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Case Report

Bortezomib induced pulmonary toxicity: a case report and review of the literature

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Abstract: Bortezomib is widely used in the treatment of Multiple Myeloma. While the most common side effects are neurological and gastrointestinal related complications, severe pulmonary problems are rarely described. The present case is a 72-year old male with multiple myeloma, who received Lenalidomide, Bortezomib, and Dexamethasone (RVD) combination regimen. He underwent 30 Gy palliative radiotherapy to the thoracic 5-9 and lumbar L1-3 vertebra due to pain and fracture risk. During the third cycle, he was admitted to hospital with dyspnea and dizziness. The thoracic CT revealed bilateral pleural effusions, a diffuse reticular pattern on the parenchyma, and ground-glass opacities that were compatible with drug-induced lung injury. The microbiological and molecular analysis excluded infectious disease, and lung biopsy confirmed the diagnosis of Bortezomib Lung Injury. The time from the first dose of Bortezomib to the lung injury was 57 days, and it was five days from the last dose of Bortezomib. His symptoms were refractory to IV steroids and supportive care. Our patient was lost despite steroids and intensive care support. Even Bortezomib induced lung injury is a rare adverse effect, based on high mortality rate, we would like to emphasize the clinical importance of this clinical scenario in light of the published literature and our presented case.

Keywords: Bortezomib, lung injury, pulmonary toxicity, proteasome inhibitor, multiple myeloma

Introduction

Drug-induced interstitial lung disease develops secondary to an exposure to a drug that induces inflammation and subsequent interstitial fibrosis in the lungs. The radiological features are rarely specific to the drug etiology; moreover, the clinical phenotype, imaging, and histopathology patterns vary significantly between drugs and between patients on the same drug. In order to exclude drug-induced interstitial lung disease, the timing between drug exposure and initiation of the symptoms, absence of other potential causes such as infection, irradiation or cardiac background, and improvement of the pulmonary functions following the cessation of the drug, with or without corticosteroids, needs to be known in detail [1]. Meanwhile, grading of drug-induced interstitial lung disease (DIILD), which is based on the "National Cancer Institute Common Terminology Criteria for Adverse" including the status of symptoms and medical intervention, is commonly used in the trials [2]. The prognosis usually depends on the underlying disease, and various degrees of glucocorticoid response could be observed, and this clinical condition may result in the death of the patient [1].

Bortezomib is a proteasome inhibitor, inducing apoptosis and reversing drug resistance in myeloma cells. The ubiquitin-proteasome path-

way is critical for cell signaling, regulation of transcription, and functional receptor control. It regulates the activation of nuclear factor-kappa B (NF-κB) by the degradation of NF-κB inhibitor. It was shown that this process's dysregulation might have a role in tumor progression, drug resistance, and altered immune surveillance [3]. Additionally, it blocks the cytokine pathways, cell adhesion, and angiogenesis, and affects the tumor microenvironment [4].

Bortezomib is commonly used in the first-line treatment of multiple myeloma (MM), combined with dexamethasone and alkylating agents, or immunomodulatory agents. It has also been approved for Mantle cell lymphoma. The most common adverse events are neurologic, mostly peripheral neuropathy, fatigue, neuralgia, headache, paresthesia, and dizziness. Hematological side effects, especially cytopenia, are dose-limiting. Infections, especially herpes zoster reactivation, are essential to follow up on during treatment. It is metabolized by the cytochrome p450 pathway, majorly CYP3A4, which is essential to pay attention to in polypharmacy [5].

Bortezomib, related to severe pulmonary complications is rarely reported in the literature. Although the mechanism is unclear, the potential proinflammatory role of Bortezomib is suspected to be the significantly responsible mechanism of this condition [6]. Herein, we report a fatal case of pulmonary complications related to bortezomib administration (Patient gave informed consent to the publication of his case at the initiation of the treatment. Koç University ethical committee [nr 2020.363.IRB1.145] approved the submission of this manuscript).

Case report

A 72-year-old male was admitted to the hospital complaining of back pain. The radiologic scan showed a fracture on the seventh thoracic vertebra. In August 2018, he underwent a kyphoplasty, and the pathologic examination was consistent with a ratio of 15% of lambda monoclonal plasma cells. Therefore, the patient was referred to our hematology department.

