# Oxcarbazepine-induced Stevens-Johnson Syndrome: A Case Report

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Although carbamazepine (CBZ) is the most common cause of Stevens-Johnson syndrome (SJS), a new anticonvulsant, oxcarbazepine, which is structurally related to carbamazepine, has been shown to induce SJS, although extremely rarely. Recently, a strong association was found between human leukocyte antigen (HLA) B*1502 and CBZ-induced SJS/TEN in a Han Chinese population. Here, we report a case with SJS, which was induced by oxcarbazepine. HLA genotyping in the patient showed HLA-B*1518/B*4001. HLA-B*1518 is a HLA-B15 variant. The genetic significance of HLA-B*1518 in association with oxcarbazepine-induced SJS needs to be further studied.

**Key Words:** oxcarbazepine, Stevens-Johnson syndrome
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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), defined by widespread blisters arising on macules and/or flat atypical targets, are diseases with homogenous clinical characteristics and a potentially lethal outcome [1]. SJS is usually associated with some types of anticonvulsants, including carbamazepine, lamotrigine, phenobarbital, phenytoin and valproic acid [2]. A new anticonvulsant, oxcarbazepine, which is structurally related to carbamazepine (CBZ), was introduced for use in patients with epilepsy. According to a review of the literature, it appears that oxcarbazepine-induced SJS has been rarely reported [3]. Recently, Chung et al found a strong association between human leukocyte antigen (HLA) B*1502 and CBZ-induced SJS/TEN in the Han Chinese population [4]. Here, we report a rare case of oxcarbazepine-induced SJS and review the related literature. In addition, HLA typing was investigated in this patient and the significance is discussed.

## Case Presentation

The patient studied was 9 years old at his first visit to the Department of Pediatrics, Kaohsiung Medical University Hospital. He was the third child of nonconsanguineous parents. Pregnancy, gestation, delivery and birth weight were all normal. His development was unremarkable. His first seizure occurred when he was 6 months old and the patient then took anticonvulsant with phenytoin for several months. When no further seizure attacks were noted, phenytoin was withdrawn.

However, seizure occurred again and he was brought to our outpatient department. His seizure was characterized by clonic movement of his hands and legs, with loss of consciousness. Physical examination was unremarkable. The results of an electroencephalogram revealed unremarkable findings. At that time, oxcarbazepine, 300 mg/day, was prescribed. One week later, the dose of oxcarbazepine was increased to 600 mg/day. Unfortunately, high fever and multiple

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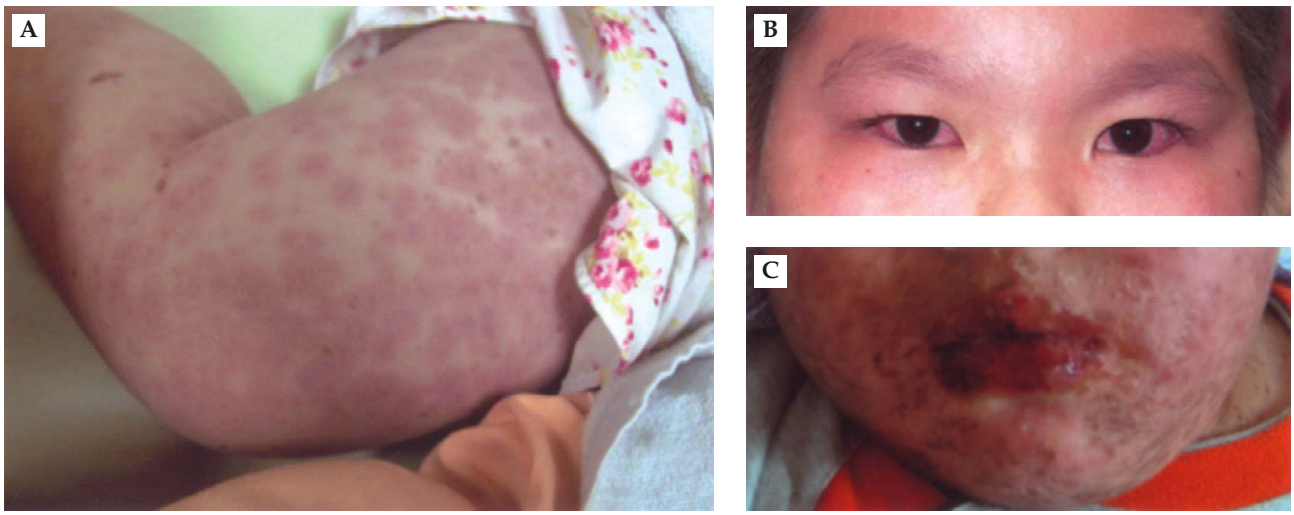


**Figure 1.** *Skin and mucosa of our patient: (A) targetoid rashes over the right thigh; (B, C) conjunctivae and oral mucosa were involved by SJS.*

maculopapule rashes were found over the patient's face and thigh initially on the 14th day after taking oxcarbazepine. Two days later, some blisters were also observed on his thigh. Then, multiple oral ulcers and hyperemic conjunctivae were also noted (Figure 1).

