Documenta Haematologica -
Revista Romana de Hematologie | 2025, Vol. 3, Nr. 4

https://doi.org/10.59854/dhrrh.2025.3.4.199

– CASE REPORT–

Diverse Presentations of Bleomycin-Induced Lung Injury: A Case Series

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Abstract

Drug-related toxicities are a well-known phenomenon, affecting any organ and potentially causing morbidity. Adriamycin, Bleomycin, Vinblastine, Dacarbazine (ABVD) chemotherapy is a standard treatment for patients with Hodgkin's lymphoma. While the adverse effects of ABVD chemotherapy are well recognised, pulmonary edema is rarely observed as a complication. Bleomycin may induce pulmonary fibrosis, leading to a decline in pulmonary function and an increase in respiratory morbidity. The mechanism of Bleomycin-induced pulmonary fibrosis remains unclear. However, various studies suggest that it results from unopposed inflammation and Bleomycin's tendency to affect the lung parenchyma. In our case series of three patients, the first patient experienced an acute onset of dyspnoea following Bleomycin infusion and was in respiratory failure. He had normal echocardiogram findings, with high-resolution computed tomography (HRCT) revealing features consistent with pulmonary edema and fibrotic changes in the parenchyma. He was managed in the ICU with corticosteroids and empirical antibiotics, along with invasive ventilation, and recovered gradually from respiratory failure. His subsequent hospital stay was uneventful. In contrast, the other two patients showed pulmonary parenchymal changes and a decline in pulmonary function tests (in one patient) following Bleomycin-based chemotherapy. They were managed with pulmonary rehabilitation, along with treatment for their underlying disease.

Keywords: *ABVD chemotherapy, Bleomycin, Lung toxicity, Non-cardiogenic Pulmonary edema, Lung fibrosis*

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Introduction

Hodgkin's Lymphoma [HL] is considered a potentially curable cancer. ABVD chemotherapy remains the standard treatment for patients with HL. This four-drug regimen achieves remission in 70-80% affected individuals.[1] While each drug has distinct toxicities, Bleomycin is mainly associated with adverse effects on lung health. It is even recommended that after two cycles of ABVD, if the patient responds well, Bleomycin can be omitted in subsequent cycles.[2] Several case reports have linked PFT abnormalities to Bleomycin; however, reports of lung parenchymal damage are underreported.[3] In our case series, we describe three patients who received Bleomycin as part of their chemotherapy for Hodgkin's Lymphoma (HL) and Germ Cell Tumour (GCT). Although cases of Bleomycin toxicity have been reported, the occurrence of pulmonary oedema remains rare. Our patients exhibited variable presentations following Bleomycin chemotherapy and were managed optimally.

Case 1

A 4-year-old boy presented with complaints of fever and a two-kilogram weight loss (reported by the mother) over one month, along with swelling on the left side of the neck for 20 days. The child had no significant medical history at the time of birth. He had received all up-to-date vaccinations, and his developmental milestones were appropriate for his age. On examination, he appeared pale, with no icterus, cyanosis, or clubbing. He had a left cervical lymph node measuring 3 cm by 2 cm, which was firm and mobile, with normal overlying skin. No hepatosplenomegaly was observed. His complete blood count showed a haemoglobin (Hb) level of 9.5 g/dL, a total leucocyte count (TLC) of 12400/microL, and platelets of 342000/microL, with neutrophils at 77% and lymphocytes at 17%. Peripheral blood smear indicated microcytic hypochromic anaemia with mild neutrophilic leucocytosis. Chest X-ray revealed mediastinal widening. Fine needle aspiration cytology suggested reactive lymphadenitis. Contrast-enhanced computed tomography (CECT) of the chest showed an anterior mediastinal mass and bulky lymph nodes on the left side of the neck. CECT of the abdomen revealed multiple enlarged periportal lymph nodes along with retroperitoneal nodes. A biopsy from the cervical lymph nodes, with immunohistochemistry (IHC), was indicative of Classical Hodgkin's Lymphoma. Bone marrow aspiration and biopsy revealed an increase in lymphoid cells. The patient was diagnosed with Hodgkin's Lymphoma, Stage IIIB.
The patient was commenced on ABVD chemotherapy and showed initial clinical improvement. While undergoing the fourth cycle of ABVD chemotherapy, he suddenly developed dyspnoea and a drop in saturation. Oxygen inhalation and supportive care were initiated. However, as saturation continued to fall, the patient was transferred to the Intensive Care Unit (ICU). He was intubated and started on mechanical ventilation. Arterial blood gases revealed respiratory acidosis. Chest X-ray demonstrated bilateral opacities consistent with pulmonary oedema. Two-dimensional echocardiography showed a normal left ventricular ejection fraction (LVEF). Routine investigations, including coagulation parameters, were within normal limits. Serum pro-calcitonin levels were 24.1 ng/ml, and CRP was 691 mg/dl. The patient's Pro-BNP was normal. A Gram stain of the endotracheal

