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Case Study

Early-Onset Severe Diffuse Alveolar Hemorrhage after Bortezomib Administration Suggestive of Pulmonary Involvement of Myeloma Cells

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Severe acute lung injury is a rare but life-threatening complication associated with bortezomib. We report a patient with multiple myeloma who developed a severe diffuse alveolar hemorrhage (DAH) immediately after the first bortezomib administration. The patient was suspected to have pulmonary involvement of myeloma, which caused DAH after rapidly eradicating myeloma cells in the lungs with bortezomib. Rechallenge with bortezomib was performed without recurrent DAH. In patients with multiple myeloma who manifest abnormal pulmonary shadow, we should be aware of early-onset severe DAH after bortezomib administration, which might be due to pulmonary involvement of myeloma cells. 〔*J Clin Exp Hematop 55(3) : 163-168, 2015*〕

Keywords: multiple myeloma, bortezomib, acute lung injury, diffuse alveolar hemorrhage

INTRODUCTION

Bortezomib is a proteasome inhibitor that has been shown to contribute to improved overall survival in patients with multiple myeloma. Although the most common toxicities associated with bortezomib are peripheral neuropathy and diarrhea,[1] few cases of severe and life-threatening acute lung injury (ALI) have been reported, including acute respiratory distress syndrome and diffuse alveolar hemorrhage (DAH).[2-9] Although several reports have suggested a severe pulmonary reaction to bortezomib, the precise mechanism is unclear. Here, we report a case of early-onset DAH after bortezomib administration, which might have been caused by the rapid disintegration of myeloma cells in lung tissues.

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CASE REPORT

A 67-year-old male was admitted with fatigue, cough, and mild hemoptysis. He had a low fever, tachypnea, and hypoxia. Whole blood cell count showed severe anemia (hemoglobin, 3.2 g/dL) and mild thrombocytopenia (98,000/mm^3) without plasmacytosis. Laboratory work-up revealed renal failure (serum creatinine, 5.1 mg/dL) and hyperproteinemia (serum total protein, 11.2 g/dL) with normal serum calcium level. Serum and urine protein electrophoresis showed monoclonal proteins of immunoglobulin A-λ type (6,653 mg/dL) and Bence-Jones proteinuria. No osteolytic lesion was found. Bone marrow aspiration led to a diagnosis of multiple myeloma (stage IIIB according to the Durie-Salmon staging system and stage III according to the International Staging System). A t(14;16) (q32;q23) translocation was found by fluorescent *in situ* hybridization. Chest X-ray and computed tomography (CT) revealed multiple bilateral small patchy ground-glass opacities (GGOs) in the lungs (Fig. 1). Sputum specimens showed no evidence of infectious microorganisms. The anti-neutrophil cytoplasmic antibodies and the anti-glomerular basement membrane antibody were negative. The patient's

