

Bortezomib Induced Interstitial Lung Disease

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Abstract

Bortezomib is an anticancer agent used for multiple myeloma in combination with other chemotherapeutic drugs. Pneumonitis and pulmonary toxicity associated with bortezomib application has been reported in a series of cases associated with multiple myeloma. A 59-year-old male patient received 16 weeks of CyBorD regimen followed by first phase of RVD regimen and bortezomib biweekly resulted in partial remission. During the second phase of RVD regimen developed cough and whitish sputum. On high resolution computed tomography showed opacities on the lungs and diagnosed as bortezomib induced interstitial lung disease. He responded to the cortecosteroid therapy and respiratory symptoms subsided. This is a clinically proven bortezomib induced interstitial lung disease on retreatment with bortezomib for a patient with relapsed multiple myeloma.

Keywords: Bortezomib, CyBorD regimen, Interstitial lung disease, RVD regimen, Pulmonary toxicity.

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INTRODUCTION

Drug induced interstitial lung disease occurs when exposure to a therapeutic agent results in inflammatory response and eventually fibrosis of the lung interstitium. More than 350 drugs have been implicated as causative factors for drug induced lung disorders. According to the American thoracic society/ European respiratory society classification drug induced interstitial lung disease is a subtype of a group of diffuse parenchymal lung diseases but it is very hard to distinguish this from interstitial pneumonia because of the clinical, pathological and radiological features associated with it [1].

Studies show that cancer drugs are the predominating therapeutic agents cause for ILD, or is it drug induced ILD) accounting for 23-51% of cases. Followed by the disease modifying anti-rheumatic drugs (DMARDs) about 6-7%, Non-steroidal anti-inflammatory drugs (NSAIDs) 0-23%, Antibiotics 6-25%. Among this all-cancer drugs identified as the leading cause of ILD in the initial search. It is hard to

distinguish the single drug which cause DILD in case of cancer drugs because most chemotherapy are given as combination regimens. Most common anticancer drugs showed causing ILD include are Bleomycin, epidermal growth factor receptor (EGFR) directed therapies, gemcitabine, immune check point inhibitors [1, 2].

Interstitial lung disease includes a large spectrum of lung diseases which are confusing and challenging for general as well as pulmonary physicians. Here in this scenario bortezomib is the culprit drug. Common adverse effects associated with bortezomib are peripheral neuropathy, cytopenias and gastro intestinal problems [3].

Here we examined a patient with multiple myeloma, treated with bortezomib well responded initially but developed interstitial lung disease on the relapsed phase during the bortezomib retreatment.

CASE

A 59-year-old businessman a known case of longstanding diabetes was evaluated for anemia and lower back ache for three-month duration. On routine lab investigation, peripheral smear revealed normocytic normochromatic anemia with rouleaux formation. Bone marrow aspiration showed hypercellular marrow with 13% mature plasma cells and 40% plasma cytoid lymphocytosis. Biopsy revealed plasma cell neoplasm, his lymphocytes count found to be reduced about 17%. His skeletal survey showed partial collapse of D12 vertebra with abnormal signal with multiple benign collapse involving the upper lumbar vertebra. For the prevention of bone resorption, He was given a dose of inj. Zolendronic acid 4mg. He was started on chemotherapy with CyBORd (cyclophosphamide, bortezomib, dexamethasone) regimen. 16 weeks of chemotherapy with CyBORd regimen resulted in partial remission. It was followed by 24 weeks of RVD

regimen (linalidomide, bortezomib, dexamethazone). It also resulted in partial remission. He was hence switched over to bortezomib biweekly. Further re assessment shows disease progression, hence he was switched back to RVD regimen.

