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CASE REPORT

Bleomycin-induced Pulmonary Toxicity in a Patient with Hodgkin Lymphoma: A Case Report

Yethindra Vityala[1,*], Sai Praneeth Duvvuri[2], Krishna Chaitanya Meduri[2], Manjula Shantaram[3], Pavani Jaladi[4]

[1]*Honorary International Faculty, AJ Institute of Medical Sciences and Research Centre, Karnataka, Mangalore, India*
[2]*Department of General Medicine, Maheshwara Medical College and Hospital, Telangana, Hyderabad, India*
[3]*AJ Research Centre, A J Institute of Medical Sciences and Research Centre, Karnataka, Mangalore, India*
[4]*Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research, Andhra Pradesh, Anantapur, India*

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* *Corresponding author.*
Yethindra Vityala
yethindravityala10@gmail.com.

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ABSTRACT

Bleomycin is an antineoplastic drug used to treat various types of cancer. It can cause pulmonary toxicity (PT) with different patterns on chest computed tomography (CT), including diffuse alveolar injury, organized pneumonia, nonspecific interstitial pneumonia, and bronchiolitis. The exact mechanism of PT remains unclear, but it is related to the generation of active bleomycin radicals in the absence of oxygen. Currently, the only effective treatment for PT is timely administration of corticosteroids to prevent severe respiratory failure and fibrosis. A case of a patient with stage IIIB Hodgkin's lymphoma who experienced clinical deterioration attributed to the toxic effects of bleomycin is presented. The patient's chemotherapy regimen was changed, and the AVD regimen was continued without bleomycin, along with oral steroid treatment for four weeks. After seven weeks, the patient's symptoms improved significantly, and imaging revealed improvement.

Keywords: Bleomycin; Pulmonary toxicity; Hodgkin lymphoma; Traction bronchiolectasis

INTRODUCTION

Bleomycin is an antineoplastic drug derived from Streptomyces verticillus[1]. It induces cell death and blocks angiogenesis, making it effective in treating lymphomas, germ cell cancers, Kaposi's sarcoma, and other related conditions[2].

The cytotoxic effects of bleomycin vary based on dosage, with a 3-5% risk of interstitial pneumonitis at 300 mg and up to 20% at 500 mg. Pulmonary toxicity (PT) can present as different patterns on chest computed tomography (CT), including diffuse alveolar injury, organized pneumonia, nonspecific interstitial pneumonia, and bronchiolitis.

Bleomycin is generally well tolerated, with a common but milder febrile response that usually occurs shortly after administration[3,4]. However, in some cases, it can cause fulminant hyperpyrexia[5], a severe and potentially life-threatening condition characterized by a sudden and very high fever followed by collapse of the heart and lungs, which can result in fatality[6].

The exact mechanism of PT remains unclear; however, it is known to be related to the generation of active bleomycin radicals in the absence of oxygen[7]. Currently, the only effective treatment for PT is timely administration of corticosteroids to prevent severe respiratory failure and fibrosis.

CASE PRESENTATION

A 56-year-old man with hypertension and hypothyroidism experienced stomach pain and unintentional weight loss for 8 months along with other symptoms. During physical examination, swollen lymph nodes in the mesenteric and retroperitoneal regions as well as abdominal swelling and fluid accumulation were observed. Tests revealed a large cluster of swollen lymph nodes and elevated levels of small erythrocytes, thrombocytes, lactic dehydrogenase, and beta-2 microglobulin, indicating a lymphoproliferative syndrome

caused by potentially aggressive lymphoma. A biopsy and contrast-enhanced neck CT scan detected suspicious lymph nodes in bilateral zones IV, left VB, and VI, and contrast-enhanced chest CT revealed blast lesions on T12 with an infiltrative appearance in the mediastinal, hilar, and retroperitoneal lymph nodes. Biopsy results confirmed nodular sclerosis-type Hodgkin lymphoma in the cervical lymph nodes, with large cells positive for CD30, CD15, weak LMP1, and PAX5, and negative for AE1/AE3, CD20, and CD3.

The patient was diagnosed with stage IIIB Hodgkin's lymphoma, and treatment was initiated with the adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD) regimen, consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine. After the third cycle, the patient's functional class declined, accompanied by symptoms, such as cough-producing white sputum, clear nasal discharge, difficulty breathing, and headache, but no fever. Chest CT tomography revealed thickening of the interlobular septa and traction bronchiolectasis with a bronchiolocentric distribution and peripheral location. These findings correlate with the aggregated zones in the organization (Figure 1). Imaging results did not show any signs of structural lung damage before treatment. The patient's clinical deterioration was attributed to the toxic effects of bleomycin, a chemotherapeutic drug. As a result, the chemotherapy treatment was changed, and the AVD regimen was continued without bleomycin, along with oral steroid treatment for four weeks. After seven weeks, the patient's symptoms improved significantly, and imaging revealed improvement.

