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Case report

Bortezomib-induced diffuse alveolar hemorrhage in a patient with plasma cell leukemia

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ABSTRACT

Bortezomib, a chemotherapeutic agent used in the treatment of hematologic malignancies, has been associated with multiple forms of lung injury including diffuse alveolar hemorrhage (DAH). We present the first reported case of bortezomib-induced DAH in a patient with plasma cell leukemia. This 59-year-old female developed hemoptysis, severe cough, and diffuse bilateral ground glass opacities on CT scan of the chest after receiving one dose of bortezomib, with DAH subsequently confirmed on bronchoalveolar lavage. Unlike most previously reported cases, she did not develop respiratory failure requiring high dose corticosteroids, and in fact did not require any supplemental oxygen. We also provide a comparative summary of all reports of bortezomib-induced DAH in the literature to date. This case provides additional insight into the spectrum of disease severity observed in DAH secondary to bortezomib therapy.

1. Introduction

Bortezomib is a selective and reversible inhibitor of the 26S proteasome. The resulting intracellular protein accumulation leads to cell cycle dysfunction and apoptosis, and these antiproliferative effects have led to the incorporation of bortezomib into various chemotherapeutic regimens. While its use is most established in the treatment of multiple myeloma, bortezomib-based therapy has also been found to improve outcomes in multiple other hematologic malignancies, including plasma cell leukemia [1–3].

Along with adverse effects including peripheral neuropathy, cytopenias, and gastrointestinal complaints [3–6], pulmonary complications associated with bortezomib use are being increasingly reported and characterized in the literature. In 2014, Yoshizawa et al. [7] described three patterns of bortezomib-induced lung disease (BILD) based on radiologic findings: interstitial pneumonia (including diffuse alveolar damage (DAD), hypersensitivity pneumonitis (HP), and non-DAD/non-HP), vascular hyperpermeability (noncardiogenic pulmonary edema), and hypoxia without significant radiological abnormalities. Additionally, bortezomib-induced diffuse alveolar hemorrhage (DAH) has emerged as a distinct clinical manifestation of BILD.

In this paper, we present a case of bortezomib-induced alveolar hemorrhage occurring after the first treatment dose in a patient with plasma cell leukemia, and provide a comparative summary of the seven previous cases of bortezomib-induced DAH reported in the literature to date.

2. Case presentation

A 59-year-old female presented to our institution with a four-week history of malaise, myalgia, chills, and unintentional weight loss. She also endorsed rhinorrhea and a non-productive cough over this time. She had no medical history or prescription medications, although she took daily supplements including Vitamin C, Vitamin D, zinc, garlic, and a multivitamin. She used marijuana intermittently but did not smoke tobacco or use any other substances. Upon presentation, she was afebrile with an oxygen saturation of 96% on room air and otherwise stable vital signs. Her respiratory, cardiac, and abdominal examinations were unremarkable.

Initial investigations were notable for a peripheral lymphocyte count of 52.2×10^9/L and flow cytometry showing 70% involvement of an immunophenotypically abnormal monoclonal plasma cell population. A bone marrow biopsy performed on Day 4 of her hospital admission confirmed a diagnosis of plasma cell leukemia. Of note, CT chest performed upon admission to hospital did not demonstrate any airspace disease.

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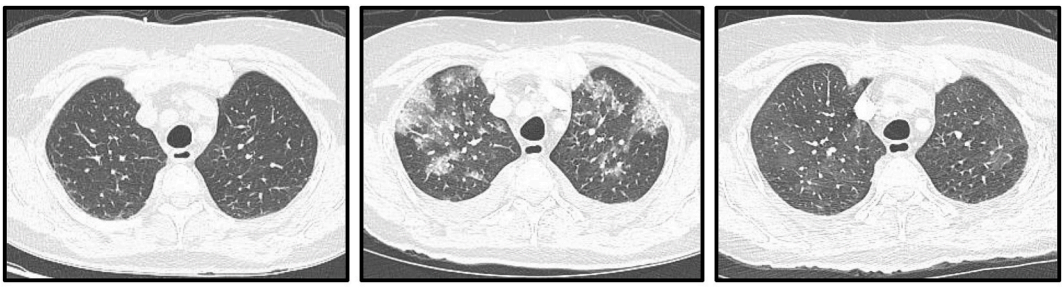

Fig. 1. Axial views of patient's chest CT scan at different points during her hospital admission. A: Six days prior to receiving bortezomib; B: Two days after receiving bortezomib; C: Nine days after receiving bortezomib.

