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Stevens-Johnson Syndrome, Drug-Induced Hypersensitivity Syndrome and Toxic Epidermal Necrolysis Caused by Allopurinol in Patients with a Common HLA Allele: What Causes the Diversity?

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Key Words

Allopurinol • Stevens-Johnson syndrome • Drug-induced hypersensitivity syndrome • Toxic epidermal necrolysis • Human leukocyte antigen

Human leukocyte antigen (HLA) diversity among patients with cutaneous reactions to drugs is one of the elements responsible for the clinical manifestation [1]. We here report cases with three different manifestations caused by one drug in patients with the same HLA allele: Stevens-Johnson syndrome (SJS), drug-induced hypersensitivity syndrome (DIHS) [2, 3]/drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN).

Case 1

A 57-year-old man was started on daily allopurinol. On day 8, fever, conjunctival injection and lip bleeding followed by general erythema developed. On day 10, he visited our hospital and was diagnosed as having SJS (fig. 1a). A patch test showed a positive reaction against allopurinol. Serological HLA typing of the patient by reverse sequence-specific oligonucleotide with polymerase chain reaction showed A31, A33, B51 and B58.

Case 2

A 77-year-old man was started on daily allopurinol. Four weeks later, he was transferred to our hospital with fever and general erythema. There were unifying erythematous macules with edema spread over the body, some of them containing pustules (fig. 1b). Blood chemistry tests showed elevated values of transaminases. The titer of anti-human herpesvirus 6 IgG, which was 20 on admission, was elevated to 2,560 in 11 days. Although neither patch test nor lymphocyte transformation test showed remarkable responses, we diagnosed this case as DIHS induced by allopurinol because of its history and clinical manifestation. HLA typing showed A31, A33, B39 and B58.

Case 3

A 93-year-old man who had been started on daily allopurinol experienced a maculopapular-type eruption and fever within 1 month. One year after his recovery, he was given allopurinol again at a nursing home. He rapidly became ill with fever and general exanthema within 2 weeks and was transferred to our hospital. There were conjunctival injection, lip bleeding and diffuse erythema with bullae and erosions (fig. 1c). No elevation of anti-human herpesvirus 6 antibody titers was seen during the course. We diagnosed the patient as having SJS/TEN. He showed HLA-A24, -A33, -B52 and -B58.

We have confirmed that SJS, TEN and DIHS/DRESS caused by allopurinol affect patients who have the serological HLA type B58 in common. B58 is exclusively associated with the HLA-B*5801 allele [4] and is extremely rare in the Japanese population ($\leq 0.6\%$) [5, 6]. It has been shown that the HLA-B*5801 allele was present in all 51 patients with allopurinol-induced severe cutaneous adverse reactions in Taiwan [7]. Another common HLA allele in the present cases, A33 (A*3303), is in linkage disequilibrium and forms an extended haplotype with B*5801 [7]. The latest report indicates that the HLA-B*5801 allele is present in 61% of patients who suffer from allopurinol-induced severe adverse drug effects in Europe [8]. Despite regional and ethnic differences, HLA-B*5801 is undeniably a common key to the pathogenesis of SJS, TEN and DIHS/DRESS induced by allopurinol.

Intracellular autopeptides are presented on the cell surface in a complex form mounted by class I MHC molecules, which T cell receptors on CD8+ cytotoxic T lymphocytes recognize. In the process, drug metabolites bind to the epitopic peptides and are recognized as antigenic epitopes by corresponding T lymphocytes. It is a reasonable hypothesis that HLA-B*5801, which is a class I MHC molecule, mounts epitopic peptides modified by allopurinol, thereby directly stimulating a specific CD8+ cytotoxic T-lymphocyte repertoire, which plays a crucial role in the pathogenesis. Also in our cases, CD8+ lymphocytes were immunohistochemically shown to be present along the dermoepidermal interface (not shown). It is unlikely that other molecules participating in innate immunity, and whose genes are in linkage disequilibrium with the HLA allele, decide the susceptibility to the drug eruptions without any correlation with the specific T-lymphocyte immunity.

Then, why do a common MHC allele and a single drug, which stimulate a specific repertoire of T lymphocytes, cause various diseases? We suggest the following hypotheses:

(1) common HLA, common peptide, common antigenic epitope, common T-lymphocyte repertoire (fig. 2a) – differences in extrathymic education of the T lymphocyte, such as infection history of the host, change the T-lymphocyte reaction and cause variations of the disease;

