Case Report

Drug Eruptions Induced by Allopurinol Associated with HLA-B*5801

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ABSTRACT

Allopurinol, a drug commonly used for treating gout and hyperuricemia, is a frequent cause of drug eruptions. Recent investigations suggest that HLA-B*5801 allele is a very strong marker for allopurinol-induced cutaneous adverse drug reactions (cADRs). In this article we report two cases of allopurinol-induced drug eruptions in patients carrying the HLA-B*5801 allele and review the literature on the association between HLA-B*5801 and allopurinol-induced cADRs based on a MEDLINE and PubMed search

Key words: Allopurinol, drug eruptions, HLA-B*5801

INTRODUCTION

Allopurinol is a frequent cause of drug eruptions and studies have shown that patients carrying the HLA-B*5801 allele are at an increased risk of developing allopurinol-induced cADRs. We report two patients who presented to our department with drug eruptions temporally related to the ingestion of allopurinol which had been prescribed to treat chronic renal insufficiency. Both patients carried the HLA-B*5801 allele.

CASE REPORTS

Patient 1

A 73-year-old male was admitted to our department with a 8-day history of fever and diffuse erythema all over the body. The patient had been on allopurinol and benzbromarone (both uricosuric agents) because of chronic renal insufficiency as also on vildagliptin (an antidiabetic) and calcitriol for 1 month. The problem started with moderate grade fever, a mildly itchy generalized erythematous maculopapular rash and bilateral pedal edema. The red blood cell count was 3.93×10^{12}/L, uric acid was 540 μmol/L, urea 30.4 mmol/L, creatinine 475 μmol/L, creatine kinase (CK) 55 U/L, CK-MB 55 U/L, lactate dehydrogenase (LD) 343 U/L, and myoglobin 200 ng/ml. On the adverse drug reactions (ADRs) probability scale,[1] the score was 7.

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Patient 2

A 49-year-old male was admitted with a 10-day history of fever and generalized itching and erythema. The patient had chronic renal insufficiency for the past 10 years for which he had been taking amlodipine, valsartan, and some Chinese medicines; allopurinol was added 1 month prior to presentation. Twenty days after initiation of allopurinol, the patient developed fever, facial edema, and generalized itching, erythema and scaling [Figure 1]. On laboratory evaluation, there was leukocytosis (total white cell count, 17.6×10^9/L) a red blood cell count of 3.84×10^{12}/L, uric acid levels of 509 μmol/L, urea levels of 15.9 mmol/L, creatinine of 205 μmol/L, alanine aminotransferase (ALT) of 131U/L, and albumin of 33.6 g/L. The case got a score of 9 according to the ADRs probability scale.[1]

In both the patients serologic HLA-B*5801 typing performed by the pyrosequencing method using a

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PG5801 DNA detection kit (Takara-Gene, Dalian, China, D9081) was found positive. This was further confirmed by polymerase chain reaction using sequence based typing (PCR-SBT) done at Beijing Genomics Institution, Shenzhen, China [Table 1]. The two cases were finally diagnosed as allopurinol-induced exfoliative dermatitis in patients carrying the HLA-B*5801 allele.

After stopping allopurinol, the patients were treated with methylprednisolone injections, 40 mg/day along with compound glycyrrhizin injection and symptomatic treatment. Both patients responded with the clinical symptoms disappearing in 1-2 weeks.

