Acute Generalized Exanthematous Pustulosis from Allopurinol with Positive HLA-B*58:01: A Case Report

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ABSTRACT:
The HLA-B*58:01 allele is associated with severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and maculopapular eruption. We describe the case of a 58-year-old male who developed non-follicular pustules on the back and flank, along with erythematous papules on the trunk and both upper and lower extremities after taking allopurinol for 2 weeks. Histopathological evaluation confirmed a diagnosis of acute generalized exanthematous pustulosis (AGEP). Genetic testing revealed HLA-B*58:01 positivity. To our knowledge, this is the first reported case of AGEP associated with HLA-B*58:01 in the context of allopurinol-induced hypersensitivity.
Key words: Acute Generalized Exanthematous Pustulosis, HLA-B*58:01, Allopurinol Hypersensitivity

Case Report

A 58-year-old Thai man presented with a 14-day history of fever and confluent, discrete follicular papules affecting the entire body. Six weeks prior to admission, he had been evaluated for left metatarsal pain and diagnosed with gout, for which he was prescribed colchicine and allopurinol.

The patient's medical history included hypertension and arrhythmia, for which he was taking amlodipine and hydralazine. He reported no known drug allergies and no personal or family history of psoriasis. Two weeks after starting allopurinol, a rash first appeared on the face and neck, progressively spreading to the trunk, arms, and thighs. Associated symptoms included fever and fatigue.

On clinical examination, the patient had confluent, discrete erythematous papules on the trunk, upper, and lower extremities, with non-follicular pustules on the back and flank. Bilaterally localized, ill-defined, non-blanchable erythematous-to-purpuric patches were noted on the lower extremities (Figure 1). The mucous membranes, hair, and nails were unaffected. Vital signs were stable except for a temperature of 38.0°C. A skin punch biopsy on the back revealed a slightly acanthotic epidermis with hyperkeratosis and parakeratosis. Large aggregates of neutrophils were found in the stratum corneum, accompanied by reduced the granular cell layers and spongiosis. The dermis showed superficial perivascular lymphocytic infiltration with scattered neutrophils and no evidence of eosinophilic component. The histopathologic differential diagnosis included both acute generalized exanthematous pustulosis (AGEP) and pustular psoriasis.

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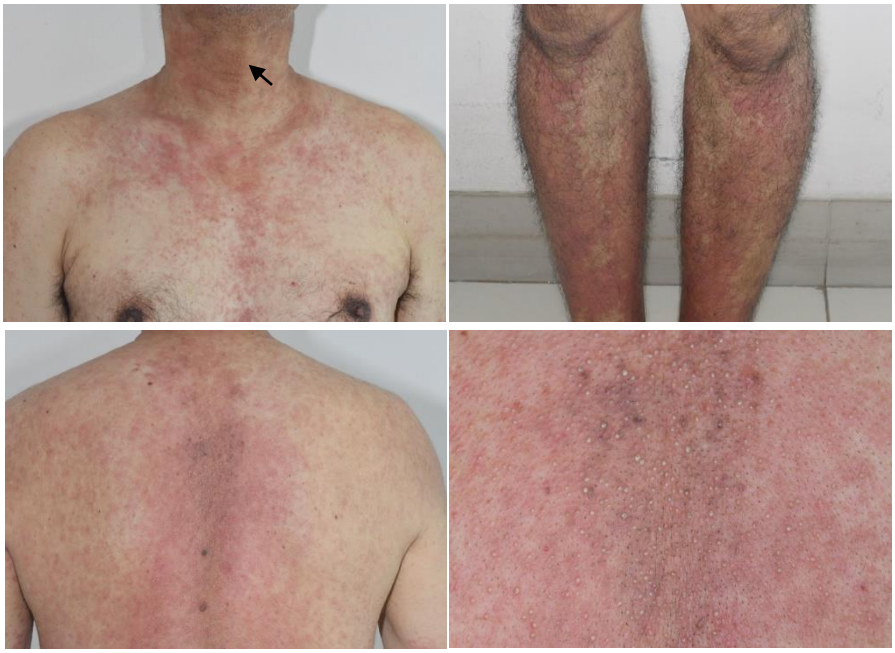

Figure 1 A confluent, discrete erythematous papules on the trunk, upper, and lower extremities

