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Case Report

A case of bortezomib (Velcade)–induced Stevens-Johnson syndrome confirmed by patch test

Gil-Soon Choi, Ho Sup Lee, and Hee-Kyoo Kim *

Department of Internal Medicine, Kosin University Gospel Hospital, Busan, Korea

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***Correspondence to**
Hee-Kyoo Kim
Department of Internal Medicine, Kosin University College of Medicine, 262, Gamchen-ro, Seo-gu, Busan 49267, Korea.
Tel: +82-51-990-6152
Fax: +82-51-990-3145
Email: naum67@naver.com

ORCID iDs
Gil-Soon Choi
https://orcid.org/0000-0003-3466-3294
Ho Sup Lee
https://orcid.org/0000-0001-5974-6884
Hee-Kyoo Kim
https://orcid.org/0000-0003-0692-1639

Conflict of Interest
The authors have no financial conflicts of interest.

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ABSTRACT

Bortezomib, a highly selective reversible inhibitor of the proteasome complex, is used to the current standard of care in the treatment of multiple myeloma. Although its most commonly reported side effects are gastrointestinal symptoms, peripheral neuropathy, neuropathic pain, and thrombocytopenia, cutaneous adverse reactions are also frequently seen. However, severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS) occur very rarely. Here we report the first case of bortezomib-induced SJS with confirmed by patch test. In this case, we performed a patch test that proved bortezomib was the offensive drug in this patient, who had been treated with multiple drugs including antibiotics, allopurinol, and anticancer drugs. Although bortezomib-induced SCARs are generally very rare, we suggest that clinicians be aware of potential adverse reactions including SJS.

Keywords: Bortezomib; Stevens-Johnson syndrome; Drug hypersensitivity; Drug eruptions

INTRODUCTION

Bortezomib (Velcade, anssen Pharmaceutica NV, Beerse, Belgium), the first proteasome inhibitor approved by the U.S. Food and Drug Administration for the treatment of multiple myeloma and mantle cell lymphoma more than a decade ago, is a targeted therapy approach that blocks the production of nuclear factor-kB-mediated proinflammatory cytokines [1], bortezomib-containing regimen is considered the standard of care for multiple myeloma. The most commonly reported side effects of bortezomib are gastrointestinal symptoms, peripheral neuropathy, neuropathic pain, thrombocytopenia, and fatigue [2]. Cutaneous adverse events are reported in 10% of cases [2]. However, most have been mild. There have been few reports of bortezomib-induced severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS). Here we describe a case of SJS induced by bortezomib in a 71-year-old woman undergoing chemotherapy for multiple myeloma.

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CASE REPORT

A 71-year-old woman was referred to our department for the management of a skin eruption that had developed during the course of chemotherapy implemented for recently discovered multiple myeloma. She had no previous history of allergic disease or drug allergies. However, she was taking medication (telmisartan 40 mg/amlodipine 5 mg) to treat hypertension. Two weeks before the skin eruption, she started chemotherapy with a bortezomib plus melphalan and prednisone regimen consisting of subcutaneous bortezomib 1.9 mg (1.3 mg/m^2) on days 1, 4, 8, and 11, melphalan 8 mg/day, and prednisolone 40 mg/day from day 1 to 4. Acyclovir, levofloxacin, trimethoprim-sulfamethoxazole, and fluconazole were used as prophylactic measures with the chemotherapy, while allopurinol was taken to prevent tumor lysis syndrome. The day after the 3rd bortezomib injection on day 8, a high fever was noted and piperacillin/sulbactam antibiotics were used. After 3 days, the antibiotic regimen was changed to doripenam and vancomycin because the fever remained uncontrolled. However, the fever persisted and a skin rash developed on neck and trunk 2 days after the antibiotic change. She was clinically diagnosed with a drug eruption induced by the antibiotics, which were then discontinued. Two days after the antibiotics were stopped, she complained of severe eye pain with conjunctival hyperemia, oral pain, and a body-wide skin rash. In an ophthalmologic evaluation, severe corneal ulceration with conjunctival injection was observed (**Fig. 1A**). Erosive lesions in the oral mucosa and laryngeal ulceration were detected on an ear, nose, and throat exam (**Fig. 1B**). Skin blistering was observed on the anterior chest. Although a skin biopsy was not performed, a clinical diagnosis of SJS was made. With stopping all other medication, the patient was treated with systemic steroids (methylprednisolone 62.5 mg), intravenous immunoglobulin (1 g/kg for 3 days), and dexamethasone/levofloxacin eye drops. She remained hemodynamically stable and did not develop multiorgan failure. The cutaneous rash and eye and oropharyngeal involvement gradually improved.