secretions did not reveal any microorganisms. Gastric aspirate for acid-fast bacilli (AFB) was negative. HRCT scans showed pulmonary edema [Image 1]. The patient was administered corticosteroids and empirical intravenous antibiotics. Gradually, he improved, and a subsequent chest X-ray demonstrated radiological resolution. The patient was extubated, and oxygen saturation was maintained on oxygen via nasal cannula. He gradually recovered from respiratory failure and was transferred from the ICU to the ward. His subsequent stay was uneventful, with resolution of HRCT findings, but with some degree of residual lung fibrosis.

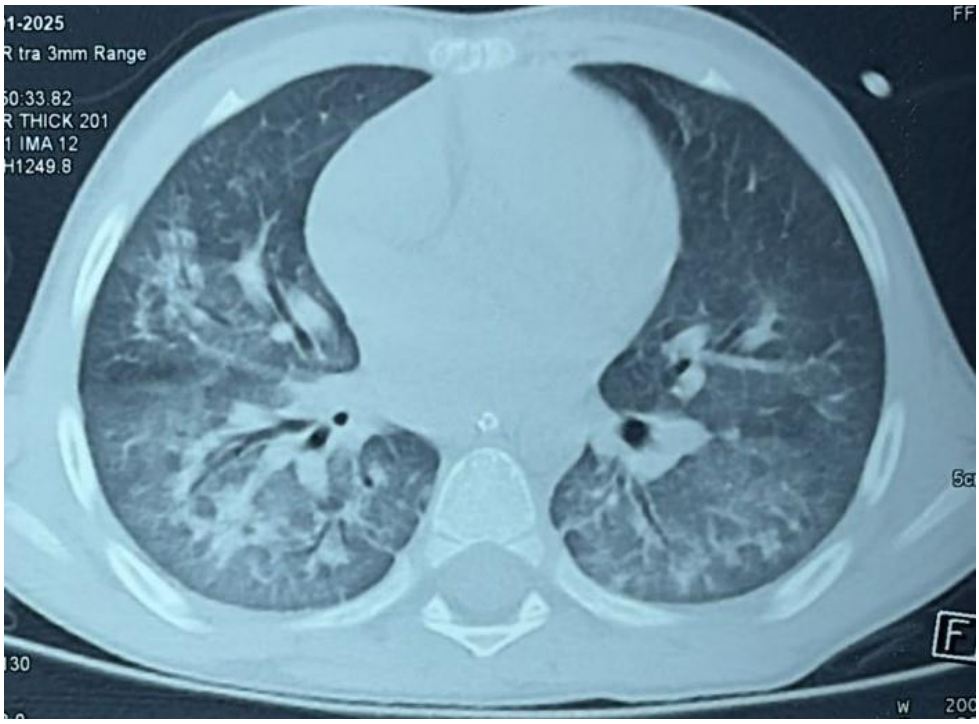

Image 1. *HRCT images depicting pulmonary edema.*

Case 2

A 53-year-old man with no comorbidities presented with a one-month history of persistent dry cough and cervical lymphadenopathy. On examination, the patient had a right cervical lymph node measuring 2 cm by 2 cm, which was firm and mobile, with normal overlying skin. No hepatosplenomegaly was observed. Contrast-enhanced computed tomography (CECT) of the thorax revealed an ill-defined, heterogeneous, enhancing soft tissue mass in the right middle lobe, along with multiple enlarged mediastinal lymph nodes. Positron emission Tomography (PET CT) showed a Fluorodeoxyglucose (FDG)-avid, heterogeneous, enhancing, ill-defined lesion in the right middle lobe, as well as multiple FDG-avid, discrete, coalescent lymph nodes in the supraclavicular and mediastinal regions. Multiple FDG-avid discrete conglomerate lymph nodes were present on either side of the diaphragm. There was heterogeneously increased FDG uptake, with some hypodense, focal FDG-avid lesions in the spleen. Multiple FDG-avid lesions were also observed in the axial and appendicular skeleton.

Excisional biopsy of the cervical lymph node confirms Classical Hodgkin's Lymphoma, Nodular Sclerosis type. Baseline pulmonary function tests were normal. The patient received two cycles of ABVD. An interim PET CT shows multiple FDG-avid lymph nodes above and below the diaphragm. Several FDG-avid and non-avid soft tissue density lesions were observed in the right lung parenchyma. Heterogeneous trace uptake, with a few mildly FDG-avid hypodense lesions, was present in the spleen. An FDG-avid lytic lesion appears in the left transverse process of lumbar vertebra L5, and a non-FDG-avid lytic lesion is seen in sacral vertebra S1, indicative of Deauville score IV. The patient underwent four further cycles of ABVD chemotherapy, followed by PET CT, which revealed FDG-avid bilateral neck, supraclavicular, right axillary, mediastinal, and abdominal-pelvic lymph nodes, along with skeletal and splenic lesions. Most of the