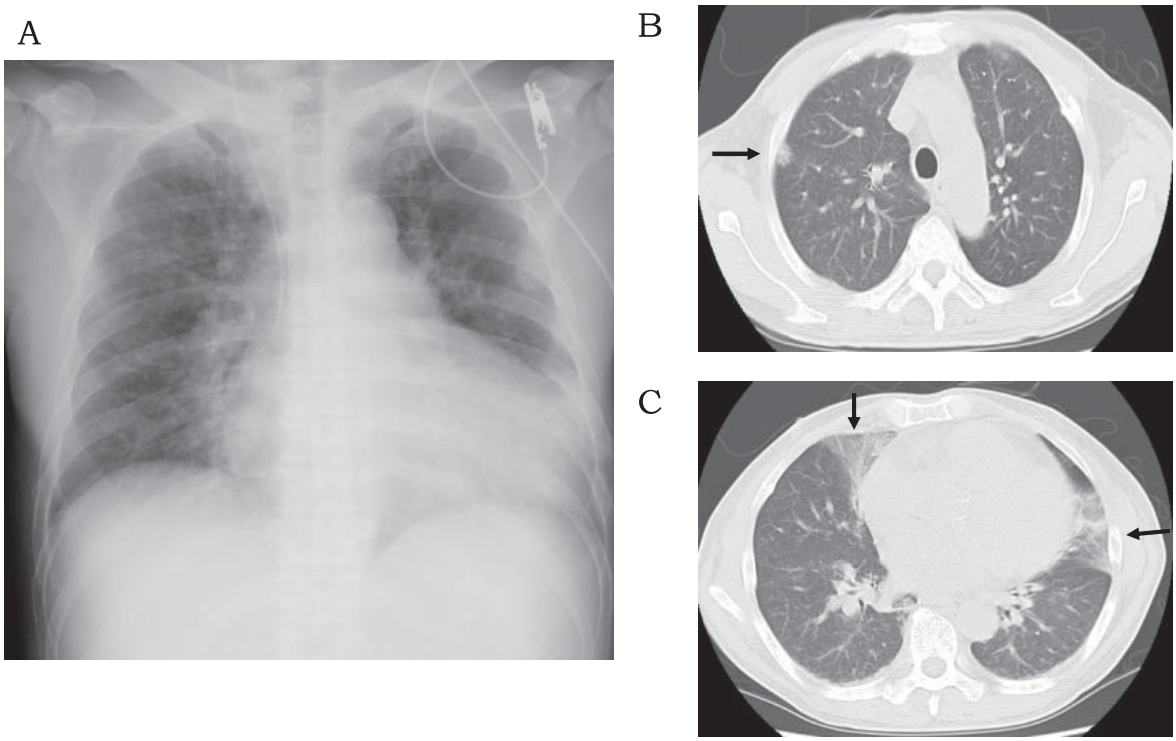

Fig. 1. Chest X-ray and computed tomography scan on admission showed multiple patchy ground glass opacities (ground-glass opacities indicated by *arrows* in *1B* & *1C*).

