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Case Report

Imatinib Treatment for Bleomycin-Induced Pulmonary Toxicity

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Abstract

The basic treatment for bleomycin-induced pulmonary toxicity is corticosteroids. However, unresponsiveness to corticosteroid treatment can be observed in some cases. We present a case of a 51-year-old man, diagnosed with seminoma, who was receiving a combination treatment of bleomycin, etoposide, and cisplatin when admitted to the hospital with progressive cough and exercise-induced dyspnea. The patient's computed thorax tomography imaging showed bilateral consolidation of lungs, bronchoalveolar lavage (BAL) showed neutrophilia, and transbronchial biopsy showed fibroblastic proliferation. The sputum and BAL cultures were all sterile, and the patient was treated with methylprednisolone for the diagnosis of acute interstitial pneumonia. However, despite the corticosteroid treatment, patient suffered a respiratory failure. On the sixteenth day, imatinib 300 mg/day was added to the corticosteroid treatment. The result of the combination therapy was successful; therefore, corticosteroid and imatinib were stopped at the fifth and ninth month of the combination treatment, respectively. The patient, who is still under follow-up without any therapy until now, demonstrated that in cases of bleomycin-induced pulmonary toxicity that is unresponsive to corticosteroids, addition of imatinib to the treatment can be an alternative option.

KEYWORDS: Bleomycin, pulmonary toxicity, corticosteroid, imatinib

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INTRODUCTION

Bleomycin, which is commonly used for germ-cell tumors and lymphomas, exerts its antitumor activity via DNA synthesis inhibition and DNA breaks, leading to tumor cell death by induction of free radicals [1]. However, the patients who are treated with bleomycin can show pulmonary toxicity in 3%-40% of the cases [1, 2].

Bleomycin-induced pulmonary toxicity is basically treated with corticosteroids. However up to 1%-4% of the patients do not respond to corticosteroids treatment, which can cause fatal pulmonary toxicity [3].

CASE PRESENTATION

A 51-year-old man, who did not have any smoking history, was admitted with a dry cough and exercise-induced dyspnea. The patient had a diagnosis of seminoma with a history of three cycles of bleomycin (total dosage 270 units), etoposide, and cisplatin (BEP) treatment; the last cycle was completed a month ago. There were bilateral crepitant rales at both basal lung areas. The chest x-ray before BEP treatment was normal; however, Computed thorax tomography (Figure 1) after BEP therapy and computed thorax tomography after the third chemotherapy cycle showed bilateral heterogenic consolidations especially in posterobasal and peripheral areas (Figure 2). Positron emission tomography CT of the patient did not show any pathological involvement of fluoro-deoxyglucose uptake.

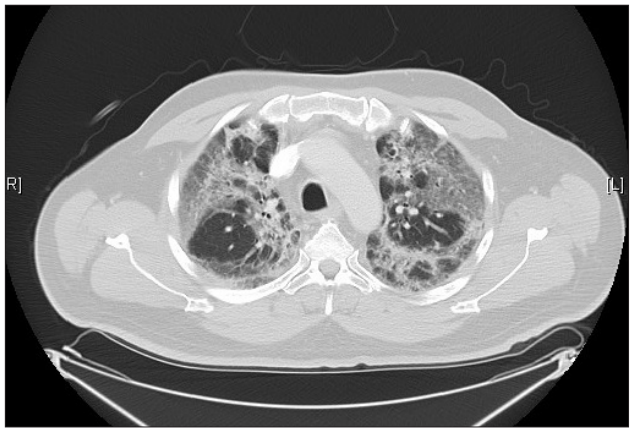

Figure 1. Computed thorax tomography. Bilateral peripheral heterogeneous irregular consolidations of lungs after BEP therapy

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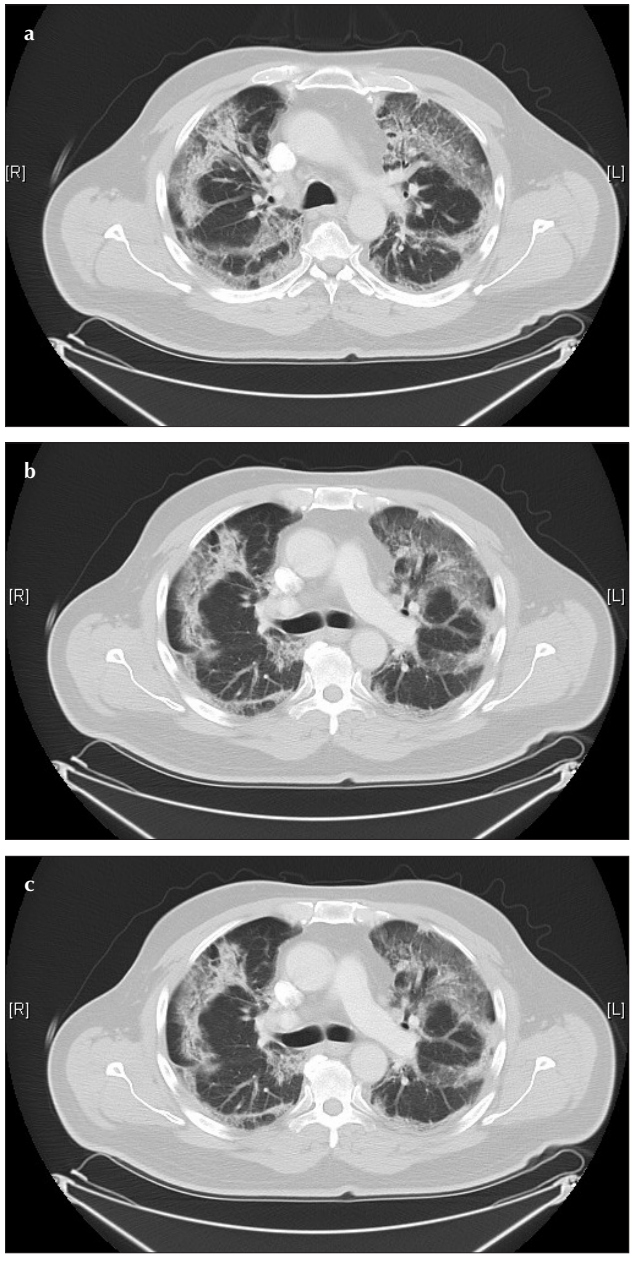