nodal diseases increased in size and metabolic activity, with some new skeletal lesions, indicating disease progression (Deauville score V). Post-chemotherapy, the patient experienced dyspnea on exertion. The CECT chest showed enlarged right paratracheal, prevascular, right hilar, and subcarinal lymph nodes, the largest measuring 24.2 mm in the right paratracheal region. It also revealed patchy ground-glass opacities, septal thickening, multiple parenchymal bands, and mosaic attenuation, mainly in the lower lobes, which may suggest viral pneumonia or drug-induced toxicity, accompanied by right-sided consolidation and a right axillary lymph node measuring 5.6 mm (Image 2). Further assessments such as pulmonary function testing, lymph node biopsy, and bone marrow examination were recommended. A repeat biopsy from the right cervical lymph node was positive for CD30, CD25, PAX5+, CD15, D20, CD5, and PAN CK, suggesting classical Hodgkin's lymphoma with a restrictive pattern on PFT (FEV1- 50%, FVC-51%, FEV1/FVC- 99%, DLCO-60%), indicative of moderate restriction. The patient received four cycles of Brentuximab Vedotin and Ifosphamide, Carboplatin, Etoposide (BV+ICE) chemotherapy. After completing three cycles of BV+ICE, an interim PET/CT scan showed a Deauville score of 2. The patient then received a 4th cycle of BV-ICE and was planned for an autologous stem cell transplant. During pre-BMT, the patient was evaluated for respiratory issues. The patient has grade 2, modified Medical Research Council (mMRC) dyspnea, and his PFT indicated a worsening restrictive pattern with low DLCO. Managed with bronchodilators, the patient underwent stem cell mobilisation with Granulocyte-Colony Stimulating Factor (G-CSF); however, the bone marrow transplant was aborted due to poor stem cell yield. After four months, the patient relapsed and was treated with a Pembrolizumab-based regimen. He is currently in remission and maintains performance status 1 (PS1) with bronchodilators and pulmonary rehabilitation.

