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1. Title of the manuscript

Beyond Conventional Therapy: Role of Pulse Steroids in Bleomycin Induced Lung Injury

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Introduction

Bleomycin is an antineoplastic agent with potential for producing pulmonary toxicity, attributed in part to its free radical-promoting ability. The central event in the development of toxicity is endothelial damage of the lung vasculature due to bleomycin-induced cytokines and free radicals, ultimately, progressing to lung fibrosis. The treatment is discontinuation of bleomycin, initiation of systemic glucocorticoid therapy and carefully titrating supplemental oxygen. Once the conventional therapy fails and the requirement of oxygen increases, pulse steroids has been associated with clinical, physiological and radiographic resolution of bleomycin induced lung disease.

Case Summary

A 65-year-old woman presented with progressive dyspnea on exertion. Six months before presentation, she was diagnosed with stage IV Hodgkin's lymphoma and was treated with 4 cycles of ABVD (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine). The patient received a total dose of 126 units of bleomycin, and her last cycle of chemotherapy was given a week before presentation. She denied fever, chills, chest pain, or cough, and does not recall any relevant exposures, recent travel, or change in medications. Family history was unremarkable. The patient also reported no smoking history. On physical examination the patient was noted to be alert and oriented with normal vital signs. Oxygen saturation on pulse oximetry was 88% while breathing ambient air. Diminished respiratory excursion and bibasilar crackles were noted on physical examination, which was otherwise unremarkable. Cardiac auscultation did not reveal any murmurs or irregularities. Laboratory diagnostics revealed white cell count of 2,200/µL with a shift to the left in the differential (55% neutrophils, 16% lymphocytes, 14% bands, 8% monocytes, 6% metamyelocytes, and 1% eosinophils) due to cell count recovery from the chemotherapy . The erythrocyte sedimentation rate (ESR) was 96. Other blood cell counts, electrolytes, renal, and liver function tests were unremarkable. An arterial blood gas (ABG) analysis showed a pH of 7.46, pCO2 of 38 mmHg, and pO2 of 68 mmHg on room air.

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Chest radiography showed bilateral pulmonary infiltrates (figure 1), followed with a chest computed tomography that revealed bilateral peripheral interstitial lung infiltrates, fibrosis and patchy ground-glass infiltrates with no evidence of pulmonary embolism (figure 2). Complete pulmonary function test (PFT) was not performed due to patient's clinical deterioration. Bed side PFT confirmed a very severe restrictive defect with functional vital capacity (FVC) of 0.74 liters (21 percent of predicted), forced expiratory volume in one second (FEV1) of 0.72 liters (27 percent of predicted), and FEV_1/FVC of 97% of predicted value. The patient was presumed to have bleomycin induced lung injury on the basis of clinical, radiographical and PFT findings. In consideration of the patient's clinical status, rather than a low dose of intravenous methylprednisolone of 1mg/kg/day, she was started on a dose of 60 milligrams every 8 hours, together with an anti-oxidant , N-acetylcysteine, in an oral and nebulized form. Supplemental oxygen was delivered via nasal cannula to maintain an arterial saturation between 89-92% on pulse oximetry. To facilitate a histological diagnosis, further plans were made for the fiber-optic bronchoscopy and transbronchial lung biopsy.

Histopathological examination of trans-bronchial lung biopsy samples revealed acute lung injury with type II pneumocyte hyperplasia, thickened alveolar walls, areas of increased interstitial cellularity, intraalveolar fibrin and fibroblast aggregates - suggesting a “mixed” pattern of organizing pneumonia and interstitial pneumonitis. There was no significant alveolar or interstitial eosinophilia. Acid fast bacilli, fungal, and pneumocystis staining were negative for micro-organisms. Cytology was negative for malignancy.

