

Correspondence

Bortezomib-induced Purpuric Rash in Multiple Myeloma

Sukhdeep Singh^{1*}, Kittu Malhi^{1*}, Hridya Karakkattil¹, Debajyoti Chatterjee², Pankaj Malhotra³, Muthu Sendhil Kumaran¹

Departments of ¹Dermatology, ²Histopathology, ³Clinical Hematology and Medical Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

*Equally contributed as joint first authors

*Corresponding author:

Muthu Sendhil Kumaran,
Department of Dermatology,
Post Graduate Institute of
Medical Education and
Research, Chandigarh, India.
drsen2017@gmail.com

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Dear Editor,

Multiple myeloma (MM) accounts for 1–2% of all cancers and more than 17% of haematologic malignancies,^[1] characterised by monoclonal plasma cell proliferation in bone marrow with production of a homogeneous immunoglobulin (M-protein). Bortezomib is the first of a new class of drugs known as proteasome inhibitors, currently used as standard of care in its treatment.^[1] It has been linked to a number of cutaneous side effects; however, not all are well characterised.^[1,2] We report two cases of drug-induced cutaneous leukocytoclastic vasculitis (LCV) following bortezomib therapy.

The first case was a 68-year-old man diagnosed case of advanced stage multiple myeloma, immunoglobulin G kappa type, presenting with asymptomatic, erythematous, non-blanchable, purpuric patches over the thighs for a week [Figure 1a]. He had received two injections of bortezomib (2 mg/m²) subcutaneously on days 1 and 4, followed by the development of the rash after the second dose on day 8. Blood reports revealed anaemia (haemoglobin – 8 g/dL) and hypercalcaemia (serum corrected calcium – 11 mg/dL).

The second case, a 44-year-old man, was a known case of multiple myeloma, advanced stage (international staging system, stage 3), immunoglobulin A λ type. He presented with asymptomatic erythematous non-blanchable purpuric patches, initially affecting the trunk and then the upper limbs for 2 days [Figure 1b]. On days 1, 4, 8 and 11, he was treated with an injection of bortezomib (2 mg/m²) subcutaneously and dexamethasone 20 mg. Full blood count, coagulation profile, liver and kidney chemistries and serum calcium were normal.

Histopathology in first case revealed vasculitis in dermal vessels in form of neutrophil infiltration, endothelial cell prominence and fibrinoid necrosis [Figure 2a]. Skin biopsy in second case was performed, with a possibility of bortezomib-induced drug rash, adenopathy and extensive skin patch overlying a plasmacytoma syndrome and drug reaction with eosinophilia and systemic symptoms [Table 1]. Histopathology revealed features suggestive of LCV [Figure 2b]. Mucosal involvement was not observed in any of the cases. Based on these findings, a diagnosis of bortezomib-induced vasculitis was proffered. Both patients were managed with bilastine 20 mg daily, mometasone lotion and emollients. There was no need for bortezomib discontinuation or dose modification, and the lesions resolved following topical steroid prescription in both our patients.

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Characteristic	Bortezomib-induced vasculitis	Drug reaction with eosinophilia and systemic symptoms	Adenopathy and an extensive skin patch overlying a plasmacytoma
Incidence	8–18%	1/10000 exposures	Very rare.
Clinical presentation	Reddish or purpuric oedematous papules and plaques.	Polymorphous (85%) and facial oedema (76%) ^[1] Other morphologies include (in descending order) pustules, purpura, infiltrated plaques, blisters, target-like lesions, urticarial lesions, an exfoliative dermatitis, eczema-like lesions and lichenoid lesions. Systemic symptoms present-hepatitis, renal insufficiency, etc.	Erythematous, slowly enlarging plaque over the chest
Sites predilection	Upper back, chest and neck	Trunk, face, extremities	Usually trunk
Triggers/recurrences	Recur in each cycle of bortezomib	Anticonvulsants (phenytoin, carbamazepine and phenobarbitone); sulfonamides; sulfones (dapsone); non-steroidal anti-inflammatory drugs (piroxicam, ibuprofen and diclofenac); beta-lactam antibiotics, vancomycin, allopurinol; minocycline	Associated with plasma dyscrasias (multiple myeloma) precede the diagnosis of the tumour by a median of 1.5 years
Histopathology	Leukocytoclastic vasculitis, neutrophilic dermatitis and perivascular lymphomononuclear or mixed infiltrates, granulomatous vasculitis ^[3]	Histology is not specific. Increased confluent keratinocyte necrosis on histology. Spongiosis epidermal change	Diffuse reactive vascular hyperplasia (angiomatosis) in oedematous mucinous stroma. ^[1]
Treatment	Oral corticosteroids can be administered before each cycle.	Withdrawal of the culprit drug. Systemic corticosteroids, cyclosporine.	Radiation therapy