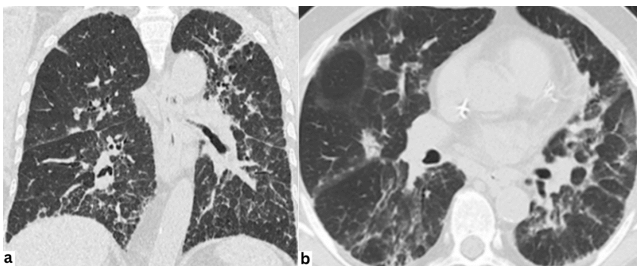

Fig. 1: High-resolution chest computed tomography scan: (a) coronal section showing signs of traction bronchiolectasis and ground-glass opacity, absence of an apico-basal gradient, (b) axial section that depicts a ground-glass pattern, consolidations with an air bronchogram, and a distribution that is focused around the bronchioles and extends to the periphery

DISCUSSION

Bleomycin is a chemotherapeutic drug that can cause skin rashes, irritation of mucous membranes, and increased sensitivity. The most severe side effect is pulmonary toxicity, which can result in a fatality rate of up to 3% and damage the alveolar and bronchial epithelium, basement membrane, alveoli, and alveolar septa. It is commonly used alone or in combination with other drugs to treat various types of cancer, including squamous cell carcinoma, testicular cancer, and Hodgkin lymphoma[2,7].

Bleomycin PT (BPT) is believed to be associated with the absence of bleomycin-inactivating enzymes (bleomycin hydrolase) in the lungs[8]. The pathogenesis involves the release of cytokines and free radicals by bleomycin, which leads to endothelial cell damage and the subsequent entry of inflammatory cells into the lungs. This process further activates the fibroblasts and causes fibrosis.

BPT is caused by its chemical reaction with Fe^{+2}, which reduces oxygen and generates free radicals[9]. These radicals harm the alveolocapillary membrane by oxidizing lipids, disrupting RNA and DNA, and hydrolyzing proteins. This damage primarily occurs in the lungs and skin due to the scarcity of bleomycin hydrolase enzymes in these organs.

BPT with CT patterns such as alveolar damage and ground-glass opacity. Oxygen administration can worsen this condition and lead to severe symptoms. During the subacute phase, it can progress into interstitial pneumonia and bronchiolitis. In the chronic stage, fibrosis patterns are common on CT images. These patterns include thickened septa, reticulation, and traction bronchiolectasis, all of which indicate pulmonary fibrosis[10–12]. Additionally, CT showed ground-glass opacities and consolidations in the subpleural and bronchovascular regions, suggesting areas of pneumonia in the process of organization or damage. The Naranjo scale was employed to assess the causality of the adverse drug reactions, which gauges the probability that the adverse drug reactions is primarily caused by medication rather than influenced by other factors[13]. In this instance, the score achieved a cumulative total of 6 points, indicating that the adverse drug reactions was likely due to bleomycin.

Treatment options include avoiding bleomycin and limiting glucocorticoids to symptomatic patients. Benefits have been shown in case series, although no controlled trials exist. Prednisone (0.75 1 mg/kg) is often recommended, with an improvement in imaging results after approximately 15 months[12].

After starting prednisolone therapy at a dose of 1 mg/kg/day, we modified the patient's AVD chemotherapy regimen, leading to significant improvement in the patient's symptoms. Three months later, chest CT was performed. Timely intervention is crucial when chemotherapy is extended, pulmonary fibrosis emerges, or patients fail to normalize symptoms and pulmonary function tests.

Patients with cancer often worry about weight loss when planning their diet, which typically includes high carbohydrate and calorie intakes. Studies have indicated that omega-3 fatty acid supplementation can be beneficial in diseases, such as diabetes, cancer, cardiovascular disease, and inflammation[14–16]. A ketogenic diet has been found to be useful in managing various health conditions such as

high cholesterol, epilepsy, cardiovascular disease, and type 2 diabetes [17,18]. Beck and Tisdale demonstrated the potential of ketogenic diets to delay cachexia in animal models of colon cancer, and that dieting was more effective than insulin therapy in reversing weight loss and inhibiting tumor growth [19]. Tisdale et al. found that using a ketogenic diet in cancer patients with cachexia could lead to an increase in body weight, possibly because of the diet nourishing healthy tissue, slowing tumor growth, and depriving cancer cells of nutrients, particularly carbohydrates [20].

CONCLUSIONS

CT is essential for identifying severe and uncommon complications of BPT as it has a poor prognosis. During the acute phase, distinct radiological patterns can be seen, which can be improved by stopping medication and using steroids. Therefore, identification of these tomographic patterns is crucial for prompt diagnosis and treatment.

Abbreviations

PT: pulmonary toxicity; BPT: bleomycin pulmonary toxicity; CT: computed tomography

Author contributions

YV, SPD, KCM, MS, PJ: Conceptualization, Supervision. YV, SPD, KCM: Clinical management, Writing-original draft, Writing-review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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