Within one week, the patient’s breathing difficulty and oxygen requirements increased , requiring admission to the intensive care unit. A repeat ABG showed a pH of 7.47, pCO2 of 44 mmHg, pO2 of 48 mmHg, and oxygen saturation of 83% on 15 liters of oxygen. She was started on 30 liters of oxygen via Optiflow to maintain an adequate oxygen saturation level. In light of the failure of standard therapy after one week, the patient was started on pulse corticosteroid therapy with methylprednisolone at 1 gram administered intravenously every day. Following 1-2 days of this therapy, the patient 's oxygen

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requirement improved from 30 liters to 6 liters of oxygen via nasal cannula. A week later, the patient showed remarkable clinical improvement, requiring only 1 liter of oxygen to maintain adequate level of saturation. The patient was subsequently discharged to an acute rehabilitation center. She showed continuous improvement of symptoms on a tapering schedule of steroids and was kept on a maintenance dose of oral prednisone 5mg daily. Her follow-up chest computed tomography in one month showed improvement of bilateral infiltrates in the lung bases with persistent fibrotic changes (figure 3).

Discussion

Bleomycin has a well-established role in the management of Hodgkin's lymphoma (ABVD and BEACOPP regimens) and testicular germ cell tumors (BEP regimen).[1, 2] Pulmonary toxicity is one of the major drawbacks of bleomycin therapy, with as many as 20% of the patients receiving this agent developing interstitial fibrosis.[3] Other forms of bleomycin induced lung injury include interstitial pneumonitis, organizing pneumonia and hypersensitivity pneumonitis.[4-6] Although lung injury is commonly associated with high bleomycin cumulative doses of over 400 units , it has also been reported with low doses of less than 50 units. [7] Though the exact mechanism by which bleomycin results in lung injury is unclear, free-radical induced oxidative damage is considered to be the primary mechanism.[8] The relative deficiency of bleomycin inactivating enzyme - bleomycin hydrolase – in the lung is also considered to be contributory and several studies in mice have suggested a role for immune mediated lung injury.[9] Patients receiving a higher cumulative dose of bleomycin, concomitant therapy with other anti-neoplastic agents or radiotherapy, and high fractions of inspired oxygen are considered to be at a higher risk for developing bleomycin induced lung injury.[10-12] Cigarette smoking and advanced age, are also considered to be the risk factors. Symptoms associated with bleomycin lung injury are often non-specific and often develop a few months following therapy.[13] Patients commonly presents with symptoms of dry cough, chest pain, dyspnea and signs of fever, tachypnea, bilateral auscultatory crackles and hypoxemia. However, the onset of symptoms resulting from bleomycin induced

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hypersensitivity pneumonitis tends to be more acute and rapidly progressive. A history of treatment with bleomycin and absence of pulmonary involvement by either malignancy or infection are pre-requisite for making a diagnosis of bleomycin induced lung injury.[14] A low diffusion capacity (DLCO) and flow volume loops indicating a restrictive pattern (decreased forced vital capacity and total lung capacity) support the diagnosis.[15, 16] High resolution computed tomography (CT) of the chest can demonstrate ground glass opacities, sub pleural nodules, linear reticular markings, or honeycombing and traction bronchiectasis depending on the underlying pathology and chronicity of disease. [17, 18]

Histopathological changes in bleomycin induced interstitial pneumonitis include type I pneumocyte necrosis, type II cell hyperplasia, and polymorphonuclear leukocytic infiltration. Bleomycin induced organizing pneumonia, on the other hand, is characterized by the presence of budding granulation tissue within the alveolar air space.[19] Hypersensitivity pneumonitis, a rare variant of bleomycin induced lung injury, is associated with eosinophilic infiltration and mild interstitial fibrosis.[6]

Discontinuation of bleomycin is the first step in the management of patients with bleomycin induced lung injury and re-initiation of bleomycin is permanently avoided in these patients. Intravenous corticosteroid therapy of 0.75 to 1 mg/kg/day (using ideal body weight) is often recommended.[4] Benefit with N-acetylcysteine (NAC), an anti-oxidant, administered orally or in a nebulized form, has also been reported in case studies.[20, 21] Steroids are tapered after four to eight weeks of therapy in patients showing response. Careful titration of supplemental oxygen to maintain a level of saturation between 89 and 92 percent is recommended as there is strong evidence to suggest a synergistic effect between previous bleomycin exposure and subsequent exposure to high-inspired oxygen concentrations, in inducing lung injury.[22]

Pulse corticosteroid therapy involves administration of “supra-pharmacological” doses (0.5–2 g)

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of methylprednisolone in an intermittent manner for a short duration. Favorable outcome of pulse steroids used to treat lung injury caused by various anti-neoplastic agents like gefitinib, irinotecan, panitumumab and erlotinib is well documented. [23-25]There are reported cases that support the use of pulse steroids in bleomycin induced lung injury, with remarkable clinical and radiographic responses.[26, 27] The time to improvement in these reports varied widely, ranging from 7 to 12 days. Bloor et al reported two fatal cases of bleomycin pneumonitis where patients were initiated on moderate doses of steroid therapy and high dose steroid therapy was not administered until later. [28] These reports suggest a possible benefit with early initiation of high dose steroid therapy.