Two weeks after recovery, the patch test was performed using drugs taken by patient, including bortezomib, to identify the causal drug. Readings performed after 48 and 72 hours revealed a positive reaction to bortezomib 1 mg/mL (**Fig. 2**). The patient was diagnosed with bortezomib-induced SJS. For the treatment of multiple myeloma, the chemotherapy regimen

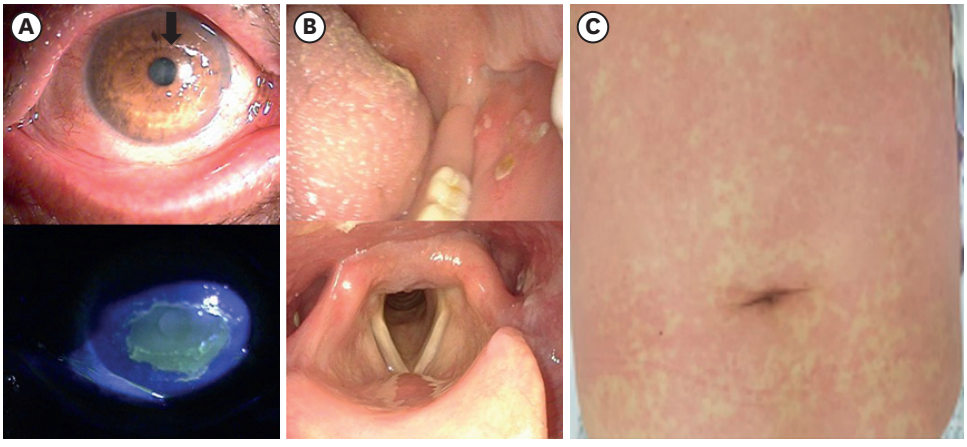

Fig. 1. Eye, oral, and skin findings at the time of the Stevens-Johnson syndrome diagnosis. (A) Eye involvement showing severe corneal erosion. (B) Erosive lesions in the oral mucosa and laryngeal ulceration. (C) Erythematous macular skin rash.

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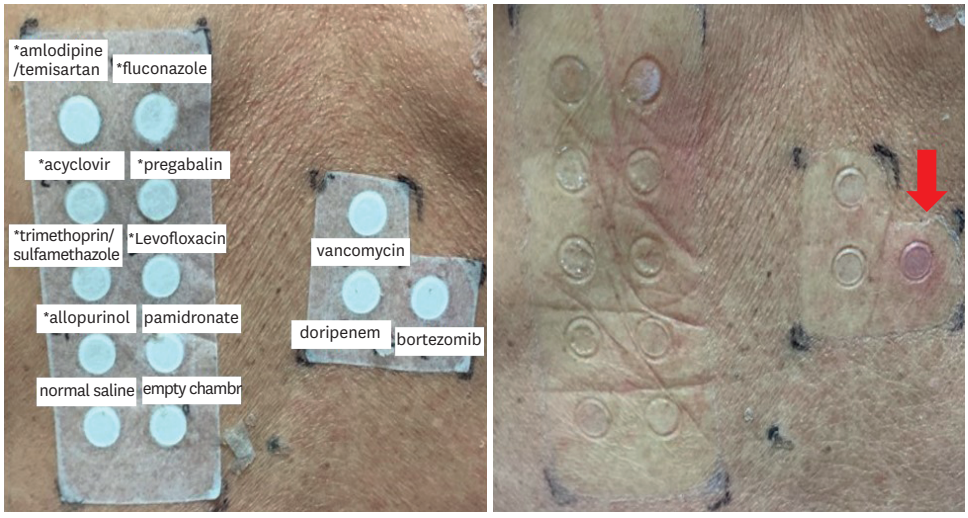

Fig. 2. Patch test result after 72 hours. The arrow indicates the positive response to bortezomib 1 mg/mL (Velcade, Janssen Pharmaceutica NV, Beerse, Belgium). *Tablets were grinded into fine powder and manipulated in vaseline to obtain a 30% concentration of the active drug. Pamidronate, vancomycin, and doripenem were prepared at concentrations of 10 mg/mL, and bortezomib at concentrations of 1 mg/mL.

was changed to lenalidomide. Other medications were also administered, but no adverse events were reported.