During the second cycle of RVD regimen he developed complaints of fever, cough and whitish sputum 3 weeks for which he was admitted in local clinic and treated with oral Levofloxacin. He got readmitted with recurrence of cough and dyspnea. On examination he was tachypneic (Respiratory rate – 24/min) with an oxygen saturation of 93% in room air. Respiratory system examination revealed mid to late inspiratory crackles bilateral infrascapular areas. His hemogram and inflammatory parameters were normal. Culture of blood and sputum showed no evidence of infection.

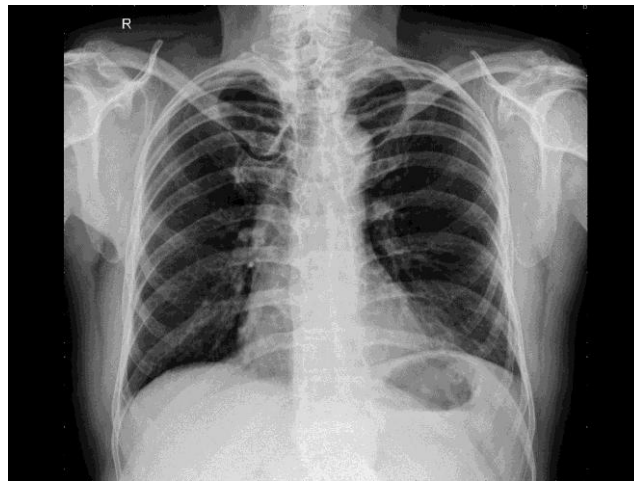


Figure-1: Chest radiograph showing bilateral lower zone and mid zone acinar shadow and reticular shadow

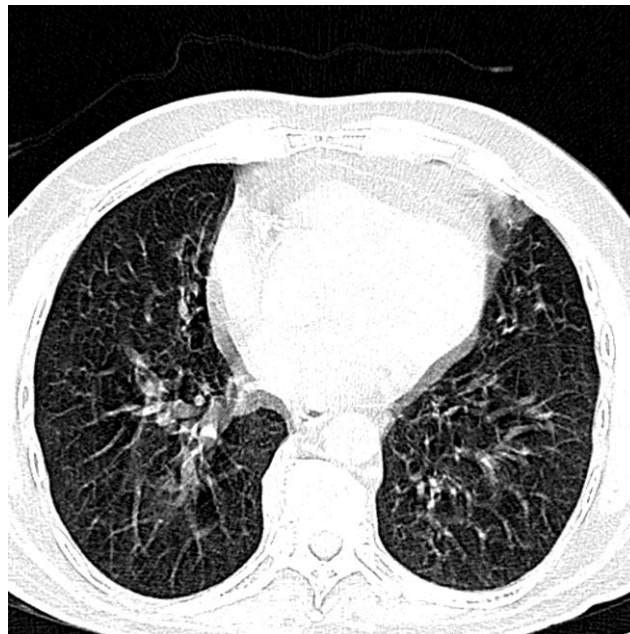


Figure 2: High resolution computed tomography image of lung showing diffuse ground glass opacity with interlobular septal thickening

Chest radiograph revealed bilateral lower zone and mid zone acinar and reticular shadow. Chest radiograph & clinical findings warranted an examination with HRCT of the thorax to rule out drug induced pneumonitis. High resolution computed tomography image of lung showing diffuse ground glass opacity with interlobular septal thickening predominantly involving both lower lobes with a small air space opacity in right upper lobe. Functional evaluation revealed a restrictive pattern in spirometry with Forced vital capacity (FVC) 1.76L (57.2%), Forced expiratory volume in 1 second -1.51 L (61.5%) and FEV1/ FVC ratio 112. In 6 Minute walk test, patient walked 460 meters with no significant dyspnea/desaturation. However, the patient had tachycardia (HR- 92/min) during walk test. Diffusing capacity for Carbon monoxide (DLCO) was reduced to 50% of the predicted. He was suspected as having Bortezomib induced pneumonitis. Hence bortezomib was stopped and he was started on pomalidomide/ dexamethasone regimen. Steroids were started at a dose of prednisolone 1mg per kg and serially tapered over 6months. After 6month of treatment with corticosteroid, oxygen saturation (SpO₂) improved 99%, chest x Ray improved with clearance of shadow, FVC improved to 67% and walked 480m with no significant dyspnea/ desaturation/ tachycardia. Repeat HRCt at 6months showed clearance of ground glass shadow and interstitial shadow. Steroids were stopped. He was evaluated with chest radiograph, spirometry, 6 minute walk test which showed stable lung function.

