEY WORDS: Allopurinol, hypersensitivity syndrome, pustulosis

Introduction

Drug hypersensitivity syndrome (DHS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), is a severe drug reaction. It was first associated with the aromatic antiepileptic drugs. The syndrome can also be caused by other drugs, such as allopurinol, sulfonamides, beta-lactam antimicrobials, antidepressants, and nonsteroidal anti-inflammatory drugs. Allopurinol hypersensitivity syndrome (AHS) is characterized by rash, fever, and internal organ involvement. Acute generalized exanthematous pustulosis (AGEP) is a very rare manifestation of AHS.[1,2] We report a case of an exceptional presentation of AGEP as a manifestation of AHS.

Case Report

A 67-year-old male was admitted to the Dermatology Department with history of widespread skin eruption since 10 days. He was started on allopurinol (200 mg/day) for hyperuricemia 8 weeks earlier. He was pyrexial above 38.5° for a few days. He was on candesartan and aspirin since many years.

Clinical examination showed maculopapular eruptions involving trunk, arms and legs, as well as pinhead-sized follicular and nonfollicular pustules on patient’s face and trunk. Laboratory investigations revealed a white blood cell count of 13.2 × 10^9/L with atypical lymphocytes and hypereosinophilia (eosinophil count 1.9 × 10^9/L). Liver enzymes were increased: Aspartate aminotransferase 76 IU/L (reference range 3–40) and alanine aminotransferase 409 IU/L (3–45). Serum uric acid and renal function tests were normal. Viral serology showed previous infection for cytomegalovirus, but was negative for Epstein–Barr virus, hepatitis B, C, HIV, parvovirus B19, and human herpesvirus 6. Skin biopsy showed subcorneal spongiform pustules and some single scattered necrolytic keratinocyte [Figure 1]. The superficial dermis was edematous, with mixed inflammatory infiltration, including numerous neutrophils and rare eosinophils consistent with the diagnosis of AGEP. AHS was highly suspected, and allopurinol was withdrawn.

The patient improved markedly within 72 h on prednisone 30 mg daily (dose of 0.5 mg/kg body weight). He became afebrile, and skin eruption disappeared within a few days. After initiation of steroid therapy, exfoliation was observed in the involved skin areas. Full dose corticosteroid therapy was continued for two weeks, and tapered by 2.5 mg every 5–7 days, with a total duration of 3 months. Liver enzymes were within normal range in 3 weeks.

Causality assessment by the Naranjo probability scale showed that AHS had probable causal association with the adverse effect.[3] The patient was firmly instructed to avoid allopurinol in the future.

Discussion

Allopurinol hypersensitivity syndrome is a rare adverse reaction characterized by a spectrum of cutaneous reactions and...
systemic manifestations. AHS is more frequently associated with chronic renal insufficiency and concurrent use of thiazide diuretics. Symptoms generally begin 2–6 weeks after the initiation of therapy. Severe forms of AHS have been associated with high mortality.

The exact pathogenesis of this syndrome is yet unclear, but different hypotheses are proposed. It seems to be related to the accumulation of allopurinol or oxipurinol (a major metabolite of allopurinol) in patients with renal insufficiency. Immunological factors, genetic factors, and human herpes virus-type 6 are also implicated.

Cutaneous manifestations of hypersensitivity syndrome are heterogeneous, ranging from mild morbilliform exanthema to severe toxic epidermal necrolysis and Stevens–Johnson syndrome. Pustular-type DHS is rare. Patients with DHS develop AGEP-like pustules particularly in the early phase. Pustules in DHS differ from the typical pattern of AGEP in which pustules are more numerous and predominant in main body folds. Antiepileptics are the most frequently reported drugs causing pustular-type DHS.

We scored both the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria for DRESS and EuroSCAR AGEP score. The score was 7 for DRESS indicating a definite case and 5 for AGEP indicating a probable case. The clinical features which most differentiated DRESS from AGEP in our patient were the delayed onset (8 weeks), protracted course and multi-organ involvement.

An extensive literature search showed only two similar reports. The first case of AHS with generalized nonfollicular pustulosis was described in a 47-year-old man. The second is a 65-year-old man who developed AHS manifested as generalized follicular pustulosis mimicking AGEP. Our patient developed both follicular and nonfollicular pustules.

The exact mechanism of pustule formation in DHS has not been elucidated. Allopurinol directly inhibits the lymphocytes enzyme purine nucleoside phosphorylase and may affect certain components of the immune system with an alteration of CD4/CD8 rate. The concomitant release of several mediators from eosinophils and/or activation of neutrophils might be important for the clinical evolution of lesions, with appearance of pustules, or aggravation of skin detachment, as well as internal organ involvement in DRESS. A drug reaction leading to folliculitis and then pustule formation has also been proposed.

Allopurinol hypersensitivity syndrome may present with different clinical forms. Clinicians should be observant of cutaneous manifestations of hypersensitivity syndrome that may be a nonfollicular and/or follicular pustular eruption as well as the more commonly associated maculopapular rash or erythroderma.

References
1. Teo WL, Pang SM, Koh HY. Allopurinol hypersensitivity syndrome with acute generalized exanthematous pustulosis manifestations. Cutan Ocul Toxicol 2011;30:243-4.
2. Huang YC, Shih PY, Chin SY, Chiang YY. Allopurinol-induced drug rash with eosinophilia and systemic symptoms mimicking acute generalized exanthematous pustulosis. J Dermatol 2012;39:1077-8.
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
4. Camous X, Calbo S, Picard D, Musetta P. Drug reaction with eosinophilia and systemic symptoms: An update on pathogenesis. Curr Opin Immunol 2012;24:730-5.
5. Matsuda H, Saito K, Takayanagi Y, Okazaki K, Kashima K, Ishikawa K, et al. Pustular-type drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to carbamazepine with systemic muscle involvement. J Dermatol 2013;40:118-22.
6. Ben Salem C, Fathallah N, Saidi W, Jeddi C, Garhani N, Hmouda H, et al. Acute generalized exanthematous pustulosis as a manifestation of anticonvulsant hypersensitivity syndrome. Ann Pharmacother 2010;44:1681-2.