We hereby report success with pulse steroid therapy in a patient with bleomycin induced lung injury. Contrary to prior case reports, we noted a dramatic improvement in the patient's clinical status with the oxygen requirement decreasing to 6 liters from 30 liters within 48 hours of initiating therapy. We recommend initiation of pulse steroid therapy in patients whose oxygen requirement increases despite being on conventional steroid therapy.

Teaching Points

1. Lung injury is a feared complication of bleomycin therapy and can be acute or chronic.

2. Care should be taken to avoid exposure of high-inspired oxygen concentrations which may induce lung injury.

3. Pulse-dose steroid therapy has a potential role in refractory bleomycin pneumonitis.

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Legends:

1. Chest X-ray showed bilateral peripheral pulmonary infiltrates with no evidence of pleural effusion and pneumothorax.

2. Chest computed tomography at admission noted bilateral interstitial pulmonary infiltrates, fibrosis and patchy ground-glass infiltrates.

3. Follow-up chest computed tomography after treatment of pulse steroids revealed bilateral mild interstitial markings with improvement of earlier noted peripheral interstitial pulmonary infiltrates and patchy ground-glass infiltrates.

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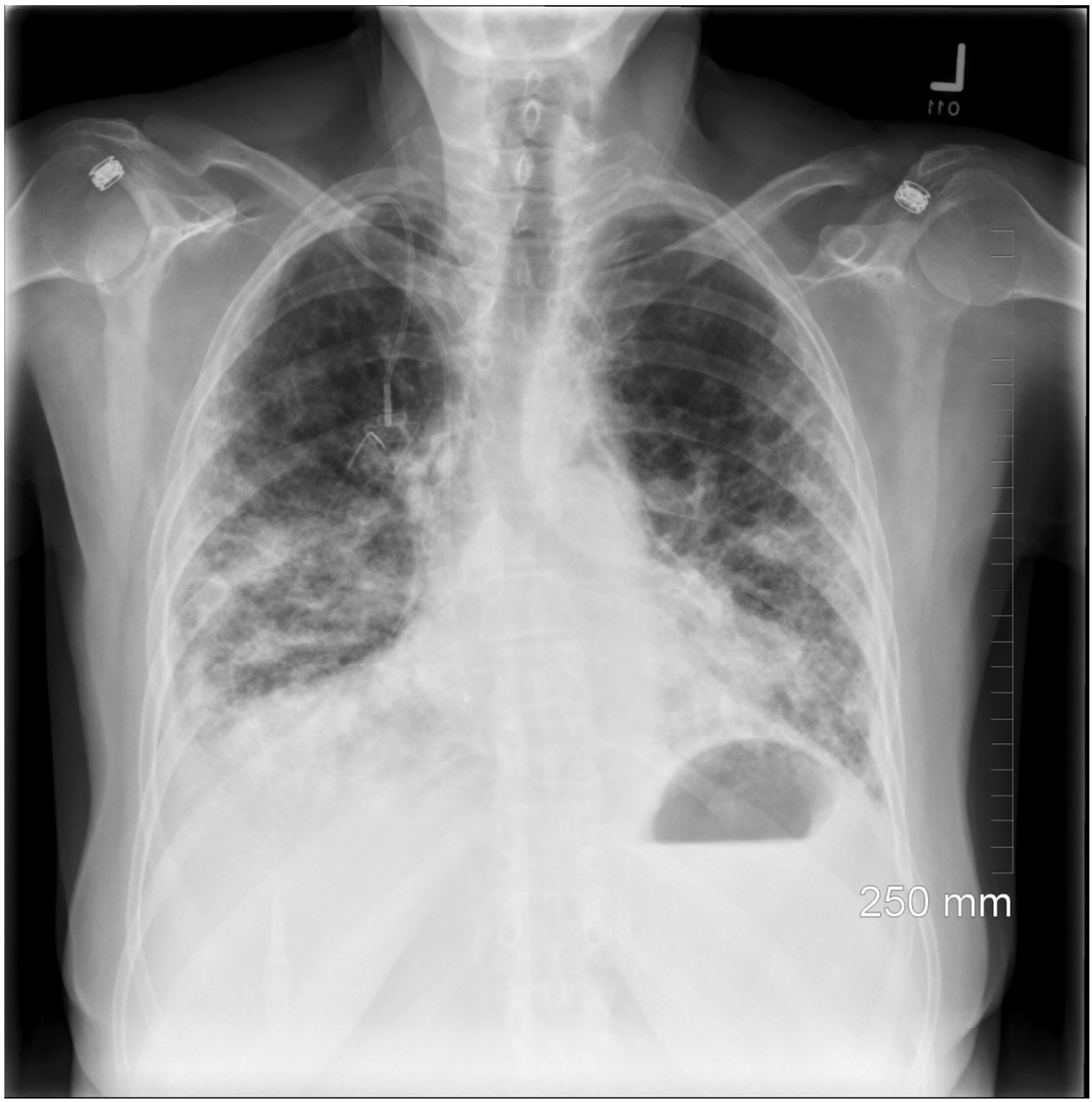

