

Fatal Bleomycin-Induced Pulmonary Fibrosis in Case of Seminoma

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Abstract

A 19-year-old man presented with progressive dyspnea at exertion, dry cough and fatigue. His medical history included: right testicular cancer associated with abdominal and thoracic metastatic lymph nodes diagnosed 6 months earlier. He had been treated by testicular resection completed with chemotherapy combining bleomycin, etoposide and cisplatin (BEP).

An interim disease evaluation was suggestive for a complete clinical, metabolic and radiologic response. Three weeks after the completion of the 4th cycle of chemotherapy, he presented a rapid progression of dyspnea and severe hypoxemia with dry cough. The CT scan showed diffuse interstitial and alveolar infiltrates associated with a pneumomediastinum. Because of acute respiratory failure, he required hospitalization in an ICU and intubation 24 hours after admission. He was treated with empiric antibiotics and corticoids in pulse therapy, IV cyclophosphamide and finally veno-venous extracorporeal membrane oxygenation (VV-ECMO) as a bridge to recovery. He finally died, due to chemotherapy acute lung injury.

Keywords

bleomycin; respiratory failure; pulmonary fibrosis; pulmonary function tests

Abbreviations

BPT: Bleomycin Pulmonary Toxicity; G-CSF: Granulocyte Colony-Stimulating Factor (G-CSF); AFP: Alpha-Fetoprotein; Hcg: Human chorionic gonadotropin; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume In 1 Second; TLC: Total Lung Capacity; TLCO: Transfer Factor for Carbon Monoxide; CRP: C-Reactive Protein; BAL: Bronchoalveolar Lavage; BNP: Brain Natriuretic Peptide; VV-ECMO: Veno-Venous Extracorporeal Membrane Oxygenation; Pfts: Pulmonary function tests; DAD: Diffuse Alveolar Damage; NSIP: Nonspecific Interstitial Pneumonia

Introduction

Bleomycin, an antibiotic agent with antitumor activity [1], is commonly used in chemotherapy for various tumor types and particularly in testicular cancer as the key drug in induction chemotherapy. It has the advantage of less myelotoxicity but with severe and potentially fatal pulmonary toxicity. The clinical manifestations of bleomycin pulmonary toxicity (BPT) vary from asymptomatic or mild disease to fatal interstitial fibrosis. The pulmonary syndromes reported as BPT were either cryptogenic

organizing pneumonia, eosinophilic pneumonia or subacute to chronic interstitial pneumonia (the most frequent type of BPT) [2,3]. The most important risk factors for developing BPT are the Bleomycin dosage, the age of the patient, renal insufficiency, prior oxygen therapy, the stage of disease at presentation, thoracic radiotherapy and co-administration of granulocyte colony-stimulating factor (G-CSF). In terms of dosage toxicity, the incidence of BPT rises to 13-17% when the cumulative dose is >450 mg [4].

In case of disseminated testicular cancer with poor prognosis the most commonly used induction chemotherapy consists of four cycles of BEP. The reported incidence of BPT varies from 6 to 10% [5].

Case Presentation

A 19-year-old man presented for fatigue and acute increase of right testicular volume. The high level of serum tumor markers: alpha-fetoprotein (AFP) at 1225ng/ml and beta human chorionic gonadotropin (hCG) at 21750 UI/L supported the diagnosis of a seminoma. A complete CT scan evaluation which showed multiple abdominal and thoracic lymph nodes. Therefore the decision for surgical resection was made. Microscopically, multiple tumor tissues were observed: teratocarcinoma, yolk sac tumor and seminoma with necrotic and hemorrhagic lesions, with some syncytiotrophoblastic cells and metastatic lymph nodes. Without delay BEP chemotherapy was started complicated by a severe neutropenia (after the 1st cycle of chemotherapy); G-CSF support was needed. The cumulative dose of Bleomycin was 360 mg.

An interim disease evaluation, after 2 cycles, was suggestive for a clinical, metabolic (serum tumor markers normalized) and radiologic response (regression of lymph nodes) and no other episode of neutropenia occurred. The patient was monitored by plethysmography and TLCO measures with normal follow-up results: forced vital capacity (FVC) \geq at 5.2L (101%), forced expiratory volume in 1 second (FEV1) at 4.9L (112%), total lung capacity (TLC) at 8.1L \geq (116%) and TLCO at 77%. However, the final respiratory evaluation made before the last cycle of chemotherapy showed worsening of FVC (from 101% to 71%) and TLCO (from 77% to 56%).