Figure 2. a-c. Computed thorax tomography. Bilateral peripheral heterogeneous irregular consolidations of lungs and ground-glass pattern

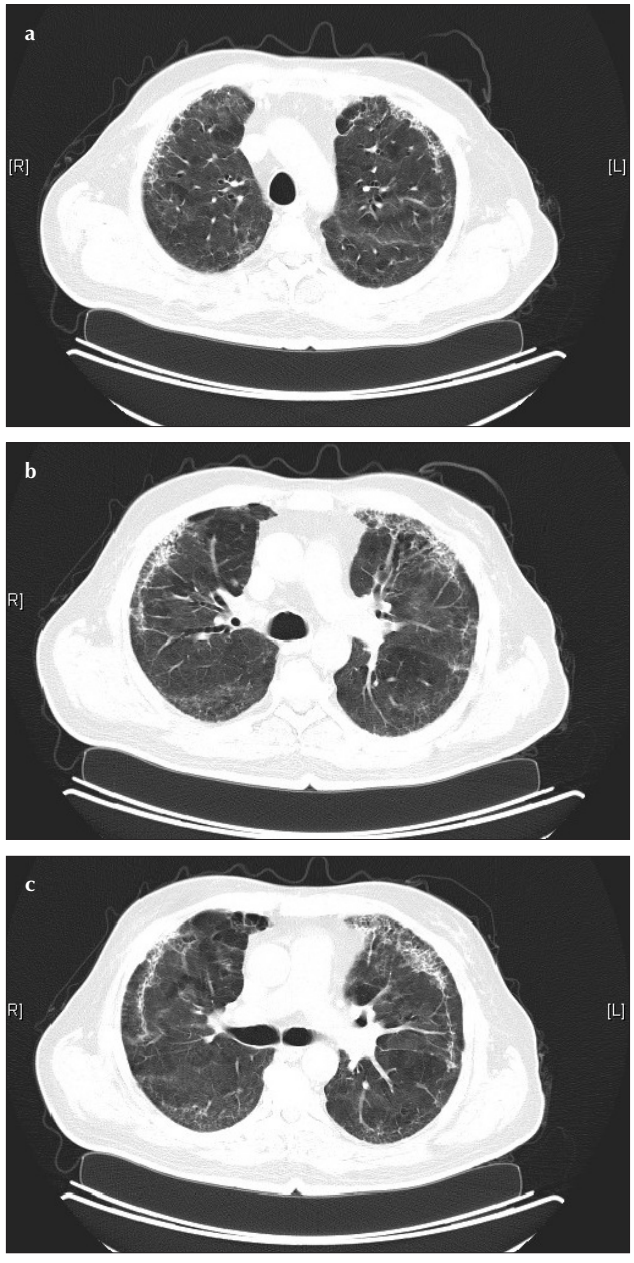

Figure 3. a-c. Computed thorax tomography after the fourth month of combination treatment. Close to a complete regression of consolidations and ground-glass pattern that was detected before the treatment

Respiratory function tests showed forced expiratory volume in one second (FEV_1) to be 2.80 L (67%), forced vital capacity (FVC) 3.34 L (63%), and FEV_1/FVC ratio 107%. Bronchoalveolar lavage (BAL) showed neutrophilia, and the transbronchial biopsy showed fibroblastic proliferation. The sputum and BAL cultures were all sterile, and the patient was treated with methylprednisolone (0.75 mg/kg/day) for the diagnosis of acute interstitial pneumonia. Although corticosteroid treatment was initiated, the patient appeared to be unresponsive to the steroid. We observed increased shortness of breath, the development of new infiltrations in the chest x-ray, and the deepening of hypoxemia and development of hypercapnia within the arterial blood gases (PaO_2=52.3 mmHg, $PaCO_2$=48.4 mmHg, O_2SAT=88.9, pH=7.454). Noninvasive mechanical ventilation was started immediately, and prednisolone dosage was increased to 100 mg/day. However, the patient remained unresponsive. Therefore, oral imatinib at a dosage of 300 mg/day was added as a combination treatment. After the first week of the combination treatment of corticosteroid and imatinib,