His medical history revealed atrial fibrillation and deep venous thrombosis, with treatment consisting of apixaban and metoprolol. Among the CRAB (calcium, renal disease, anemia, and bone disease) parameters, which are the treatment indicators for MM, our patient had lytic lesions only, and the serum albumin and B2-microglobulin levels were normal. The levels of serum IgA was 1280 mg/dl, free-lambda 86.3 mg/l, free-kappa (fk) 14.8 mg/l, fL/fK 5.83, total-lambda (t/L) 3680 mg/l, total-kappa (t/K) 1540 mg/l, and tL/tK 2.38. The serum and 24-hour urine immunofixation electrophoresis showed IgA/Lambda type monoclonal bands.

The bone marrow biopsy result was in accordance with the previous surgical specimen's evaluation, confirming the diagnosis of multiple myeloma (MM). The kongo red staining was negative. The conventional cytogenetic analysis of the bone marrow aspiration reported 46XY in all the metaphases, and no mutation was detected in the FISH analysis.

A whole-body magnetic resonance imaging scan showed a compression fracture in the sixth, eighth thoracic vertebrae, and third lumbar vertebrae. Additionally, nodular lesions with secondary deposits on the left scapula, pelvic bones, and ribs were detected.

Considering the status of the bone disease, our patient was staged as Durie-Salmon Stage III. His ISS and R-ISS categories were both 1. Bortezomib, lenalidomide, and dexamethasone (VRD) q28d combination regimen with zoledronic acid was administered. In September 2018, the patient received 30 Gy palliative conformal radiotherapy to the sternum, right rib, thoracic vertebrae 5-9, and lumbar vertebrae 1-3. The mean lung doses for the left and the right lung were 8 Gy and 12 Gy, respectively.

After receiving two cycles of VRD, the serum and 24-hour urine immunofixation electrophoresis showed normalized serum and urine immunofixation electrophoresis and an fK/fL ratio.

Following the second cycle of VRD and ten fractions of radiotherapy, the ECOG performance score was 0, and the third cycle of the VRD was started in December 2018. On the 15th day of the 3rd cycle, the patient was admitted to our hospital with dyspnea and dizziness.

His cardiologic assessment demonstrated no ventricular arrhythmia, and his fingertip satura-