DISCUSSION

Bortezomib is an anticancer drug which is used for the treatment of multiple myeloma in combination with some other chemotherapeutic agents like cyclophosphamide, doxorubicin, melfalan etc. The mechanism of bortezomib lung injury is unknown but it induces pulmonary toxicity by the suppression of nuclear factor (NF) κB causing inflammatory mediators to release [4]. This proteasome inhibitor produces apoptosis, growth arrest and reverse chemoresistance in multiple myeloma cells. Which offers a novel approach to the persisting treatment to the multiple myeloma cases producing rapid control in the disease state [5]. Though most of the adverse effects include peripheral neuropathy, cytopenias etc. but pulmonary associated adverse events are being increasingly reported. Bortezomib induced lung injury is one of the serious but under responded serious adverse effect with a considerable mortality rate. There are three types of bortezomib induced lung diseases according to the radiological findings, they include interstitial pneumonia which compromise of diffuse alveolar damage, vascular hyper permeability also known as non-cardiogenic pulmonary edema and hypersensitivity pneumonitis [3]. One study conducted in patients who are taking bortezomib, that most familiar pulmonary complications associated with them were dyspnea about 81.3%, respiratory failure 81.3%, cough for about

31.3%, fever in 62.5% and most radiological findings shows pulmonary infiltration for about 56.3%, pulmonary effusion 37.5% and ground glass opacities about 25% [6]. The treatment is usually with steroid therapy and oxygen in case of breathing difficulty in another study of bortezomib induced alveolar hemorrhage involving patients with multiple myeloma between 51 and 82 years of age, six out of seven patients were developed respiratory failure, treated with steroids and three out of seven were died [3]. Majority of the patients are well tolerated with the use of steroids to reduce the symptoms associated with BLI but the dose and duration of the steroid course may vary with individuals. Finding different treatment mechanism can be helpful in patients who are not tolerated by the steroid therapy [7, 14]. A study done by Jingbo Li, Shuda Chen, Yinghong Hu, and Jing Cai, in that a group of people who were on the bortezomib in combination with dexamethasone, half of the total population showed no clinical improvement in the steroid therapy. It is essential to keep an eye when these two drugs are combined in the treatment, most of them resulted in severe pulmonary complications [6, 12, 13]. Our patient showed well tolerated response to the therapy, so steroid application and supportive care are beneficial for the recovery of underlying disease condition with immediate bortezomib withdrawal. The figure 1 shows reticular shadow in the bilateral lower region and figure 2 showing diffuse opacity in the lung, ADR associated with bortezomib administration. The long duration usage of bortezomib may cause developing obstructive spirometric patterns in the lung field [4]. Therapeutic approach in our case showed beneficial and patient improved clinically faster. Early detection and rapid implementation of therapy is essential in these types of clinical cases which produce fast improvement in the disease progression, similarly our case is one of the clinically proven bortezomib induced interstitial lung disease which is being completely treated with cortecosteroid and supportive treatment strategies.

CONCLUSION

Interstitial lung disease is a life-threatening condition if it is undertreated. Pulmonary pneumonitis and pulmonary toxicity cases are increasing with the use of antineoplastics drugs like bortezomib, pomalidomide etc. They shows more prominent toxicity effects lungs rather than other adverse effects. Proper monitoring and care should be maintained during the treatment using such medications and the physicians must be aware of the adverse effects associated with them.

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