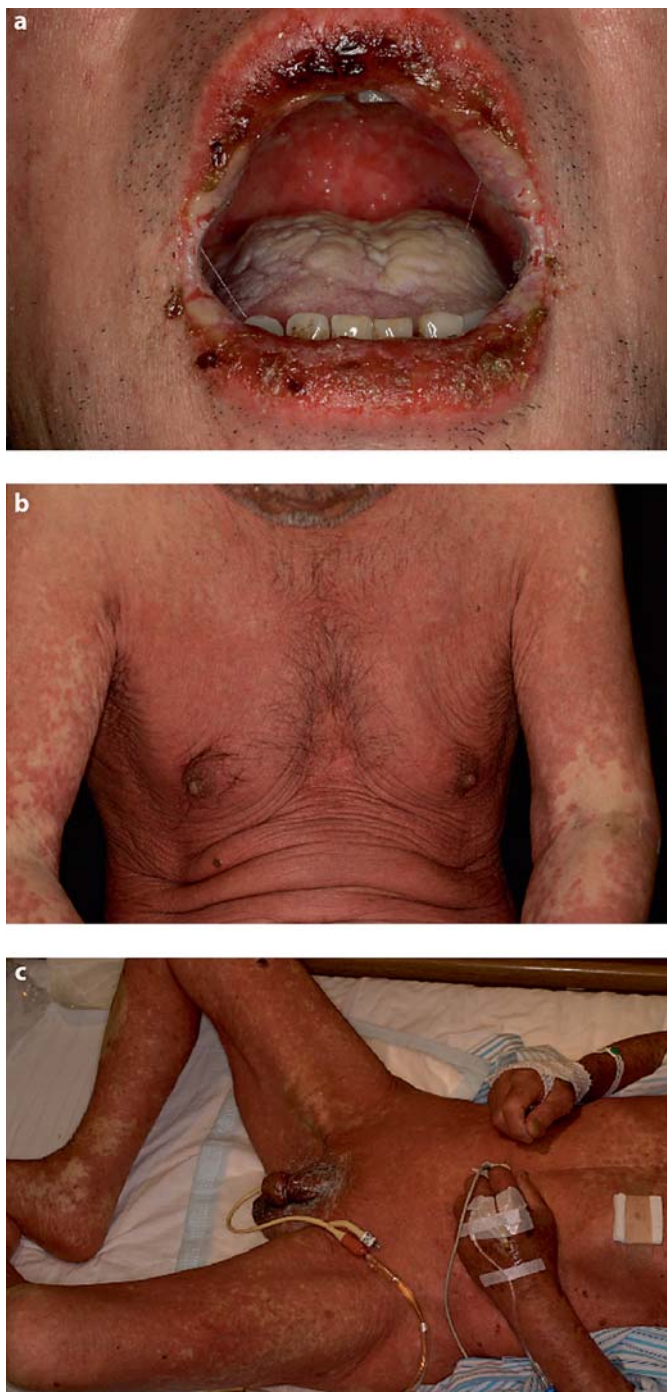


Fig. 1. **a** Case 1: SJS. **b** Case 2: DIHS (DRESS). **c** Case 3: TEN.

(2) common HLA, common peptide, common antigenic epitope, different T-lymphocyte repertoire (fig. 2b) – a congenital viral infection affects the intrathymic selection of T lymphocytes and causes development of a different T-lymphocyte repertoire;

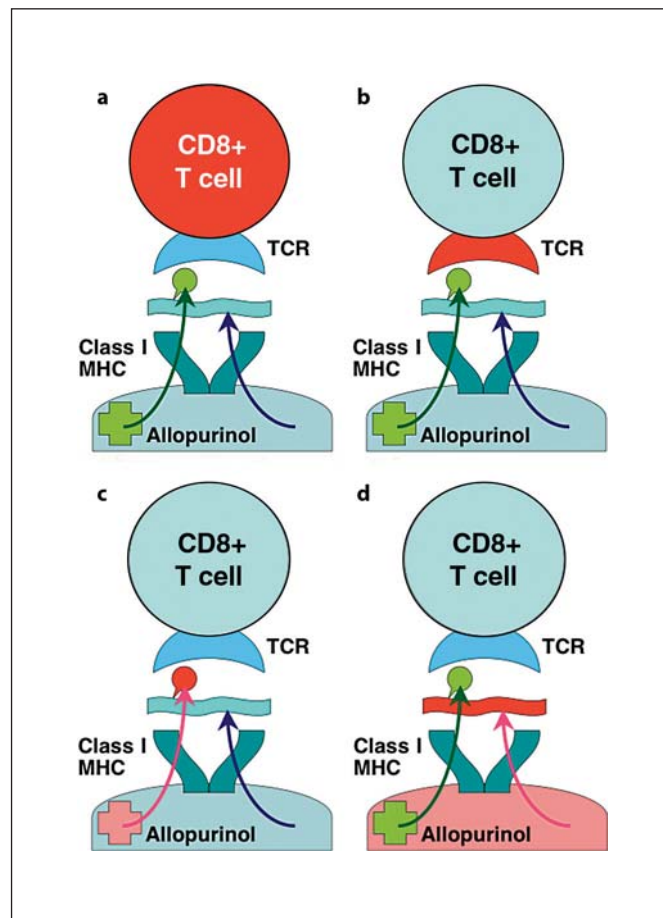


Fig. 2. The hypothesis of diversity in the adverse reaction to drugs involves four potentially responsible steps: variation in T-cell function (**a**), in T-cell receptor (TCR) repertoire (**b**), in drug metabolism (**c**) and in autopeptides (**d**).

(3) common HLA, common peptide, different antigenic epitopes, different T-lymphocyte repertoire (fig. 2c) – differences in drug metabolism among each organ and host cause variations in epitopic substrate and/or its dose; reportedly, there is no significant association between any of the cytochrome P450 single-nucleotide polymorphisms and occurrence of carbamazepine-induced SJS [9]; however, this hypothesis could be of value in further investigations;

(4) common HLA, different peptide, common antigenic epitope, different T-lymphocyte repertoire (fig. 2d) – host-derived antigenic peptides mounted on the MHC molecules differ in their sequences or doses among each organ and host.

Every investigator recognizes the bewildering complexity of adverse drug effects [10]. However, we can now assume that SJS, TEN and DIHS/DRESS due to allopurinol share a considerable part of the pathogenesis, which accompanies some variations caused by infection or indeterminate factors [11]. It is noteworthy that for carbamazepine HLA-B*1502 is a risk factor for SJS and TEN but *not* for DIHS/DRESS (communication at the 7th Cuta-

neous Adverse Drug Reaction Meeting, Paris, 2006). These seemingly contradictory phenomena will be pieces of a puzzle to unlock the mystery of drug reactions in the near future.

In any case, HLA profiling is a useful tool in making the diagnosis and, moreover, serves as a guide that can help to prevent life-threatening adverse drug reactions. National projects are required to address the problem in each region of the world.

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