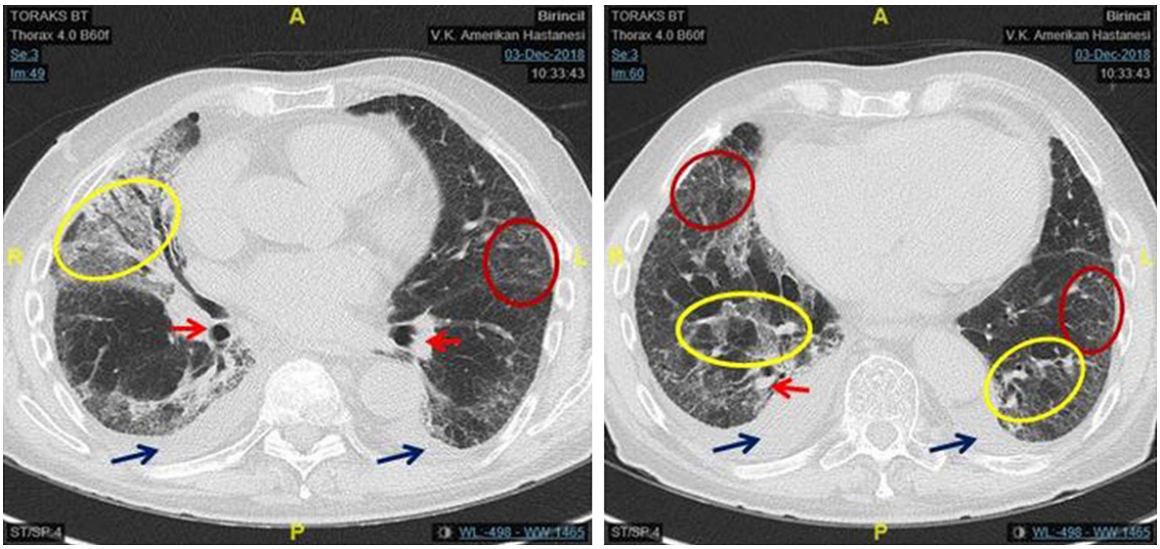

Figure 1. Thoracic CT was showing bilateral ground-glass opacity (red circle), diffuse reticular pattern of the parenchyma (yellow circle), peribronchial thickening (red arrow), and bilateral pleural effusion (blue arrow).

tion was 98%. The results of the echocardiogram showed normal left ventricular functions, with an ejection fraction of 56%.

His physical examination revealed a fever, symptomatic dyspnea with effort, hypoxemia, and prolonged expirium, and inspiratory crackles in the middle zone of the right lung. The Thoracic CT reported bilateral pleural effusions, diffuse reticular pattern on the parenchyma, and a ground glass opacification appearance denser on the right side, which was evaluated to be compatible with drug-induced lung toxicity (**Figure 1**). There was no pulmonary embolism detected.

The differential diagnosis included pulmonary hemorrhage and infection. Accordingly, a bronchoscopy was performed. The bronchoalveolar lavage fluid was evaluated for gram stain, aerobic culture, fungal culture, and direct immunofluorescent test and PCR for the Pneumocystis Jirovecii, and cytomegalovirus DNA, and all the results were negative.

The pathological examinations of the lung biopsy taken during the bronchoscopy showed thickening in the interstitial spaces, hyperplasia in type 2 pneumocytes, vacuolar degeneration, and foam cell accumulation in the alveolar lumen (**Figure 2**). There were no morphological findings suggesting infection or neoplasia, and the amyloid dyes were also negative. Therefore, the current findings were primarily attributed to drug-induced toxicity.

Methylprednisolone (1 mg/kg) was initiated. However, the hypoxemia promptly worsened, and our patient was transferred to the intensive care unit (ICU). Broad-spectrum antibiotics and antifungal drugs were empirically added to the treatment. Pulsed steroid therapy was also started to improve the pulmonary functions. He was first placed on the High Flow Nasal Cannula Oxygen therapy system (40 L/min flow and FiO_2: 1.0), which did not improve the respiratory distress and low SpO_2 status. Non-invasive mechanical ventilation also failed, and so invasive mechanical ventilation was initiated. The protective ventilation strategy was used for the severe acute respiratory distress syndrome (according to the Berlin definition) presentation [7]. Six sessions of prone positions (6-17 hours of duration) were performed during the invasive ventilation period. Despite medical support and treatment, he died due to respiratory failure in January 2019.

Discussion

The incidence of drug-induced interstitial lung disease widely differs, ranging from <1% to 60% in various studies [1]. The most common causes are cancer drugs, followed by disease-modifying anti-rheumatisms, antibiotics, non-steroidal anti-inflammatory drugs, psychiatric