He was brought to our emergency department and admitted under the presumed diagnosis of SJS. Laboratory investigations showed leukocytosis (WBC, 13,930/μL; reference value, 4,000–10,000/μL), and elevated C-reactive protein (50.59 μg/mL; reference range, 0–5 μg/mL).

After obtaining informed consent, we carried out genotyping and took photos of the patient. HLA genotyping showed HLA-B*1518/B*4001. A skin biopsy was also performed. The layer stratum corneum appeared to be normal. There was marked liquefactive degeneration in the lower half of the epidermis with some dyskeratotic keratinocytes. The dermis showed predominant CD8+ lymphohistiocytic infiltration around the blood vessels and scanty eosinophils (Figure 2). The skin pathology finding was consistent with SJS.

After steroid and antihistamine treatment for 7 days, the patient improved and was discharged in a good general condition 12 days later.

## Discussion

The diagnosis of SJS is based on clinical manifestations with acute onset of rapidly expanding targetoid erythematous macules, necrosis and detachment of the epidermis along with erythema, erosions and crusting of two or more mucosal surfaces [5]. The patients usually develop a hypersensitivity reaction between 2 and 12 weeks after starting medicine [6]. Our patient had skin targetoid erythematous rashes and mucosa involvement 2 weeks after starting oxcarbazepine treatment. During these 2 weeks, he took no medicine except for oxcarbazepine. The skin pathology finding revealed lymphohistiocytic infiltration around the blood vessels and scanty eosinophils, which was consistent with SJS.

In this case, during the first week, we used 7.5 mg/kg/day oxcarbazepine for seizure control, and then increased the dose to 15 mg/kg/day. Both the initial and titration doses were slightly lower than the recommended doses (15–45 mg/kg/day). It has been reported that higher daily doses of drugs are associated with increased risk of SJS than lower doses, which is the case for allopurinol [7]. However, there is no evidence about the relationship between oxcarbazepine dosage and SJS.

Although many factors have been proposed as risk factors of SJS, including adverse drug effects, malignant disorders or graft-versus-host disease and infections, most of them were induced by drugs. The most common drugs are anticonvulsants, particularly CBZ [8]. In Taiwan, CBZ is the leading cause and accounts for 25% of all cases of drug-induced SJS/TEN [4]. To our knowledge, there are no reports of a Taiwanese case of oxcarbazepine-induced SJS. According to the Food and Drug Administration, the incidence of