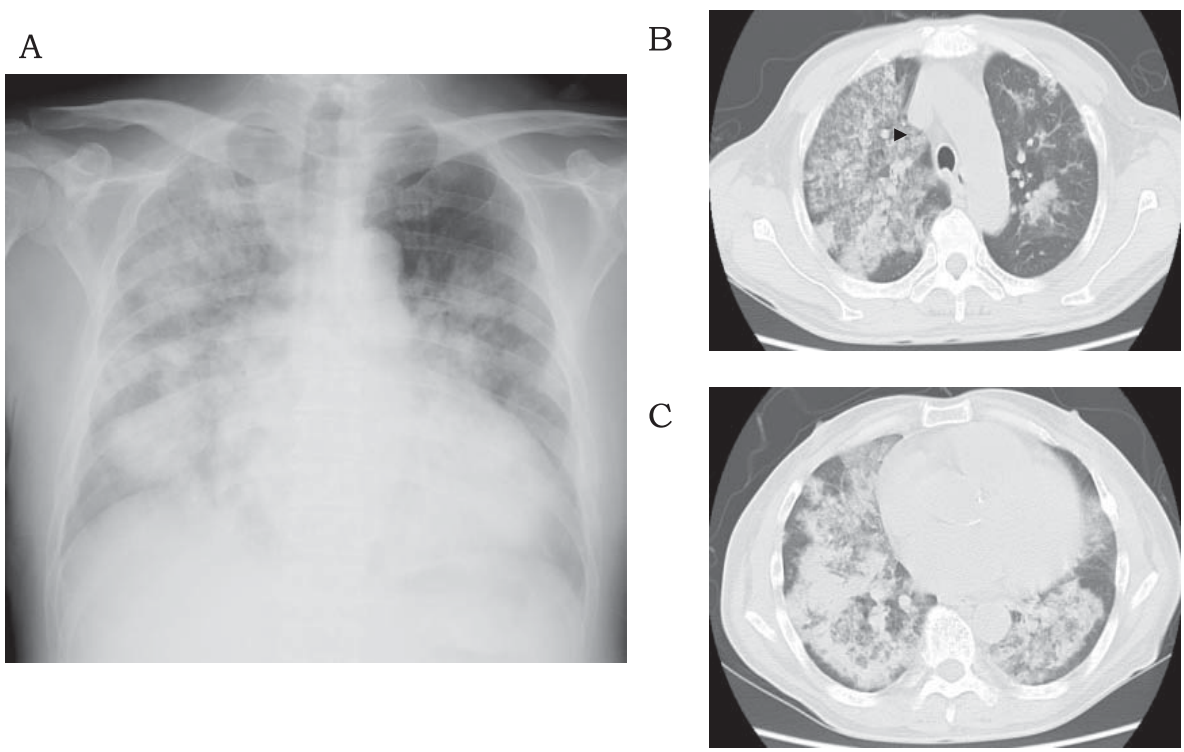

Fig. 2. Chest X-ray and computed tomography scan on day 3 of the first cycle of bortezomib treatment showed severe diffuse parenchymal consolidations, which were compatible with diffuse alveolar hemorrhage. An *arrowhead* in Fig. 2b indicates it.

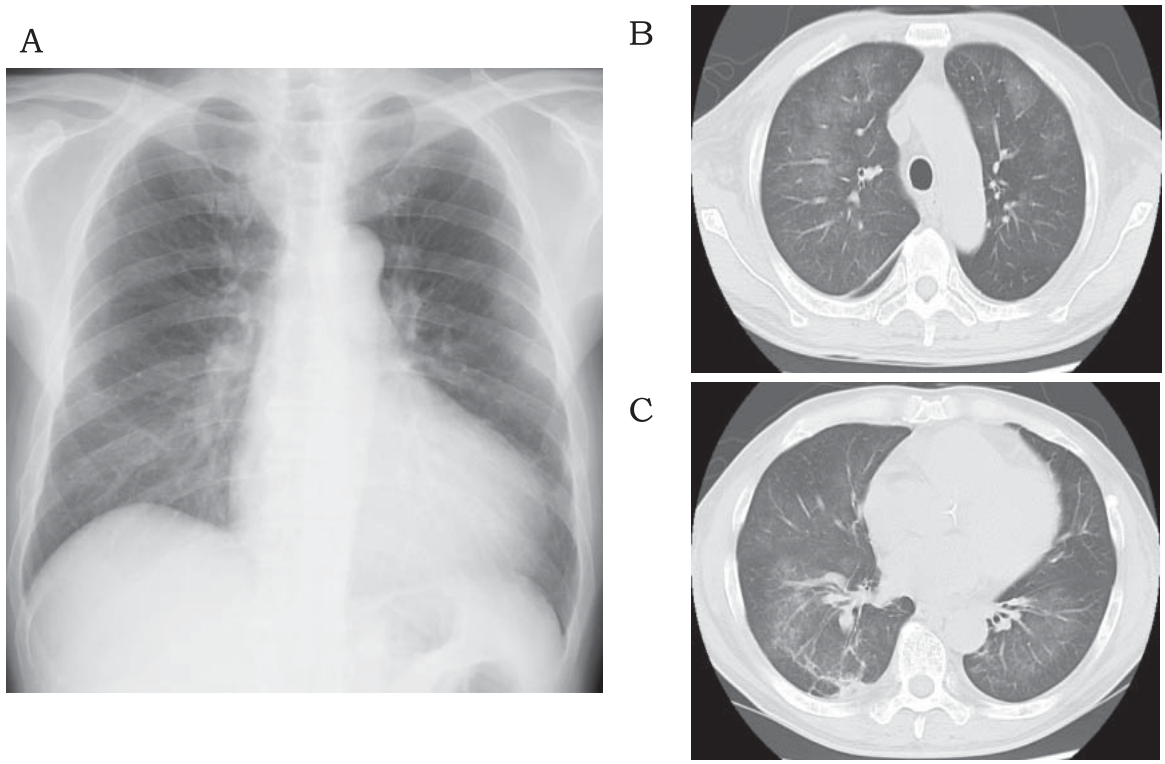

Fig. 3. Chest X-ray and computed tomography scan on day 25 of the first cycle of bortezomib treatment showed not only the resolution of diffuse consolidations due to diffuse alveolar hemorrhage but also the disappearance of ground-glass opacities, which were observed on admission.