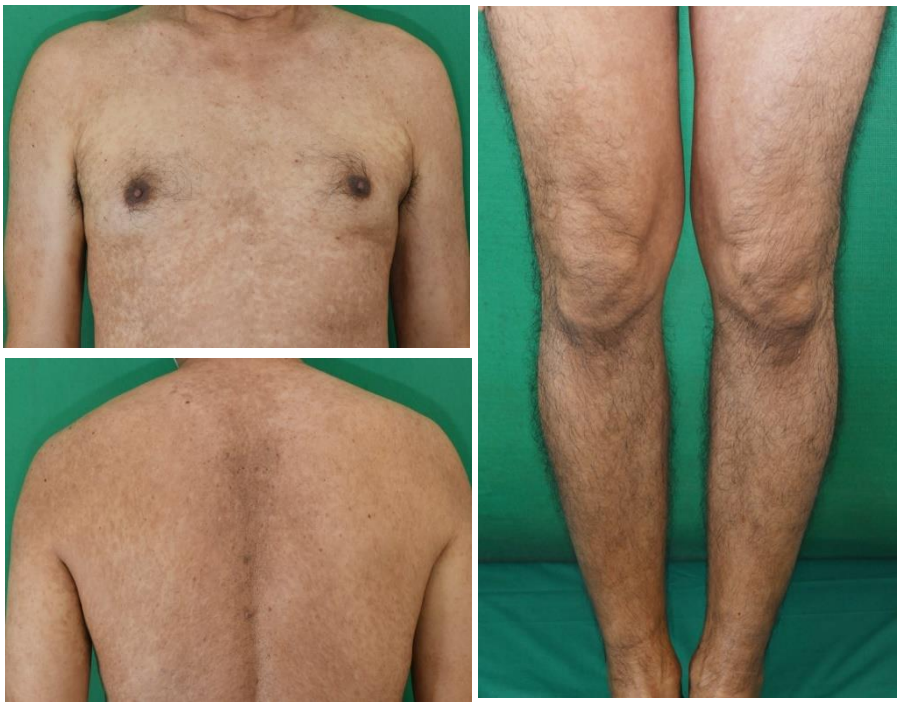

Figure 2 A dramatic response observed two weeks after initiating systemic corticosteroid treatment.

Laboratory investigations revealed a white blood cell count of 6410/μL with a differential of neutrophils 64.5%, lymphocytes 25%, monocytes 9.4%, and eosinophils 0%. Haemoglobin was 13.9 g/dL, and the platelet count was 265,000/μL. Liver function tests showed elevated alanine aminotransferase (88 IU/L) and aspartate aminotransferase (36 IU/L), with total bilirubin of 0.73 IU/dL and alkaline phosphatase of 197 IU/L. Renal function tests revealed a blood urea nitrogen level of 18.63 mg/dL and serum creatinine of 1.40 mg/dL, consistent with the patient's baseline range of 1.20–1.50 mg/dL. Inflammatory markers included a C-reactive protein level of 0.96 mg/dL.

Serologic tests for dengue virus, measles virus, rubella virus, and hepatitis B and C viruses were negative. Antinuclear antibody was also negative. A perilesional biopsy for direct immunofluorescence was negative. HLA-B*58:01 was positive.

Blood cultures were sterile. The patient denied any prior adverse drug reactions and reported no personal or family history of psoriasis. Allopurinol was promptly discontinued, and treatment with prednisolone at a dose of 40 mg/day (0.5 mg/kg/day) was initiated for seven days and subsequently tapered. He initially showed improvement after 7 days of treatment and was completely cured at the 2-week follow-up (Figure 2).

Discussion

Acute generalized exanthematous pustulosis (AGEP) is a type of cutaneous adverse drug reaction (CADR), typically characterized by rapidly progressive non-follicular sterile pustules on a diffuse, edematous erythema primarily in the intertriginous area and/or on the face, which spreads to the rest of the body within 24 to 48 hours. The skin lesions begin to resolve within 2 weeks with desquamation after discontinuing the drug[1]. Systemic manifestations during the acute phase may include fever, leukocytosis with neutrophilia, and elevated CRP levels[2-3]. Other possible systemic involvement includes elevated liver enzymes, hepatomegaly, renal insufficiency, respiratory distress, and bone marrow involvement[4]. In more than 90% of cases, drugs have been reported to be the cause of AGEP. Pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulphonamides, terbinafine, and diltiazem are the most commonly associated drugs[5]. Although allopurinol, a xanthine oxidase inhibitor commonly used in the management of gout, has been implicated in various CADRs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), its association with AGEP is relatively rare[5-8]. In the present case, the temporal relationship between allopurinol initiation and the onset of symptoms, combined with the absence of other potential causative agents, strongly suggests allopurinol as the culprit. According to the EuroSCAR study, a validation score framework can be utilized to assess AGEP[1]. The EuroSCAR score of seven points in this case is interpreted as "probable" AGEP (Table 1).

The differential diagnosis, based on the skin biopsy, included pustular psoriasis. The rapid disappearance of pustules after discontinuation of allopurinol and high-dose corticosteroids further supports an etiological role for AGEP.