Few weeks after the completion of the 4th cycle of chemotherapy he presented increasing dyspnea associated with dry cough and severe fatigue. His chest examination revealed inspiratory crackles of both lungs. The chest X-ray showed diffuse predominantly basal, bilateral infiltrates with normal cardiac shadow (Figure 1). The HRCT scan (Figure 2) showed diffuse interstitial and alveolar infiltrates in the lower zones of the lungs (areas of consolidation and ground glass opacities) associated with an important pneumomediastinum. Echocardiography described a normal left ventricular function (systolic fraction at 60%) but with elevated systolic pulmonary pressure at 40 mmHg. The laboratory results were as follows: hyperleukocytosis at 16000/mm³ and C-reactive protein (CRP) at 115 mg/l. The first hypothesis was an infectious pneumonitis and therefore an empiric antibiotherapy with piperacillin-tazobactam and ciprofloxacin was started. The respiratory status is rapidly worsening with severe dyspnea with tachypnea, mild fever (38.5°) and severe hypoxemia with hypercapnia: from PaO₂ 71.5 mmHg and PaCO₂ 47 mmHg while under O₂ therapy (5 L/min) to PaO₂ 70 mmHg and PaCO₂ 84.5 mmHg with a need of 10 L/min of 2, 3 days after.

He was finally diagnosed as BPT progressing to pulmonary fibrosis and severe respiratory failure.

He was submitted in the ICU for intubation and mechanical ventilation. Complications occurred 24 hours later with a left pneumothorax which required thoracic drainage. A tracheoesophageal fistula was excluded at bronchoscopy and the bronchoalveolar lavage (BAL) showed an alveolar hemorrhage (2430000 red cells/mL) without siderophages. The cellular counting showed: 46% macrophages, 41% neutrophils, 12% lymphocytes, 1% eosinophils. The BAL cultures revealed *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* multidrug resistant (both susceptible to Colimycine) and more than 40 *Candida albicans* colonies. PCR for *Pneumocystis jirovecii* was negative. The antibiotic treatment was switched to Colimycin, Ciprofloxacin and Fluconazole was added. At this time, laboratory tests showed a normal renal and hepatic function, normal brain natriuretic peptide (BNP 45 ng/dL) and negative procalcitonin (0.47 µg/L). A pulse cortico therapy was initiated (500mg/day for 3 days) continued by high dose corticoids (1mg/kg/day).

He was nursed predominantly in prone position to allow better lower lobe ventilation and inhaled NO was added. Despite best supportive care the ARDS was worsening with a very low pulmonary static compliance, between 8-12 ml/mmHg and PaO₂/FiO₂ ratio < 100 mmHg. Persistent hypercapnia was present (approx. 60 mmHg) after a 2nd right pneumothorax (Figure 3).

After a multidisciplinary discussion we decided to start a pulse therapy of Cyclophosphamide (500mg) associated to VV-ECMO assistance as a bridge to recovery treatment. Despite all these treatments, sadly he finally succumbed to the irreversible hypoxemia due to bleomycin-induced lung injury.

The histologic analysis of post-mortem lung biopsies showed a collagen fibrosis at Masson's trichrome associated with hyaline membranes, twisted capillaries with fibrin thrombi and micro-abscess (Fig 4) consistent with diffuse alveolar damage (DAD) due to pulmonary fibrosis secondary to bleomycin treatment.

Discussion

Bleomycin is a key component of chemotherapy strategy of curable malignancies like germ-cell tumors, lymphomas, cervical cancer and squamous cell carcinomas of the head and neck, although pulmonary toxicity is the most important and potentially lethal adverse side effect of this drug [4-6]. The lung and the skin are more predisposed to bleomycin toxicity due the deficiency of bleomycin hydrolase enzymes in these tissues. There are some risk factors implicated in higher predisposition of BPT: cumulative dose of bleomycin >300 to 500 U, age > 40 years, renal insufficiency, thoracic radiotherapy, concomitant administration of G-CSF, exposure to high concentration of oxygen therapy [7-12]. Our patient had 360 mg of cumulative dose of Bleomycin and he was treated with G-CSF due to an episode of chemotherapy-induced neutropenia. During the period of hospitalization the renal function of our young patient maintained normal and he didn't undergo chest radiotherapy prior to BPT.