medical history was unremarkable, with no history of smoking. Induction therapy was initiated using high-dose dexamethasone (40 mg/day intravenously) on days 1-4, 9, and 10. The patient's cough and hemoptysis resolved within several days; however, serum total protein and creatinine levels remained elevated. Consequently, bortezomib plus dexamethasone (BD) therapy (bortezomib, 1.3 mg/m^2 intravenously; dexamethasone, 20 mg/day intravenously) was initiated on day 11. On day 12, the serum total protein level decreased remarkably from 10.4 to 7.4 mg/dL; however, the patient developed severe cough, hemoptysis, and hypoxia that required intubation and mechanical ventilation. Chest X-ray and CT revealed severe diffuse parenchymal consolidations (Fig. 2). Bronchoalveolar lavage aliquots were hemorrhagic, consistent with DAH, without detecting any infectious microorganisms or malignant cells. The patient did not present with disseminated intravascular coagulation, but a lung biopsy was not performed because of the patient's poor condition. No evidence was found of bacterial, fungal, mycobacterial, Pneumocystis, or cytomegalovirus infection in the sputum, blood, and serum samples. Serum KL-6 was not elevated. An echocardiogram showed normal ventricular wall motion. Methylprednisolone (1,000 mg/day) was administered from days 12 to 15. The patient's respiratory condition and hemoptysis resolved rapidly, and chest radiography showed gradual improvement. BD therapy was resumed on day 19, after reducing the bortezomib dose to 0.7 mg/m^2 on days 1, 8, and 15 in combination with 20 mg/day of dexamethasone. With no recurrence of DAH, the patient was extubated on day 21. Chest X-ray and CT on day 25 showed not only the resolution of DAH-associated diffuse consolidations but also the disappearance of GGOs, which had been observed on admission (Fig. 3). Subsequent bortezomib doses were increased to 1.0 mg/m^2 on days 1, 4, 8, and 11, without recurrence of DAH. The serum creatinine level decreased to 2 mg/dL, and the patient was able to avoid hemodialysis. Although the patient achieved a very good partial response with 3 additional courses of BD therapy, the treatment was switched to lenalidomide and dexamethasone as a consequence of severe neuropathy. The patient died of disease progression at 1 year from diagnosis.

DISCUSSION

In the Assessment of Proteasome Inhibition for Extending Remissions trial, grades 3 and 4 dyspnea after bortezomib treatment occurred in 5% and 0.3%, respectively.[1] To the best of our knowledge, 17 cases of ALI have been reported