DISCUSSION

Drug eruption is an adverse drug reaction which is difficult to predict from the known pharmacology of the drug.[2] The risk for development of a drug eruption is determined by several factors including age and gender of the patient and the dose and the nature of the medication itself. Allopurinol, a commonly prescribed medication for gout and hyperuricemia, is a frequent cause of severe cutaneous adverse reactions (SCARs), which include drug hypersensitivity syndrome, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).[3] Recent investigations suggest that HLA-B*5801 is a very strong marker for allopurinol-induced cutaneous adverse drug reactions, especially severe cutaneous adverse reactions (SCARs)[4-12] [Table 2]. A total of 10 studies with 219 patients with allopurinol-induced cutaneous adverse drug reactions were identified, and 193 (87.3%) of these patients were found to carry the HLA-B*5801 allele. The figure was even higher in patients who had developed severe cutaneous adverse reactions (SCARs). In contrast, the presence of this allele was lower (13.3%) in healthy population controls, in patients who had SCARs induced by other medications, and patients who were allopurinol tolerant. Lee *et al*.[4] in a study to determine the presence of HLA-B*5801 allele in the immediate family members of a HLA-B*5801 allele positive male patient who experienced allopurinol-induced Stevens-Johnson syndrome, found his brother who had taken allopurinol for 10 years for gouty arthritis to be HLA-B*5801 allele negative. Interestingly, eight patients who developed milder cutaneous adverse drug reactions such as erythema multiforme major or a maculopapular rash did not carry the allele. Even though our two patients

Table 1: The polymerase chain reaction-sequence-based typing results from Beijing Genomics Institution

Patient	HLA-B*
1	40:01; 58:01
2	40:01; 58:01

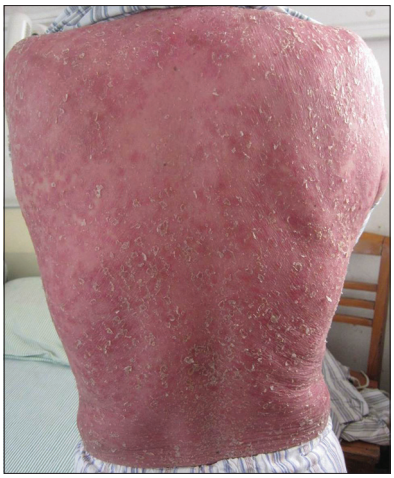

Figure 1: The lesions of patient 2. Diffuse erythema and scaling on his back

Table 2: Summary of studies of HLA-B*5801 and drug eruptions

Years	Source	Number of cADRs patients/number of patients carried HLA-B*5801/percentage	Number of SCAR induced by other medicines/ number of subjects carried HLA-B*5801/percentage	Number of Allopurinol tolerant subjects/number of subjects carried HLA-B*5801/percentage	Number of healthy subjects/number of subjects carried HLA-B*5801/percentage
2013	Han China (our cases)	2/2/100			
2013	Han China	1/1/100		1/0/0	3/1/33.3
2012	Han China	38/38/100		63/7/11.1	572/80/14.0
2012	Han China	20/19/95		30/4/13.0	
2011	Korea	16/9/56.2		432/41/9.5	
2011	Korea	25/23/92		57/6/10.5	
2009	Thai	27/27/100		54/7/13.0	
2008	Japanese	10/4/40	48/1/2.1		
2008	European	31/19/61			62/20/32.0
2005	Han China	51/51/100		135/20/15.0	93/19/20.0

manifested exfoliative dermatitis and not severe cutaneous adverse reactions (SCARs), both carried the HLA-B*5801 allele.

There is an ethnic variation in the frequency at which HLA-B*5801 allele is present in patients who develop allopurinol-induced cutaneous adverse drug reactions. Tassaneeyakul *et al*.[11] noted that all 27 Thai patients who developed allopurinol-induced drug reactions carried the HLA-B*5801 allele. Similarly, 99.1% of the 112 Chinese Han patients who developed allopurinol-induced drug reaction carried the HLA-B*5801 and only 1 patient who had developed erythema multiforme major did not carry the allele. In contrast, the frequency of the HLA-B*5801 allele in patients with allopurinol-induced cutaneous adverse drug reactions is much lower in the Europeans (55-61%) and the Japanese (40%).

There are anecdotal reports of this allele being present in patients who developed Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) to other drugs as well. Kaniwa *et al*.[10] observed that of the five carriers of HLA-B*5801 allele in their 58 patients of SJS/TEN patients, 1 patient had not received allopurinol.

Based on these studies, we believe that a screening test for the HLA-B*5801 allele is important when patients need to take allopurinol, as it should effectively reduce the risk for allopurinol-induced cutaneous adverse drug reactions, particularly severe cutaneous adverse reactions (SCARs).

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