DISCUSSION

This is the first case developed SJS during bortezomib treatment in Korea. SJS or toxic epidermal necrolysis (TEN) comprise a spectrum of unpredictable fatal mucocutaneous adverse reactions characterized by rapidly progressing atypical target-like rashes with blisters, cutaneous sloughing, and mucosal involvement [3]. SJS is differentiated from TEN according to the degree of skin epidermal detachment; SJS, 10% or less of total body surface area involvement; TEN, 30% or greater involvement [4]. SJS is mostly caused by drug exposure. The most commonly implicated drugs are antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, and allopurinol [5, 6]. It is not easy to identify the culprit drug of delayed-type hypersensitivity reactions such as SJS/TEN in cancer patients with polypharmacy; therefore, a more severe and fatal reaction may occur after the readministration of the culprit drug. Actually, antibiotics or allopurinol were initially suggested as causal drugs in the present case considering the cause of SJS/TEN reported in the literature. In clinical practice, it is not possible to use an *in vitro* test to determine which drug was responsible for SJS. Although the patch test has been used to diagnostically identify offending drugs causing delayed hypersensitivity reaction, it does not appear to be very sensitive for SJS/TEN and its sensitivity could be particularly dependent on the drug [7]. Therefore, the patch test is rarely used in clinical practice. Here we performed a patch test to identify the causal drug, which was bortezomib.

Generally, patch test was performed at least 3–6 weeks after complete healing of the cutaneous adverse drug reaction, but the guidelines differ slightly. European Network on Drug Allergy guideline recommends waiting 3 weeks to 3 months after complete resolution, whereas European Society of Contact Dermatitis advised waiting 6 weeks to 6 months to

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patch test [8]. In this case, we performed patch test at 2 weeks after recovery, because we couldn't delay treatment for underlying multiple myeloma any longer.

The most common side effects of bortezomib are gastrointestinal symptoms, fatigue, and anorexia, while the most troublesome side effect is painful/sensory peripheral neuropathy. Myelosuppression, toxic hepatitis, or tumor lysis syndrome are also frequently encountered [2]. Bortezomib-induced cutaneous reactions are also common, but usually mild and variable in presentation such as erythema, edema, urticaria, pruritic rash, sweating, dry skin, or leucocytoclastic vasculitis [2, 9, 10]. Among the SCAR, only one case of SJS and TEN have been reported in the literature [11, 12]. Skin lesions due to bortezomib are reported to mainly occur during the second, third, or fourth treatment cycle and resolve within a few days after treatment [13], and subcutaneous administration appears to be associated with fewer overall side effects [14]. In present case, the patient developed SJS after the 2nd injection, similar to patients in previous reports.

In this case, severe ocular involvement with corneal ulceration was also observed although patients showed mild skin detachment. Ocular manifestations occur acutely in conjunction with skin involvement or after the skin eruption [15]. The most common ocular condition is bilateral conjunctivitis, which occurs in 15%–75% of patients [15, 16]. Although the severity of ocular inflammation in the acute phase does not always correlate to skin severity, it has been reported that acute ocular damage occurred more frequently in patients with epidermal detachment > 10% of the total body surface area [17]. It was also reported that patients with SJS or TEN who are <18 years of age have poorer ocular outcomes than older patients and that early treatment with steroid or immunoglobulin therapy improves ocular outcomes [18]. It is necessary to carefully observe for eye involvement in patients with bortezomib-induced SJS.

In conclusion, this is the first case report of bortezomib-induced SJS that diagnosed by a patch test. Although bortezomib-related SCAR is generally very rare, we suggest that clinicians be aware of potential adverse reactions including SJS.

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