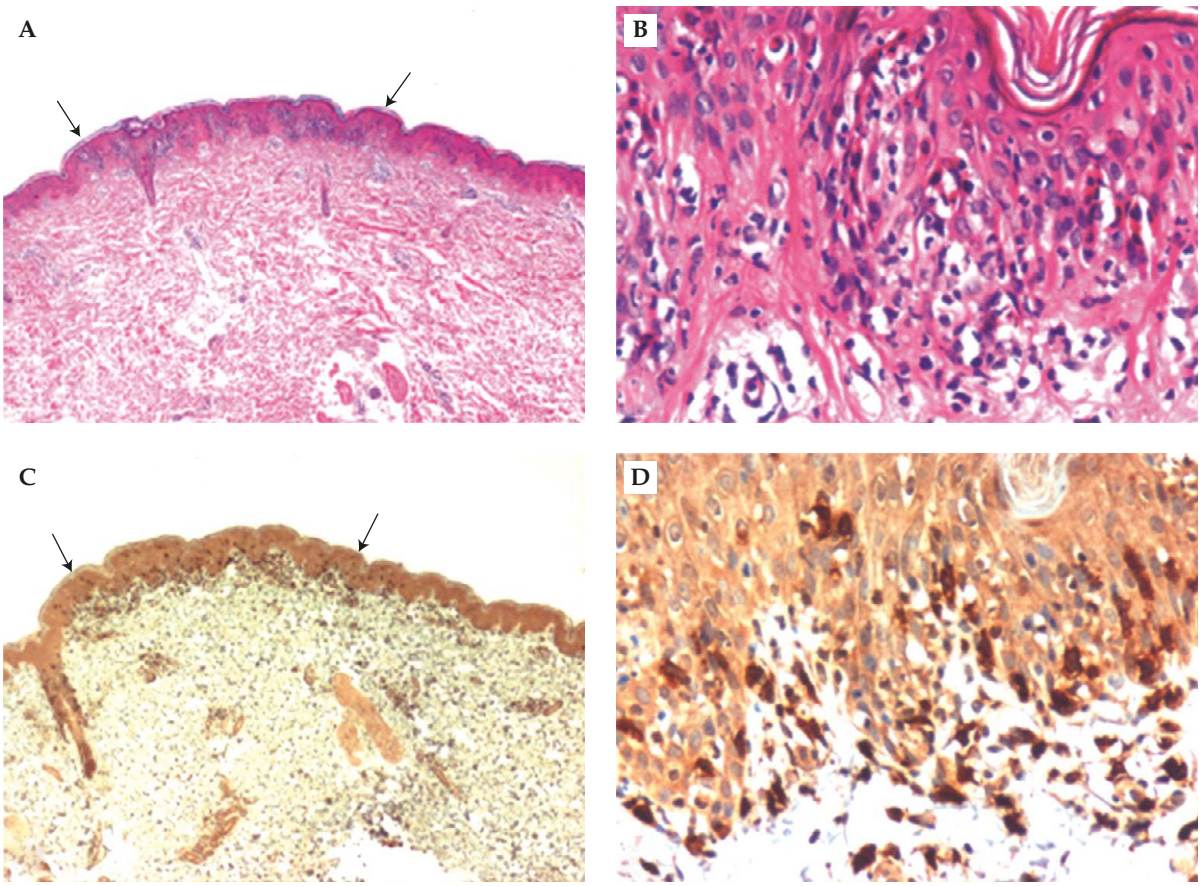


**Figure 2.** *Microscopic findings of skin biopsy. (A, C) Low power field view shows tagging of lymphocytes along the dermoepidermal junction and superficial perivascular lymphoid infiltrate in the lesion (areas between the arrows) (original magnification, 40×). (B, D) High power field view shows abundant CD8+lymphocytes approximating the dermoepidermal junction with vacuolization of the basal cell layer (original magnification, 400×). (A, B: hematoxylin & eosin; C, D: CD8 immunohistochemical staining.)*

oxcarbazepine-induced SJS/TEN is estimated to range between 0.5 and 6 cases per 1 million people per year within the general population [9]. The incidence of oxcarbazepine-induced SJS is estimated to be one in every 10,000 exposures in Taiwan, while the incidence of CBZ-induced SJS/TEN is estimated to be 1:2,000, which is higher than that for oxcarbazepine-induced SJS. The reason why oxcarbazepine has fewer side effects is that oxcarbazepine is almost completely metabolized through reduction and conjugation to yield an active monohydroxy derivative. In contrast, the oxidation of CBZ to 10,11-epoxide is regarded as the most common cause of adverse effect [10]. Although the pathogenesis of SJS remains unclear, Yang et al reported that HLA-B*1502 represents an MHC molecule that is strongly associated with CBZ-induced SJS/TEN [11]. The fact that there is a nearly 100% association of HLA-B*1502 with CBZ-induced SJS/TEN implies that HLA-B*1502 is not only a genetic marker, but is also a participant in the pathogenesis of SJS [11]. Considering that oxcarbazepine possesses a related structure that might share a pathogenesis similar to CBZ-induced SJS/TEN, we performed HLA genotyping on this patient. The results were HLA-B*1518/B*4001. This differs from HLA-B*1502, although HLA-B*1518 is still a HLA-B15 variant. In addition, the allele frequency of HLA-B*1518 was only 0.5% in Taiwanese Minnan. In an extended study, Chung et al showed that some CBZ-induced SJS/TEN patients who did not have the HLA-B*1502 gene had HLA-B*1558, another HLA-B15 variant [12]. The role of HLA-B*1518 in the immune reaction of SJS by oxcarbazepine is currently unclear because findings are limited to a single case.

There is considerable debate about whether to treat SJS with systemic steroids. However, Lam et al found that the early use of short-term systemic steroids for 3–5 days lacked any significant side effects and did

not increase mortality or morbidity in children [13]. Our patient was treated with intravenous steroid and antihistamine for 7 days. He improved and was discharged 12 days after admission. No sequelae were found during 2 months of follow-up.

In conclusion, we have described the first case of oxcarbazepine-induced SJS in Taiwan. The HLA typing of the patient is HLA-B*1518/B*4001. We need to recruit more patients to elucidate the pathogenesis and genetic markers of oxcarbazepine-induced SJS.

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# Oxcarbazepine 誘發史帝文 - 強森症候群 — 個案報告

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**Carbamazepine** 是最常見引起史帝文 **-** 強森症候群的一種藥物，另一種新的抗癲癇藥物 **-oxcarbazepine** 雖然結構上跟 **carbamazepine** 類似，卻極少引起史帝文 **-** 強森症候群，最近在漢民族的研究顯示 **carbamazepine** 引起史帝文 **-** 強森症候群是跟人類白血球組織抗原 (**human leukocyte antigen**) **HLA-B*1502** 有強烈的相關性，本篇文章報告一個由 **oxcarbazepine** 誘發史帝文 **-** 強森症候群的病患，這個病患的人類白血球組織抗原的檢驗結果為 **HLA-B*1518/B*4001**，而 **HLA-B*1518** 是 **HLA-B15** 的異構體，因此 **HLA-B*1518** 在 **oxcarbazepine** 誘發史帝文 **-** 強森症候群的相關性還須進一步研究。

**關鍵詞：oxcarbazepine**，史帝文 **-** 強森症候群

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