On Day 8, she began therapy with bortezomib 1.3 mg/m^2 weekly, dexamethasone 40 mg weekly, and lenalidomide daily. She was afebrile and her oxygen saturation was 95% on room air. The next day, her cough worsened significantly from earlier in the admission, and the sputum contained small volumes of dark blood. The hemoptysis and severe cough persisted on Day 10; she remained afebrile with an oxygen saturation of 96% on room air. A CT scan of the chest demonstrated bilateral patchy ground glass opacities with regions of crazy paving and new small bilateral pleural effusions (Fig. 1).

Bronchoscopy was performed on Day 11. Sequential bronchoalveolar lavage demonstrated increasingly hemorrhagic returns. Microbiologic testing for bacterial and fungal cultures, COVID-19, influenza, RSV, TB, PJP, and galactomannan was negative, and cytology did not demonstrate any malignant cells. A workup for alveolar hemorrhage was initiated. Anti-nuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), extractable nuclear antigen (ENA) panel, anti-nuclear cytoplasmic antibodies (ANCA), anti-glomerular basement membrane antibodies (anti-GBM), complements C3 and C4, cryoglobulin, anti-cardiolipin antibodies, and lupus anticoagulant testing were all within normal limits. CRP was 82.1 mg/L (2.9 mg/L on admission).

The patient remained clinically stable on room air, with no further hemoptysis after Day 12 of her admission and with gradual improvement in her cough. Therefore, she was not immediately initiated on corticosteroids, aside from the 40 mg of weekly dexamethasone in her chemotherapeutic regimen. However, she became febrile on Day 13 and on Day 14, out of concern that the fevers may be a delayed manifestation of a bortezomib-related reaction, she was started on prednisone 70 mg daily. A septic workup was negative, and the fevers subsided.

A repeat CT scan of the chest on Day 17 of her admission showed near complete resolution of the ground glass opacities, with some residual mosaicism in the upper lung zones, and a decrease in the size of the effusions. She was discharged home shortly afterward and continued therapy with lenalidomide and a tapering dose of steroids; our service advised that she not be rechallenged with bortezomib. She has not had any recurrence of her respiratory symptoms.

3. Discussion

Table 1 summarizes the cases of bortezomib-related DAH reported in the literature. All prior cases involved males with multiple myeloma between 51 and 82 years of age. Six out of seven patients developed respiratory failure (at least three of whom required mechanical ventilation), all were treated with high dose steroids, and three of the seven died. In addition to being the first reported case in a female patient and in a patient with plasma cell leukemia, our patient is unique in that she was not hypoxemic despite BAL findings of DAH and recovered without immediately receiving high-dose steroids.

It is important to note that while some BILD patients in the literature did undergo bronchoscopy/BAL [13], most did not [7,14,15]. It is therefore possible that some cases with significant airspace disease on CT scan may have been unrecognized DAH since not all patients with DAH present with hemoptysis [16]. Accordingly, attempts to draw distinctions between BILD patients with DAH and those without, must be undertaken with caution.

Nevertheless, when comparing the cases of bortezomib-induced DAH to reports of BILD without demonstrated pulmonary hemorrhage, there is a noticeable difference in the ethnicity of the affected patients. While the majority of reported non-hemorrhagic BILD cases have occurred in Japanese patients [7,14,17], most reported cases of DAH involved Caucasians. The overall high rate of BILD seen in Japanese patients may simply reflect closer monitoring for pulmonary complications in Japan compared to other countries; however, Shimazaki et al. [18] proposed that the Japanese population may have a genetic predisposition toward developing interstitial pneumonitis. Future epidemiological studies involving patients of varying ethnic backgrounds would provide further clarification.

There are also similarities between BILD patients with known DAH and those without. Kharel et al. [15] reported a BILD mortality rate of 37.2% in the literature, which is consistent with the 37.5% mortality rate among bortezomib-induced DAH cases, as shown in Table 1. They [15] also reported a higher mortality risk among patients with a prior stem cell transplant; while our DAH data set (Table 1) is too small for such an analysis and is further limited by missing data, we note that the one DAH patient with a known prior stem cell transplant did survive. Additionally, the number of bortezomib doses received prior to the onset of DAH (ranging from 1 to 9 doses) does not differ significantly from those reported for BILD without alveolar hemorrhage [7,13–15,17–19].