Table 1. Previously reported cases of acute lung injuries following bortezomib

Case No. [Reference]	Age/ sex	Race	MM type/ D&S	Previous therapy	History of lung disease	Regimen	No. of Bor dose (days)	Accompanied symptom	Therapy (dose)	Outcome (Day from onset, Cause of death)
#1 [2]	31/F	JP	IgG/EM	Allo SCT	BOOP	Bor	5 (31)		mPSL	Dead (33 days, ARF)
#2 [2,3]	48/F	JP	IgD/3A	Allo SCT	None	Bor	4 (15)	Fever	mPSL (0.5 g/day)	Re-challenged without recurrence Alive (1.5 months)
#3 [2,3]	47/F	JP	IgG/3B	HD-Mel	IPA	Bor	4 (18)	Cough	Dex (40 mg/day)	Re-challenged, but recurred Dead (40 days, ARF)
#4 [2,3]	59/F	JP	IgA/3B	HD-Mel, Thal	PE	Bor	4 (14)	Fever, wheezing	mPSL (1 g/day)	Alive (3 months)
#5 [2,3]	53/F	JP	BJP/3B	HD-Mel, Thal	None	Bor + Dex	1 (1)	Wheezing	mPSL (1 g/day)	Dead (1 day, ARF)
#6 [2]	66/F	JP	IgG/1A	Yes (NR)	None	Bor + Steroid	1 (5)	Fever	None	Dead (36 days)
#7 [2]	64/M	JP	IgG/2A	HD-Mel x 2	None	Bor	3 (13)	Fever	Steroid	Dead (69 days, Sepsis)
#8 [4]	66/M	AA	NR	Thal + Dex	None	Bor	9 (NR)	Fever, cough	PSL (60 mg/day)	Alive (8 months)
#9 [5]	65/M	AA	WM	Flu, Rix, Thal	None	Bor	3 (9)	Fever	None	Alive (1 month)
#10 [6]	51/M	NR	IgG/NR	Thal	None	Bor	9 (NR)		mPSL (1 g/day)	Alive (0.5 month)
#11 [7]	66/M	NR	NR	Yes (NR)	COPD	Bor + Dex	8 (NR)		mPSL (0.5 g/day)	Alive (1 month)
#12 [8]	72/M	CH	IgG/3A	Yes (NR)	None	Bor + Dex	8 (29)	Fever, cough	mPSL	Dead (NR, ARF)
#13 [8]	51/M	CH	IgD/3A	Yes (NR)	None	Bor + Dex	2 (5)	Fever	mPSL	Dead (NR, ARF)
#14 [8]	72/F	CH	IgG/3A	None	None	Bor + Dex	2 (8)		mPSL	Dead (NR, ARF)
#15 [8]	68/F	CH	IgG/3A	Yes (NR)	None	Bor + Dex	2 (4)	Fever	mPSL	Dead (NR, ARF)
#16 [8]	72/M	CH	IgG/3A	Yes (NR)	None	Bor + Dex	8 (32)	Fever	mPSL	Dead (NR, ARF)
#17 [9]	67/M	NR	IgG/3A	None	None	Bor + Dex	4 (14)	Fever, chest pain	PSL	Re-challenged, but recurred Dead (1.5 month, ARF)
Present case	67/M	JP	IgA/3B	None	None	Bor + Dex	1 (1)	Cough, hemoptysis	mPSL (1 g/day)	Re-challenged without recurrence Dead (1 year, Myeloma)

AA, African American; ARF, acute respiratory failure; BOOP, bronchiolitis obliterans with organizing pneumonia; Bor, Bortezomib; CH, Chinese; COPD, chronic obstructive pulmonary disease; Dex, dexamethasone; D&S, Durie-Salmon stage; EM, extramedullary myeloma; Flu, fludarabine; IPA, invasive pulmonary aspergillosis; JP, Japanese; NR, not reported; PE, pulmonary embolism; Rix, Rituximab; Thal, Thalidomide; WM, Waldenström's macroglobulinemia; F, female, M, male; Allo SCT, allo-stem cell transplantation; HD-Mel, high-dose melphalan; mPSL, methyl prednisolone

(Table 1). Fifteen (88%) subjects had relapses or refractory myeloma. Twelve (71%) were Asian, and 4 (24%) had a history of lung disease. The median number of bortezomib doses before the development of ALI was 4 (range, 1-9), and the median time to the development of ALI from the first bortezomib administration was 13.5 days (range, 1-32 days). The major type of ALI was acute respiratory distress syndrome; DAH was observed in only 2 subjects. Nine (53%) died of respiratory failure, including 2 with relapsed ALI after rechallenge with bortezomib.