Figure 1

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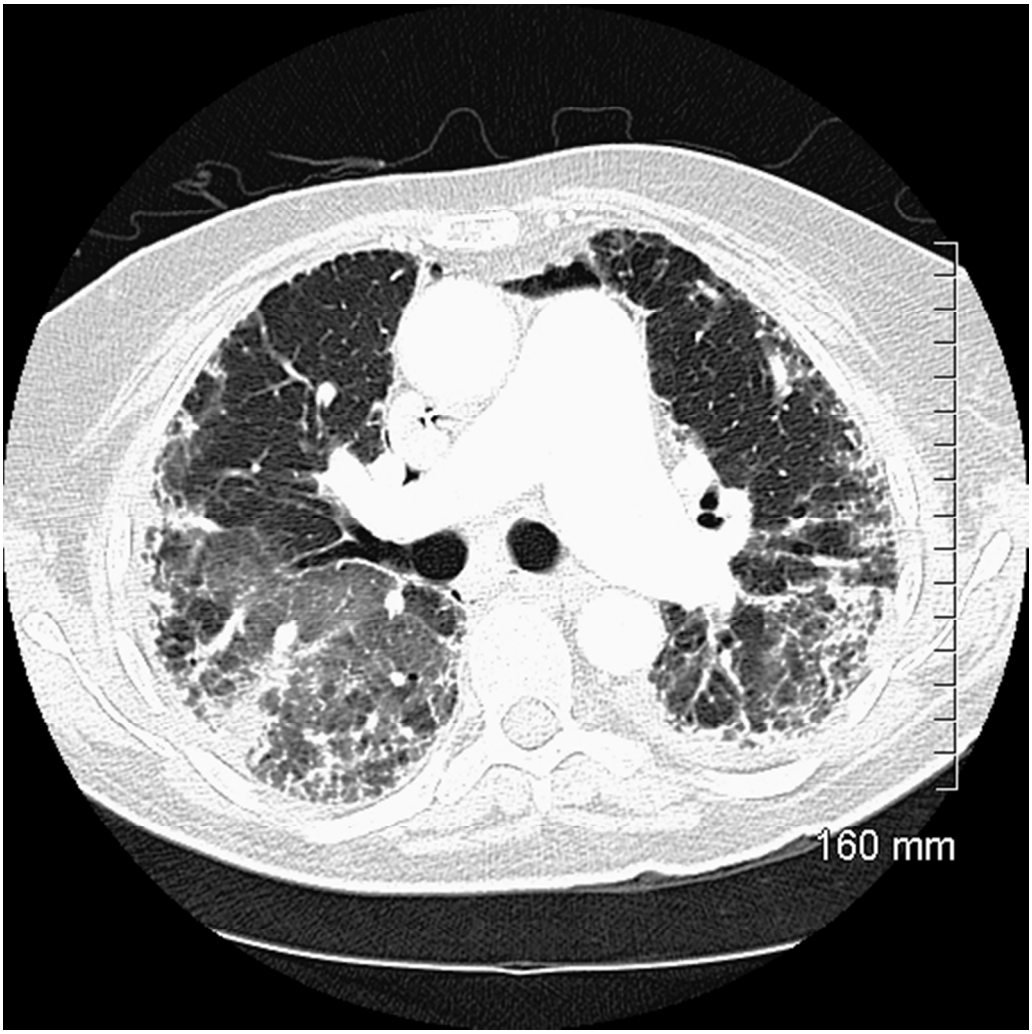