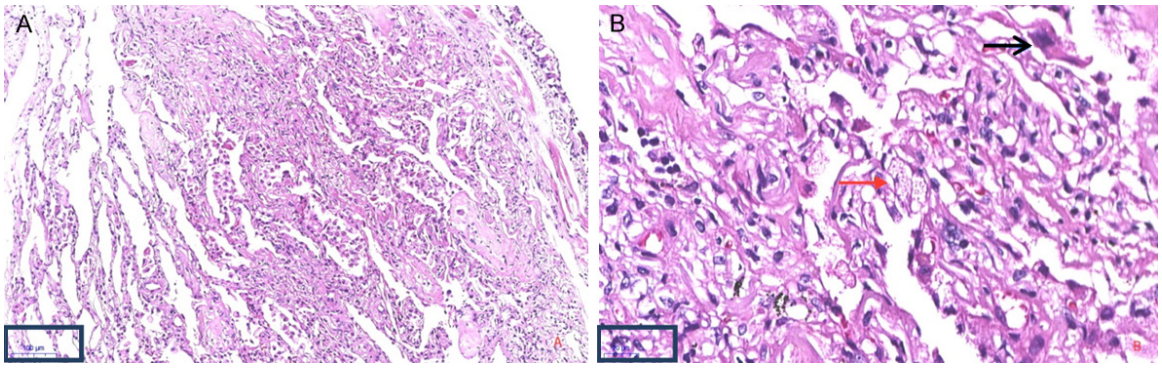

Figure 2. Pathological examinations of the lung biopsy. A. Patchy interstitial thickening and alveolar macrophage accumulation. 10× Hematoxylin and Eosin. B. Foamy cells (red arrow) and pneumocyte type 2 hyperplasia (black arrow). 58.8× Hematoxylin and Eosin.

agents, and anti-arrhythmic molecules. Among the cancer therapeutics, bleomycin, gemcitabine, epidermal growth factor receptor-targeted agents, the target of rapamycin protein (mTOR) inhibitors, and immune checkpoint inhibitors are mostly identified [1]. In the literature, Bortezomid related pulmonary fibrosis has been scarcely reported, and by presenting our patient's case, the patient who had no response to steroids and intensive care, we would like to emphasize the importance of this clinical situation for routine practice as there is no specific period between drug and respiratory symptoms as well as no purely identified risk factors. Unlike many other agents, the risk does not appear to be dose related. To date, 28 cases were reported with bortezomib-induced interstitial lung disease, and we correlated the clinical course with the published literature in a table (**Table 1**).

The use of invasive procedures such as bronchoscopy for bronchoalveolar lavage combined with transbronchial lung biopsy or surgical lung biopsy is not recommended frequently for drug related interstitial lung diseases. Increased white blood cell differentials in the bronchoalveolar lavage may be shown in various inflammatory or infective conditions. The reversal of the CD4:CD8 ratio may also be detected; however, it is not a specific finding. Although there were no specific or pathognomonic features in the lung biopsy specimens, likewise in this case, the pathologic examination as well as the bronchoalveolar lavage results may be helpful in the differential diagnosis at least for the exclusion of infection and malignant involvement of the lungs. As a result, we can conclude that the use of invasive procedures for the diagnosis of drug-induced lung diseases in selected cases may be preferred during the evaluation without delay. Glucocorticoids and cessation of the causative agent is the common treatment approach [4].

Bortezomib related pulmonary toxicities are rarely reported. Although the incidence of Bortezomib induced lung injury (BLI) is unknown, in a large registry study of 1010 MM patients, 45 patients were reported to have BLI by their physician. However, the causality could only be constituted in 26 patients (2.6%), with 5 of them resulting in death despite steroid treatment [8]. Additionally, there are scarce detailed case reports and a small case series published in the literature [6, 9-21] (**Table 1**). In the case reports, the average number of RVD cycles until the toxicity was presented was 6.9, and the period between the development of pulmonary toxicity and the first dose of Bortezomib was 31.1 days. This period for our case was 57 days, and it was five days from the last dose of Bortezomib.

Miyakoshi et al. reported 13 Japanese MM patients (M/F: 4/9) with a median age of 54. Four patients had pulmonary complications, and two patients died. It is worth emphasizing that these cases had refractory MM, and both had had previous autologous stem cell transplantation (ASCT) [6]. In another Japanese retrospective analysis on seven patients with Bortezomib induced lung injury, six patients were female, and one of them had a history of irradiation. The history of the SCT was reported to be a risk factor, and a combination of

Table 1. Detailed characteristics of patients with Bortezomib induced severe lung injury