There are no guidelines for a perfect screening and prevention of BPT. The prevention measure is to perform pulmonary function tests (PFTs) at baseline and every three weeks during treatment period. In general practice, Bleomycin should be discontinued with patients who have a constant decline in TLCO of 40-60% from baseline [13]. Our patient presented a significant worsening of PFTs with diminished TLCO at 68% and FVC at 71%.

Different histologic patterns have been described in relation to BPT : cryptogenic organizing pneumonia, eosinophilic pneumonia, nonspecific interstitial pneumonia (NSIP) and, most frequently, diffuse alveolar damage (DAD) [5,14-16]. Spontaneous pneumothorax and pneumomediastinum have also been described with patients presenting BPT [8]. In our case the postmortem histopathologic examination of the lungs confirmed diffuse alveolar damage. Pneumomediastinum and recurrent pneumothorax have probably been favored by mechanical ventilation [16].

Some previous studies showed a variable response to corticosteroid therapy for patients presented with drug-induced DAD which depended on the severity of inflammatory reaction, the delay of treatment initiation and the inciting drug [17]. Normally, the patients who survive the acute period of BPT tend to have a complete resolution of respiratory symptoms and recovery of pulmonary function [18]. In our case the respiratory status continued to worsen despite optimal treatment, corticotherapy at high dose and cyclophosphamide bolus. He developed a severe ARDS with irreversible hypoxemia despite inhaled NO and respiratory assistance by VV-ECMO. This could be explained by the extensive histological injuries like collagen fibrosis with hyaline membranes, twisted capillaries with fibrin thrombi and micro-abscess, proof of a late proliferative phase of interstitial fibrosis [19,20].

Conclusion

In conclusion, DAD is a severe and sometimes fatal side effect of bleomycin, which is still an important component of chemotherapy for testicular cancer. The clinical, radiologic and pathologic findings are not specific and therefore the initial diagnosis may be difficult. In our case, the patient presented only a moderate worsening of the PFTs which couldn't predict the severe DAD that occurred a few weeks later. There is no effective treatment for BP, nor did a respiratory assistance by VV-ECMO succeed to stop the rapid worsening of the respiratory failure.

Figures

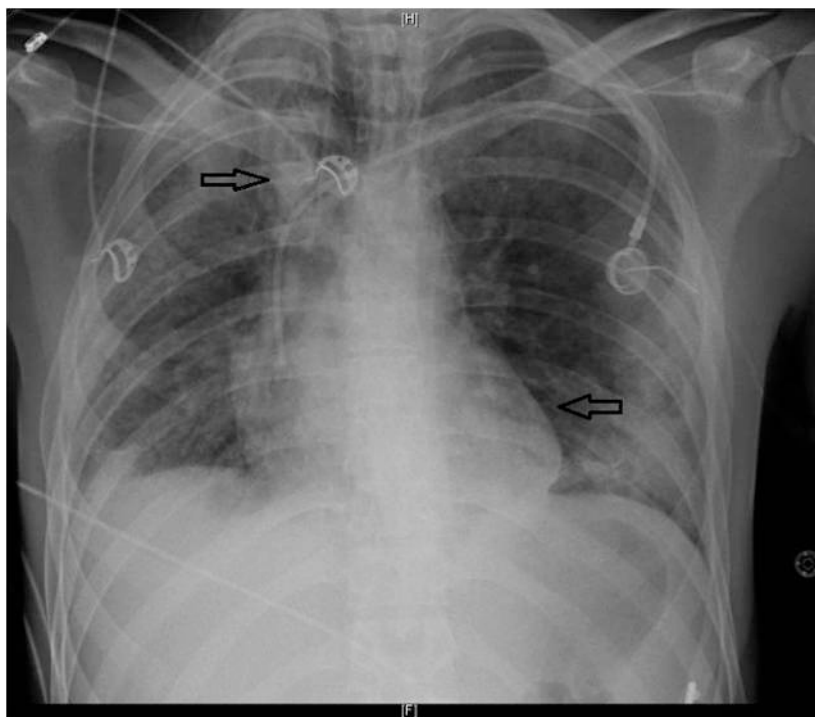


Figure 1: Chest radiography (anteroposterior view) showing diffuse bilateral infiltrates, predominantly involving the lower lobes and suspected pneumomediastinum (arrow).