Figure 2

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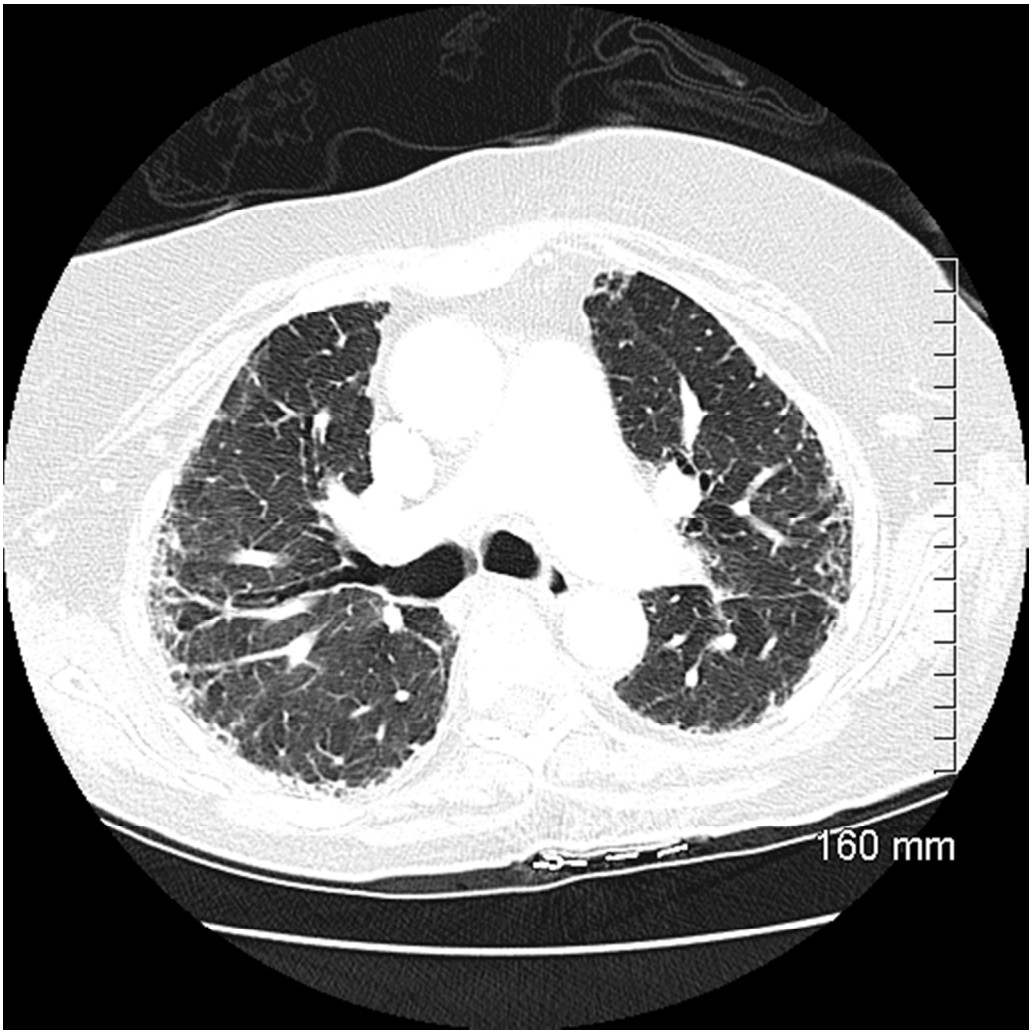

Figure 3