	Age	Sex	Type	Background pulmonary disease	Previous stem cell transplantation	Radiation history	Bortezomib courses	Days to the lung injury	Treatment	Response
Miyakoshi [6]	47	F	IgG	Invasive pulmonary aspergillosis	Autologous	None	8	1 day after the last dose	40 mg of dexamethasone for 4 days	Recovered
								3 days after the last dose	antibiotics, antifungal, methylprednisolone for 3 days; 125 to 1000 mg	Death due to respiratory failure
	59	F	IgA	Pulmonary embolism	Autologous	None	4	4 days after the last dose	antibiotic; methylprednisolone 1000 mg for 4 days	Recovered
	48	F	IgD	None	Unrelated allogeneic	Total body irradiation	4	5 days after the last dose	antibiotics, methylprednisolone 500 mg	Recovered
	53	F	NA	None	Autologous	None	1	1 day after the last dose	Methylprednisolone 1000 mg for 2 days	Death due to respiratory failure
Gotoh [9]	31	F	IgG	Bronchiolitis obliterans	Allogeneic (Twice)	NA	5	31 days from the initiation of the cycle	Pulse steroid	Death due to respiratory failure
	48	F	IgD	None	Allogeneic	NA	3	7 days from the initiation of the cycle	Steroids	Recovered
	47	F	IgG	Aspergillosis	Autologous	NA	4	19 days from the initiation of the cycle	Dexamethasone	Recovered
								12 days from the initiation of subsequent the cycle	Pulse steroid	Death due to respiratory failure
	59	F	IgA	Pulmonary embolism	Autologous	NA	4	10 days from the initiation of the cycle	Pulse steroid	Recovered
	53	F	NA	None	Autologous	NA	1	1 day from the initiation of the cycle	Pulse steroid	Death due to respiratory failure
	66	F	IgG	None	None	NA	1	5 days from the initiation of the cycle	NA	Unresponsive to treatment; death not due to respiratory failure
	64	M	IgG	None	Autologous (Twice)	NA	3	13 days from the initiation of the cycle	Steroids	Responded to treatment; death due to sepsis
Dun [10]	72	M	IgG	None	NA	NA	2nd cycle	29 days after first bortezomib administration	Methylprednisolone 160-640 mg/24 hours for 1-10 days, antibiotics	Death due to respiratory failure
	51	M	IgD	None	NA	NA	1st cycle	5 days after first bortezomib administration		Death due to respiratory failure
	72	F	IgG	None	NA	NA	1st cycle	8 days after first bortezomib administration		Death due to respiratory failure
	68	F	IgG	None	NA	NA	1st cycle	4 days after first bortezomib administration		Death due to respiratory failure
	72	M	IgG	None	NA	NA	2nd cycle	32 days after first bortezomib administration		Death due to respiratory failure
Boyer [11]	66	M	NA	None	None	None	9	14 days after the last dose	antibiotics, diuretics for congestive heart failure, prednisolone 60 mg 7 day slowly tapered over 5 months	Recovered
Chew [12]	66	M	IgG	NA	Autologous	NA	6	6 days after the last dose	40 mg of dexamethasone for 2 weeks	Recovered with 40 mg of dexamethasone for 2 weeks
							8	6 days after the last dose	Antibiotics	Death

Duek [13]	50	F	IgA	NA	Autologous	None	1	NA	Steroids	Death due to respiratory failure
Pitini [14]	51	M	IgG	None	Autologous	NA	9	2 days after the last dose	methylprednisolone 1000 mg for 5 days, than continued on 1 mg/kg/day	Recovered
Zappasodi [15]	66	M	NA	Chronic obstructive pulmonary disease	None	None	8		Methylprednisolone 500 mg/day for 2 days, maintained on oral dexamethasone for 2 weeks	Recovered
Kang [16]	67	M	IgG	None	None	NA	4	NA	Steroids for 6 weeks	Recovered
Vandeix [17]	74	M	IgG	None	None	NA	8	3 days after the last dose	Antibiotics, methylprednisolone 1 mg/kg/day	Recovered
Wirk [18]	67	M	IgG	None	None	NA	8	5 days after the last dose	antibiotics, methylprednisolone 2 mg/kg/day	Death due to respiratory failure
Yamaguchi [19]	64	M	IgG	None	Autologous	NA	16 doses before auto and 2 doses after	5 days after the last dose	methylprednisolone 1 mg/kg/day	Recovered
Li [20]	62	M	IgG	None	None	None	6	NA	antibiotics, IVIG, methylprednisolone 120 mg/day	Recovered
Kharel [21]	64	M	NA	NA	None	Thoracic spine	8	14 days after the last dose	High dose methylprednisolone	Death due to respiratory failure
Current Case	72	M	IgA	None	None	Sternum, right ribs, T5-9, L1-3	12	4 days after the last dose	Antibiotics, antifungals, methylprednisolone 1 mg/kg/day and pulse steroid	Death due to respiratory failure

Abbreviations: NA: not available.