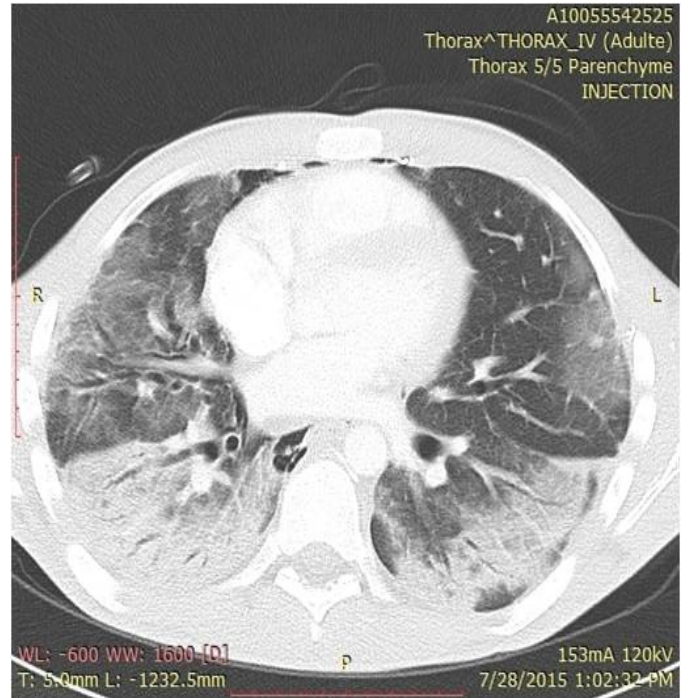


Figure 2: HRCT showing diffuse ground-glass opacities predominantly in lower lobes and areas of consolidation with air bronchogram. A pneumomediastinum was confirmed.