Figure 1: (a) Erythematous, non-blanchable purpuric patches over thighs with few lesions over abdomen over injection sites of bortezomib in patient 1. (b) Erythematous, non-blanchable purpuric macules and patches involving the trunk and extremities in the second case.

Cutaneous LCV in the background of MM represents a manifestation of paraneoplastic syndrome or it may be linked to other common causes of LCV such as cryoglobulinaemia and infections.^[3] Cutaneous manifestations in MM, although rare, consist of multiple erythematous or violaceous nodules

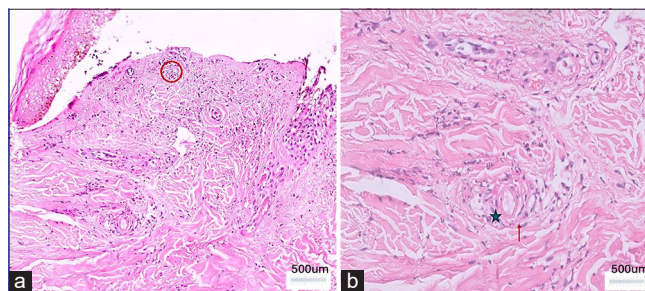


Figure 2: (a) Histopathology in the first case showing vasculitis in dermal capillaries with leukocytoclasia, perivascular inflammatory infiltrate, plump endothelial cells and dermal oedema (red circle). Haematoxylin and eosin. ×200 magnification. (b) Histopathology in the second case revealed dermal capillaries with plump endothelial cells (red arrow), neutrophilic debris with extravasation of red blood cells along with mild periadnexal and perivascular lymphomononuclear inflammation suggestive of small vessel vasculitis (blue star). Haematoxylin and eosin stain. ×400 magnification.

or plaques. LCV is even rarer in multiple myeloma; in a study of 2357 patients with a diagnosis of MM, only eight patients were found to have LCV.^[4] Bortezomib is utilised as combination therapy to treat newly diagnosed or relapsed cases of MM due to its high efficacy and low toxicity. Bortezomib-related cutaneous side effects are noted

in 10–24% of patients, necessitating a change of dose or discontinuation.^[5] Cutaneous side effects associated with bortezomib therapy include injection site reactions (57%), varicella reactivation (21%), morbilliform rash (13%), sweets syndrome and rarely toxic epidermal necrolysis.

The more commonly reported ones include asymptomatic erythematous nodules or plaques, mainly involving the trunk, neck and proximal limbs. It may not appear immediately; some patients may experience rash in the second cycle and even in the seventh or ninth cycle of bortezomib.^[2] The rash is asymptomatic, resolving with topical or systemic corticosteroids; it recurs with drug rechallenge.^[4] Our experience as well as data currently available in the literature support the safe continuation of bortezomib when topical steroids are administered concurrently. Most of these patients are already receiving a high dose of dexamethasone (40 mg/week) as part of their chemotherapy regimen. In certain cases, isolated cutaneous vasculitis may actually indicate a more robust response to bortezomib in terms of treatment outcome. In a study by Gericitano *et al.*,^[4] response to bortezomib in patients developing rash was 73% compared to 33% in those not developing it. Serious systemic side effects are rarely encountered in practice, although bortezomib-induced hepatotoxicity and bortezomib-induced paralytic ileus warrant adequate monitoring of the patient during therapy.^[5] LCV secondary to bortezomib as in our patient is rarely reported and is commonly associated with thalidomide and granulocyte-colony stimulating factor (G-CSF) in the context of MM management. It is critical to distinguish between bortezomib-associated cutaneous vasculitis and potentially fatal drug-or infectious event interactions to allow oncologic treatment to proceed without interference. This can be achieved with constant follow-ups to dermatology clinics to observe for the progression of the rash. To minimise therapy disruptions, maximise patient outcomes and improve quality of life, we stress the significance of early detection and appropriate care of skin toxicities.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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