Bortezomib with corticosteroids appeared to reduce the risk of lung injury [9]. Our case had BLI during the third cycle of the first-line treatment and had 30 Gy radiotherapy to the sternum, thoracic vertebra, and lumbar vertebra.

The mean lung dose during radiotherapy is a known risk factor for radiation pneumonitis, which may be a potential background for BLI. In the literature, the data about irradiation is absent. However, in three published patient cases who received irradiation to the thoracic area, only one recovered from BLI [21]. More studies evaluating the optimal radiotherapy technique and lung dose-volume parameters must be analyzed from the perspective of this knowledge. Also, patients who were treated with radiotherapy need to be followed up on closely for pulmonary signs and symptoms. Our case's mean lung dose was less than 12 Gy, which has been generally accepted as a standard dose-volume parameter to prevent radiation pneumonitis.

The pathogenesis of Bortezomib induced lung injury is undefined. The proinflammatory role of Bortezomib with increased levels of IL-6, TNF-alpha and genetic factors were suspected [6]. In addition to circulating endothelial cells, increased C reactive protein levels were detected in the peripheral blood of a BLI case, showing the presence of cellular inflammation, vascular destruction, and tissue necrosis [14]. A review of the studies shows that the development of pulmonary toxicity with even a single dose of the drug was higher in the Japanese patients when compared to the American and European patients. This finding supports the idea that ethnic and genetic factors may have a role in the development of toxicity [11].

The acute and severe presentation of drug-induced lung disease accompanied by hypoxemia (by definition severe ARDS according to the Berlin classification [7]), which was the case in our patient, are the most critical risks for mortality. Additionally, males and being over 65 years of age are also related to mortality [1]. Our patient also had a history of atrial fibrillation and deep venous thrombosis. Atrial fibrillation may be accepted as a complication of the macrovascular dysfunction associated with systemic endothelial dysfunction [22]. We know that the mechanisms having a role in deep venous thrombosis have an association with endothelial dysfunction in both the venous and arterial system [23]. Additionally, our patient received palliative radiotherapy to the fields involving the lungs. Although it was a low dose procedure, radiation is also known for causing hypoxic endothelial damage [24]. The subsequent administration of the Bortezomib resulted in pulmonary fibrosis. In summary, our case had four predisposing factors of endothelial injury: 1-basic macrovascular background, 2-deep venous thrombosis, 3-radiotherapy, and 4-bortezomib administration.

The clinical signs and radiological findings of BLI are not specific, and it is challenging to differentiate BLI from the acute exacerbations of underlying pulmonary diseases. The acute presentation of Bortezomib administered patients with dyspnea worsened with physical effort, and hypoxemia, accompanied by radiological findings, should be a warning to the clinician about the possibility of BLI. Invasive procedures are generally withheld, and empirical treatment approaches are preferred due to the general medical and physical condition of the patient. In the case of deterioration or lack of improvement under empirical antibiotherapy, invasive procedures are performed; however, this approach causes retardation of the diagnosis. On the other hand, this could cause a lack of diagnosis if the disease improves spontaneously and the clinician may re-administer Bortezomib, which may result in fatal complications. We may assume the last bortezomib dose of our case caused the initiation of the vicious cycle to start the BLI. We propose that Bortezomib should be used with caution in patients with a high risk of endothelial dysfunction. We cannot comment on the re-use of Bortezomib or another proteasome inhibitor in the case of recovery. Therefore, Bortezomib related lung toxicity should be considered in the differential diagnosis in case of presentation with pulmonary signs and symptoms, especially with a high background of vascular dysfunction. Further long-term analysis of Bortezomib's previous studies and new clinical trials focusing on the pulmonary adverse effects of proteasome inhibitors are needed to deeply analyze this potentially fatal toxicity.

Disclosure of conflict of interest

None.

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