MAIN POINTS

- Bleomycin treatment is often complicated by pulmonary toxicity,which can be severe.
- In this case report, we describe a patient with bleomycin-induced acute interstitial pneumonia who did not respond to corticosteroid treatment but has successfully been treated with a combination therapy of corticosteroid and imatinib.
- This case report adds to the limited literature on the use of imatinib in BIP.

the patient's respiratory failure resolved and noninvasive mechanical ventilation was stopped. Computed thorax tomography showed a complete cure and regression after 4 months of treatment (Figure 3).

After the achievement of complete clinical and radiographic cure and regression, initial corticosteroid therapy was stopped at the fifth month of combination therapy, and then imatinib was stopped at the ninth month. The patient is still under follow-up without any treatment for 3 years.

The patient provided written informed consent for publication.

DISCUSSION

In this case report, we describe a case of bleomycin-induced pulmonary toxicity that did not respond to corticosteroid treatment alone and was successfully treated with a combination therapy of corticosteroid and imatinib.

Bleomycin-induced pulmonary toxicity has been observed at total dosages exceeding 400 units [4]. However, 1%-3% of bleomycin-induced pulmonary toxicity cases have been reported with total dosages of less than 300 units. O'Sullivan et al. [1] reported that patients above 40 years of age have pulmonary toxicity rates 2.3-3.5 times more than other patients at dosages less than 300 units and exceeding 300 units, respectively. Nephrotoxic medicine usage, renal insufficiency, concomitant granulocyte stimulating factor usage, tobacco and smoking addiction, oxygen therapy requirement, mediastinal radiotherapy, the infusion rate of the medicine, and concomitant cisplatin usage can increase the risk of bleomycin-induced pulmonary toxicity [5, 6]. Our patient was 51 years old, his bleomycin total dosage was 270 units, and he received concomitant cisplatin.

Exercise-induced dyspnea and nonproductive cough are main complaints of bleomycin-induced pulmonary toxicity. Computed thorax tomography depending on the underlying conditions shows diffuse alveolar damage, hypersensitivity pneumonia, organizing pneumonia, and eosinophilic pneumonia [7]. In our case, we showed bilateral posterobasal and peripheral heterogeneous irregular consolidations, ground-glass pattern, and thickening of pleura.

Corticosteroids are the main treatment for bleomycin-induced pulmonary toxicity. The classic dosage of corticosteroid treatment for bleomycin-induced pulmonary toxicity is 0.75 mg/kg/day. On the other hand, it is not recommended to exceed 100 mg/day [8]. The results of corticosteroid treatment for bleomycin-induced pulmonary toxicity are variable depending on the degree of the toxicity. Bleomycin-induced hypersensitivity pneumonia and organizing pneumonia respond usually well to corticosteroid treatment, although relapses and especially development of interstitial fibrosis that are unresponsive to corticosteroid treatment have also been reported [9]. In our case, we started with a 0.75 mg/kg/day (60 mg/day) dose of corticosteroid for treatment. However, after respiratory failure, the steroid dosage was increased to 100 mg/day.

Specific tyrosine kinase inhibitor, imatinib, is a chemotherapeutic medicine that is used for chronic myeloid leukemia, chordoma, dermatofibrosarcoma protuberance, and gastrointestinal stromal tumors [10]. Studies showed that imatinib causes TNF-a, IL-1b, IL-6, PDGF and TGFb-1 inhibition [11, 12]. Carnevale-Schianca et al. [13] described a good response to imatinib at dosages 300 mg/day with a bleomycin-induced pneumonitis case that did not respond to corticosteroid treatment alone. Banaakh et al. [14] reported a case that did not respond to corticosteroid treatment alone, and the patient started on a combined treatment of 75 mg of corticosteroid and 300 mg/day of imatinib, but the patient died due to gastrointestinal hemorrhage. Both cases described in the literature were diagnosed as Hodgkin's lymphoma, in which bleomycin-induced pulmonary toxicity occurred and were treated with imatinib. Our case is the only case diagnosed as seminoma, and bleomycin-induced pulmonary toxicity was successfully treated with imatinib. In our case, we increased the corticosteroid dose to 100 mg/day, but there was no response and the patient suffered a respiratory failure; therefore, we added imatinib as a combination therapy, and we got a very successful response for this fatal pneumonitis case. We did not stop corticosteroid treatment in our patient since there are only few case reports about this topic in the literature in which corticosteroid and imatinib were used together [13]. Our patient's pulmonary toxicity started at an earlier stage of bleomycin treatment (third month) when compared with other two cases described in the literature. Moreover, high-resolution CT findings in our case showed much more severe fibrotic changes than other two cases. Also, our case did not show pneumothorax, unlike Banaakh et al.'s [14] case.

In summary, imatinib is a safe and effective option that can be added to the treatment of bleomycin-induced pneumonitis cases unresponsive to the corticosteroid treatment.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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