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Toxic Epidermal Necrolysis in a Patient with HLA-B*5901 Haplotype Caused by Topical and Oral Carbonic Anhydrase Inhibitors

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Dear Editor:

Toxic epidermal necrolysis (TEN) and Stevens—Johnson syndrome (SJS) are severe life-threatening mucocutaneous diseases that involve different extents of epidermal detachment and severity¹. Carbonic anhydrase inhibitors (CAIs) are used to decrease intraocular pressure (IOP) in glaucoma² and may rarely induce TEN/SJS. Moreover, strong genetic associations between human leukocyte antigen (HLA)-B*5901HLA alleles and methazolamide-induced TEN/SJS have been discovered in Koreans³. Herein, we report a case of TEN in a Korean woman with HLA-B*5901 haplotype, who had taken methazolamide for 1 day and instilled brinzolamide for 10 days.

An otherwise healthy 33-year-old Korean woman presented with pruritic, multiple, coalescent, erythematous patches with vesicles on the face and trunk involving erosive oral mucosa (Fig. 1A). Twenty days prior, she visited an ophthalmic clinic complaining of blurred vision after taking phendimetrazine, an anorectic agent, for 2 days.

Her IOP was elevated and was treated with methazolamide, brinzolamide 1%/timolol 0.5%, brimonidine 0.15%, and prednisolone 1% eye drops for 1 day. Nevertheless, her IOP remained elevated, and both eyes were treated with argon laser iridotomy. Brinzolamide 1%/timolol 0.5% and brimonidine 0.15% eye drops were administered for an additional 9 days. Two days after stopping the eye drops, she noted pruritic erythematous macules on the face. Her cutaneous lesions were aggravated and expanded distally with conjunctival and oral mucosal involvements over several days. She had no history of drug allergies, including sulfonamide antibiotics. Personal and family histories were unremarkable. Routine laboratory test results were normal. HLA typing showed B*5901 and B*5204. She was initially treated with dexamethasone 10 mg daily for 2 days, but epidermal necrolysis worsened and became confluent (Fig. 1B, C). Intravenous immunoglobulin (3.5 g/day) was infused for 4 days. Her skin lesions gradually improved

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Fig. 1. (A) Coalescent erythematous macules, papules, and patches with vesicles on the face. (B) Widespread sheet-like epidermolytic detachment on the dorsum. (C) Histopathologic findings show subepidermal bullae, diffuse epidermal necrosis, and mild upper dermal inflammatory infiltrations on high-power view (H&E, $\times 200$).

within 3 weeks.

In the present case, topical timolol and brimonidine were administered for 10 days. However, there has been no report of timolol- or brimonidine-associated TEN/SJS. Moreover, neither timolol nor brimonidine appears to cause TEN/SJS, because the relative risk of timolol or brimonidine for TEN/SJS is much lower than that of CAIs. Therefore, CAIs appear to have induced TEN in this patient. Twelve days before the first cutaneous manifestations, she took methazolamide for 1 day while simultaneously instilling brinzolamide for 10 days. Therefore, it is reasonable to postulate that 2 types of CAIs contributed to the induction of TEN in this patient, because either topical or oral CAIs can induce TEN/SJS⁴. The first methazolamide administered appears to have played a role in initial phase of sensitization, whereas continual brinzolamide administration appears to have played crucial roles in maturation and/or the initial phase.

TEN/SJS encompass idiopathic hypersensitivity reactions to specific drugs and usually occur in people with a genetic predisposition¹. A strong and unique genetic association between HLA alleles and drug-induced TEN/ SJS has been discovered. In Koreans, HLA-B*5901 is strongly associated with methazolamide-induced TEN/SJS³. The gene frequency of HLA-B*5901 allele in the Korean po-

pulation is reported to be 2.06%⁵ and HLA-B*5901 allele was detected in this patient.

In summary, both topical and oral CAIs should be administered cautiously in Koreans.

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