The pathogenesis of bortezomib-associated ALI remains unclear. Previous case reports hypothesized that the inhibition of NF-$\varkappa$B by bortezomib may play an important role in the development of lung injuries.[2,8,9] Some reports suggested that inhibiting NF-$\varkappa$B during the resolution of inflammation may protract the inflammatory response.[2,9] In contrast, Dun *et al*. hypothesized that the withdrawal of bortezomib may activate NF-$\varkappa$B-induced proinflammatory factors, leading to inflammatory responses.[8] A rapid response to steroids favors this hypothesis. In the present case, these hypotheses are unlikely to explain the cause because DAH developed immediately after the first bortezomib administration, which may have been too early to develop an inflammatory reaction. Furthermore, the patient did not have a fever, which is a commonly observed manifestation in bortezomib-induced ALI.[2] Additionally, we found no evidence of other causes of DAH, such as pulmonary infection, acute pulmonary edema due to heart failure, or vasculitis. Pulmonary amyloidosis can also cause hemoptysis,[10] but the acute onset and rapid resolution after dexamethasone therapy would not favor this hypothesis. ALI caused by autoimmune disease was unlikely, because there were no other clinical or laboratory findings suggestive of autoimmune disease; moreover, ALI developed after high-dose dexamethasone. Because no blood transfusion was performed within 6 h of developing ALI, transfusion-related acute lung injury was ruled out.

Miyakoshi *et al*. reported a case of early-onset ALI (Pt. #5 in Table 1) in which the patient developed ALI on the day following the first bortezomib administration. They hypothesized that the rapid disintegration of myeloma cells in lung tissues may have contributed to the pathogenesis of ALI.[3] This mechanism may also have been involved in the present

case. The present patient developed ALI on the day following the first bortezomib administration. The rapid decrease in serum total protein level after the first bortezomib administration showed that the highly effective treatment may have caused a rapid disintegration of myeloma cells, thus consequently leading to DAH. Although high-dose dexamethasone could relieve the respiratory symptoms, such as cough and hemoptysis, via its anti-inflammatory effect as a corticosteroid, it could not decrease the tumor burden of myeloma because the serum total protein and creatinine levels remained elevated despite the administration of high-dose dexamethasone for 6 days.

Although we could not obtain histological evidence, the presentation of multiple pulmonary GGOs on admission suggests that the present patient had pulmonary involvement of myeloma cells. In a previous series of 958 myeloma patients, 4 cases were considered to show pulmonary involvement, only 1 of which was proven by cytology and pathology.[11] In addition, only a few cases with histologically proven pulmonary involvement have been reported in the literature.[12-18] These findings suggest that the histological diagnosis of pulmonary involvement in myeloma is extremely difficult, particularly after bortezomib treatment, as in the present case. In patients with multiple myeloma who manifest abnormal pulmonary shadowing, pulmonary involvement from myeloma cells may be possible; therefore, lower doses of bortezomib should be initially administered to avoid severe DAH.

In patients who develop drug-induced severe adverse events, re-treatment is generally contraindicated. Some have suggested that rechallenge with bortezomib could cause a relapse of ALI.[3,9] Currently, in Japan, the rechallenge of bortezomib is not the only applicable treatment option. In addition, it may be an option to continue treatment with high-dose dexamethasone as it is. However, Pt. #5 from Table 1 developed ALI by the same mechanism as in the present case and was successfully rechallenged with bortezomib in combination with hydrocortisone;[3] we considered this to be the only applicable treatment option for a highly aggressive disease in a patient with severe renal dysfunction. Therefore, we decided to rechallenge with bortezomib with dexamethasone. Fortunately, rechallenge with bortezomib was successful without recurrent DAH. Furthermore, GGOs on chest CT on admission (Fig. 1) disappeared by day 25 after bortezomib treatment (Fig. 3). These findings support our hypothesis of pulmonary involvement in myeloma, suggesting that the first bortezomib administration may have completely eradicated pulmonary involvement of myeloma cells, and consequently, the second administration did not cause DAH.

In conclusion, although the mechanism of bortezomib-associated pulmonary complications remains unclear, some cases suggest pulmonary involvement in myeloma, which may develop into immediate lung injury by the eradication of myeloma cells in the lungs. In patients with multiple myeloma who manifest abnormal pulmonary shadow, we should note that pulmonary involvement of myeloma cells may be possible, and should be aware of rapidly developing severe DAH after bortezomib administration.

CONFLICT OF INTEREST: The authors have no potential conflict of interest.

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