The mechanism by which bortezomib leads to BILD, including DAH, has not been fully elucidated but several hypotheses have been presented. This drug is known to modulate inflammation through the inhibition of NFκB, a proinflammatory transcription factor. Some authors have proposed that reactivation of NFκB following the withdrawal of bortezomib provokes a rebound inflammatory response in the lungs [13,14,18], while Wirk [9] suggested that the presence of bortezomib during the resolution of an inflammatory process (although the initial trigger for that inflammation is unclear) prolongs the inflammation. Alternatively, it has been proposed that metabolites of bortezomib may cause direct injury to the lung [13–15]. Further, Sugita et al. [11] hypothesized that the alveolar hemorrhage observed in their patient resulted from the rapid disintegration of multiple myeloma cells in the lung following the first dose of bortezomib, and Miyakoshi et al. [14] proposed the same mechanism in one of their patients. However, this mechanism is unlikely to be applicable in our case because, unlike Sugita et al.'s patient who had patchy ground glass opacities on CT prior to the initiation of treatment, our patient's initial CT scan had no abnormalities suggestive of leukemic infiltration of the lung parenchyma.

Table 1
Summary of BAL-confirmed cases of DAH secondary to bortezomib.

Case report	Demographics	Diagnosis	SCT prior to borte-zomib	Corticosteroids administered with bortezomib cycle	Pulmonary findings while on bortezomib, prior to DAH diagnosis	Number of bortezomib doses prior to DAH diagnosis*	Clinical presentation at time of DAH diagnosis	CT chest findings	Treatment and outcome
Pitini et al., 2006 [8]	51 M Italian	MM	Yes	Unknown	No	9	Dyspnea, hypoxemia	Bilateral infiltrates	Methylprednisolone 1g daily Survived
Wirk, 2012 [9]	67 M American, ethnicity not specified	MM	No	Yes	Yes (bibasal consolidation with negative workup including BAL after 4th dose)	8 (twice-weekly dosing)	Fever, hypoxemic respiratory failure requiring intubation and ventilation	Diffuse bilateral GGO	Methylprednisolone 2mg/kg daily Died
Ayed et al., 2014 [10]	67 M Caucasian	MM	Unknown	Unknown	Yes ("respiratory symptoms" after 4th dose)	8 (twice-weekly dosing)	Fever, dyspnea, hypoxemia, respiratory failure	Bilateral infiltrates and GGO, interlobular septal thickening	High dose steroids Died
	72 M Caucasian	MM	Unknown	Unknown	No	2 (twice-weekly dosing)	Fever, cough, hypoxemia, respiratory failure	Bilateral infiltrates	High dose steroids Survived
	55 M Caucasian	MM	Unknown	Unknown	No	1 (1.5mg/m^2)	Fever, hypoxemia, respiratory failure	Bilateral infiltrates	High dose steroids Died
Sugita et al., 2015 [11]	67 M Japanese	MM	No	Yes	No, but had small patchy GGO prior to start of treatment	1	Hemoptysis (also present prior to bortezomib), cough, hypoxemic respiratory failure requiring intubation and ventilation	Diffuse bilateral GGO and consolidation	Methylprednisolone 1g daily with clinical improvement Rechallenged at a reduced dose with no recurrence Survived
Do and Dew, 2018 [12]	82 M Caucasian	MM	No	Yes	Yes (RLL infiltrates and effusions beginning Day 8, in the setting of sinus node dysfunction)	Unknown (diagnosed 33 days after beginning bortezomib)	Respiratory failure requiring intubation and ventilation	GGO, bilateral pleural effusions	Methyprednisolone 1g daily Survived
Current report, 2020	59 F Caucasian	PCL	No	Yes	No	1	Hemoptysis, cough, delayed fever	Bilateral patchy GGO, crazy paving, bilateral pleural effusions	Prednisone 70 mg daily, 5 days after symptom onset Survived

BAL = bronchoalveolar lavage, DAH = diffuse alveolar hemorrhage, SCT = stem cell transplant, MM = multiple myeloma, PCL = plasma cell leukemia, GGO = ground glass opacities, RLL = right lower lobe. *Bortezomib dosing 1.3mg/m^2 unless otherwise specified.

4. Conclusion

Along with being the first case of bortezomib-induced DAH described in a female patient and in a patient with plasma cell leukemia, our case differs notably from most previously published reports in that our patient did not develop respiratory failure. As such, it provides additional insight into the spectrum of disease severity observed in DAH secondary to bortezomib therapy. Continued research is warranted to better characterize the varying forms of BILD, risk factors, and underlying mechanisms.

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Declaration of competing interest

The authors do not declare any conflicts of interest.

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