Table 1 A EuroSCAR scoring system for diagnosis AGEP[1]

	EuroSCAR Points	Case presented
Morphology		
Pustules		
Typical†	+2	+2
Compatible	+1	
Insufficient	0	
Erythema		
Typical	+2	
Compatible	+1	+1
Insufficient	0	
Distribution/pattern		
Typical	+2	
Compatible	+1	+1
Insufficient	0	
Postpustular desquamation		
Yes	+1	+1
No/insufficient	0	
Course		
Mucosal involvement		
Yes	-2	
No	0	0
Acute onset (< 10 days)		
Yes	0	
No	-2	-2
Resolution (< 15 days)		
Yes	0	0
No	-4	
Fever ($ 38°C)		
Yes	+1	+1
No	0	
Neutrophil count (≥7 X 10^9/L)		
Yes	+1	
No	0	0
Histology		
Other diseases	-10	
Not representative/no histology	0	
Exocytosis of neutrophils	+1	
Subcorneal and/or intraepidermal non-spongiform or NOS pustule(s) with papillary oedema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary oedema	+2	
Spongiform subcorneal and/or intraepidermal pustule(s) With papillary oedema	+3	+3
Total points		7

†Compatible: not typical, but not strongly suggestive of other disease. Insufficient: lesions cannot be judged (mostly because of late stage of the disease or poor quality of pictures). Typical: typical morphology.
Interpretation: # 0, no AGEP; 1–4, possible AGEP; 5–7, probable AGEP; 8–12, definite AGEP. AGEP, acute generalized exanthematous pustulosis; NOS, not otherwise specified

HLA-B alleles are increasingly utilized as pharmacogenetic predictors for drug-induced CADRs across diverse populations. The HLA Class I (HLA-A, -B, and -C) genes encode the MHC Class I proteins, which are involved in T-cell-mediated immunological reactivity through the presentation of HLA molecule antigens as a result of drug molecules and reactive metabolites[9]. The association between allopurinol-induced SCAR and HLA-B*58:01 is particularly strong in patients from the Southeast Asian population[10]. HLA-B*58:01was previously linked to CADRs, including SJS, TEN, DRESS and maculopapular eruption (MPE). The sensitivity of HLA-B*58:01 for predicting allopurinol-induced DRESS was found to be 100%, indicating that all patients who developed DRESS tested positive for the allele. The specificity was 96.0%. Furthermore, the positive predictive value of HLA-B*58:01 for DRESS was calculated to be 76.43%. This suggests that among patients who tested positive for the allele, there is a 76.43% likelihood of developing DRESS upon exposure to allopurinol[11]. A study conducted in Malaysia identified a strong correlation between HLA-B*58:01 and SJS/TEN, but HLA-B*58:01 was absent in a patient diagnosed with AGEP[12].

This case report of late-onset AGEP associated with HLA-B*58:01is novel. In this patient, the presence of HLA-B*58:01 appears to have predisposed not only to SJS/TEN but also to AGEP. Among Thai population, the frequency of the HLA-B*58:01 allele varies across different studies. A study involving 986 Thai individuals reported that the frequency of HLA-B*58:01 was 8.62%[13]. In a regional analysis, HLA-B*58:01, associated with allopurinol-induced SJS, TEN, was reported at 9.00% in the northeast and Bangkok areas, while lower frequencies were observed in the northern (6.38%), central (5.00%), and southern regions (4.50%) of Thailand. These results indicate that HLA-B*58:01 is relatively common in the Thai population, with frequencies ranging from approximately 6% to 9%, depending on geographic and methodological factors[14].

Testing for HLA-B*58:01 should be conducted prior to initiating allopurinol therapy. A blood sample (1-3 ml) is collected in an EDTA tube and mixed thoroughly with the anticoagulant to prevent clotting. If immediate delivery is not possible, the sample must be refrigerated at 4°C and sent the next day. Testing is conducted using sequence-specific amplification techniques and melting-temperature analysis via real-time PCR. If the result is positive, allopurinol treatment is contraindicated, and alternative medications should be considered. A negative result indicates a lower risk for developing SJS or TEN, allowing for the use of allopurinol according to standard dosing guidelines. However, it does not completely eliminate the risk of CADRs, especially in populations with lower HLA-B*58:01 allele frequencies[15].

Given the established role of HLA-B*58:01 in predicting severe allopurinol-induced cutaneous adverse reactions, this case underscores the need for genetic screening before initiating allopurinol therapy in susceptible populations. Such preventive measures could significantly reduce the incidence of severe and potentially life-threatening drug reactions.

In conclusion, this case report highlights a novel association between HLA-B*58:01 and AGEP in the context of allopurinol hypersensitivity. While the correlation between HLA-B*58:01 and severe cutaneous reactions like SJS and TEN is well-documented, this case expands the spectrum of HLA-B*58:01-related drug reactions to include AGEP. Further research is warranted to explore the mechanisms underlying this association and to evaluate the potential benefits of pre-emptive HLA-B*58:01 screening in preventing adverse reactions to allopurinol.

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