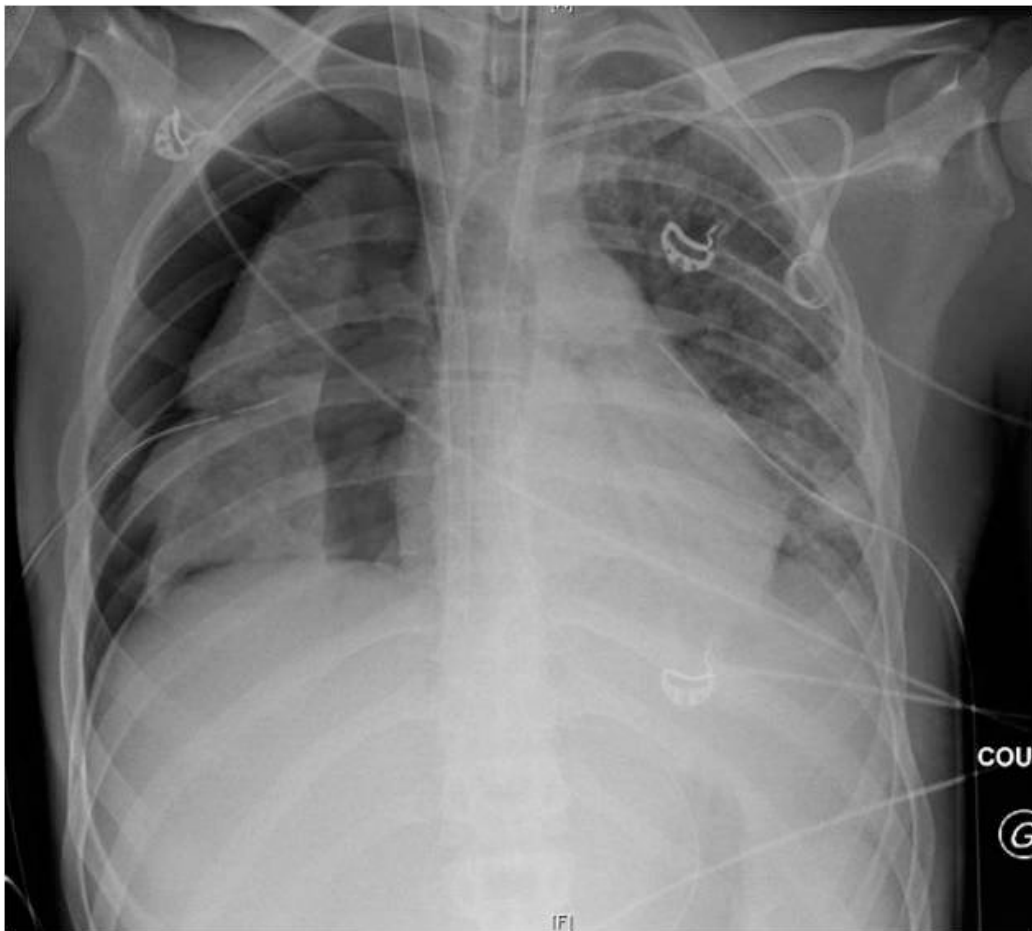


Figure 3: Chest radiography (anteroposterior view) showing a complete left pneumothorax with persistent diffuse bilateral infiltrates.

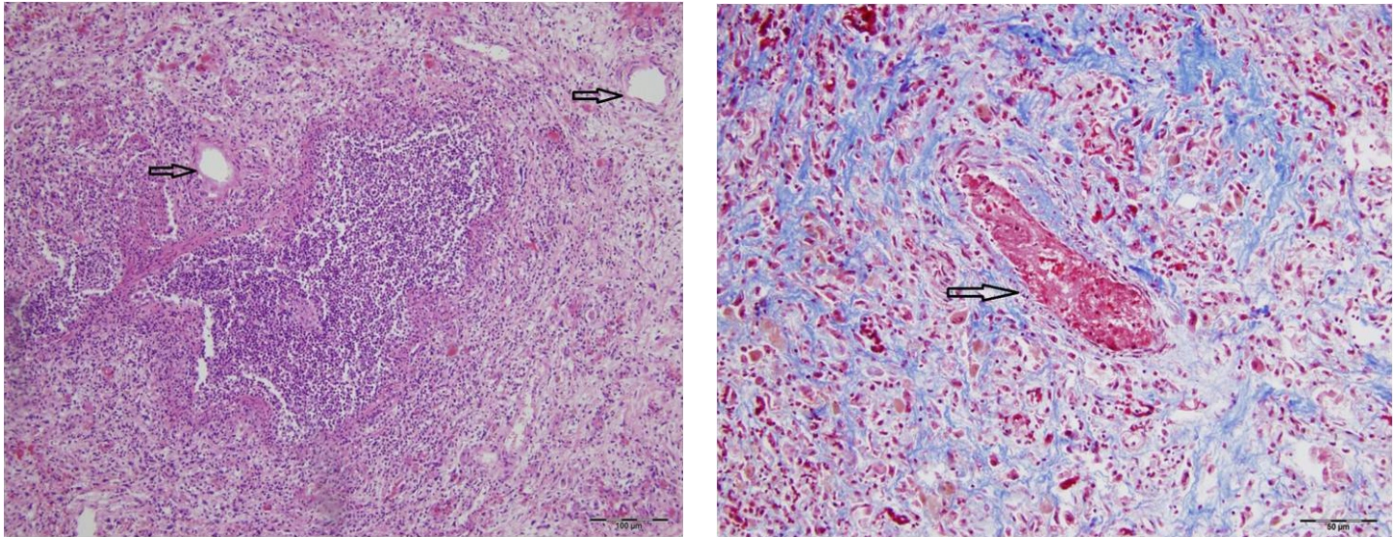


Figure 4: Histopathologic features of post-mortem lung biopsies specimens of the right lower lobe. Top: extensive fibrosis replacing lung parenchyma and cystic remodeling (arrow) (Masson's trichrome). Bottom: twisted capillaries and fibrin thrombi (arrow).

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