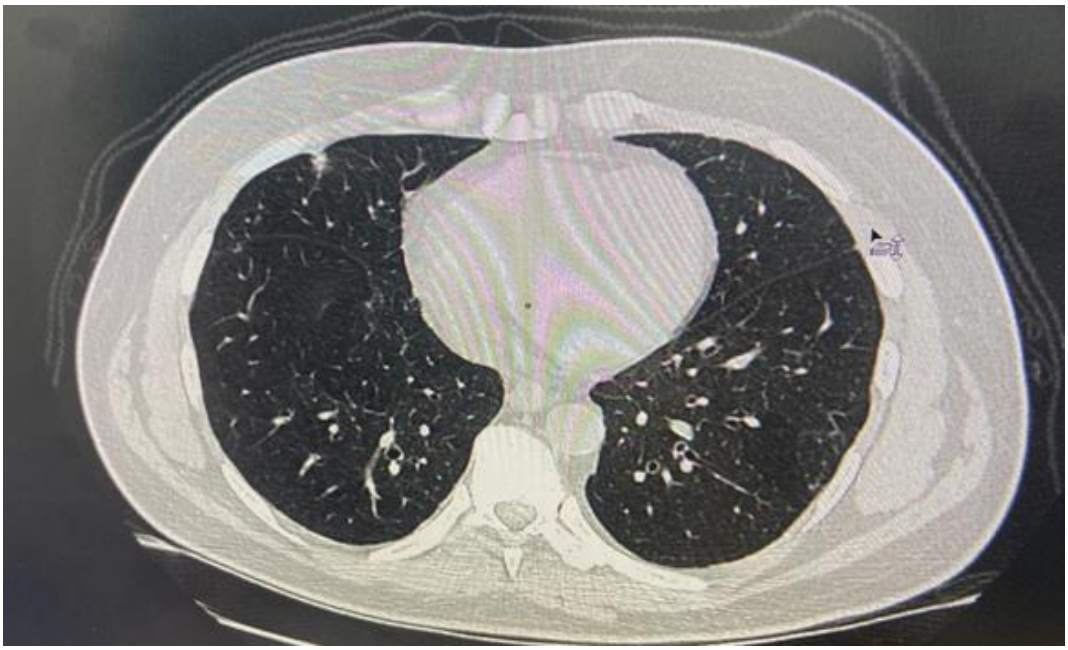

Image 2. *HRCT image showing traction bronchiectasis, septal thickening, and sub-pleural fibrosis*

Case 3

A 36-year-old man, a non-smoker with a known history of hypertension for one year on antihypertensive medication, presented with intermittent lower abdominal and back pain lasting one month. Computed tomography (CT) revealed a mass measuring 114 x 83 x 98 mm with retroperitoneal infiltration into the dorsal vertebrae from D12 to L3. PET CT showed uptake in the left testis, and biopsy indicated a non-seminomatous germ cell tumour. The patient underwent left high inguinal orchiectomy. He received four cycles of Bleomycin, Cisplatin, and Etoposide (BEP). Post-therapy PET CT indicated a partial response. After two cycles of BEP, he developed grade III febrile neutropenia requiring admission and

administration of granulocyte-stimulating factor (GCSF). Following four cycles, he developed grade II MMRC dyspnea; a 2D echocardiogram showed trivial mitral and tricuspid regurgitation, left ventricular hypertrophy, and an ejection fraction (EF) of 40%. Despite optimisation of cardiac management, his dyspnea persisted. Chest CT scans revealed bronchiectasis, septal thickening, and fibrotic parenchymal changes, as illustrated in Image 3. The patient was enrolled in a pulmonary rehabilitation programme with bronchodilators, which alleviated his symptoms.

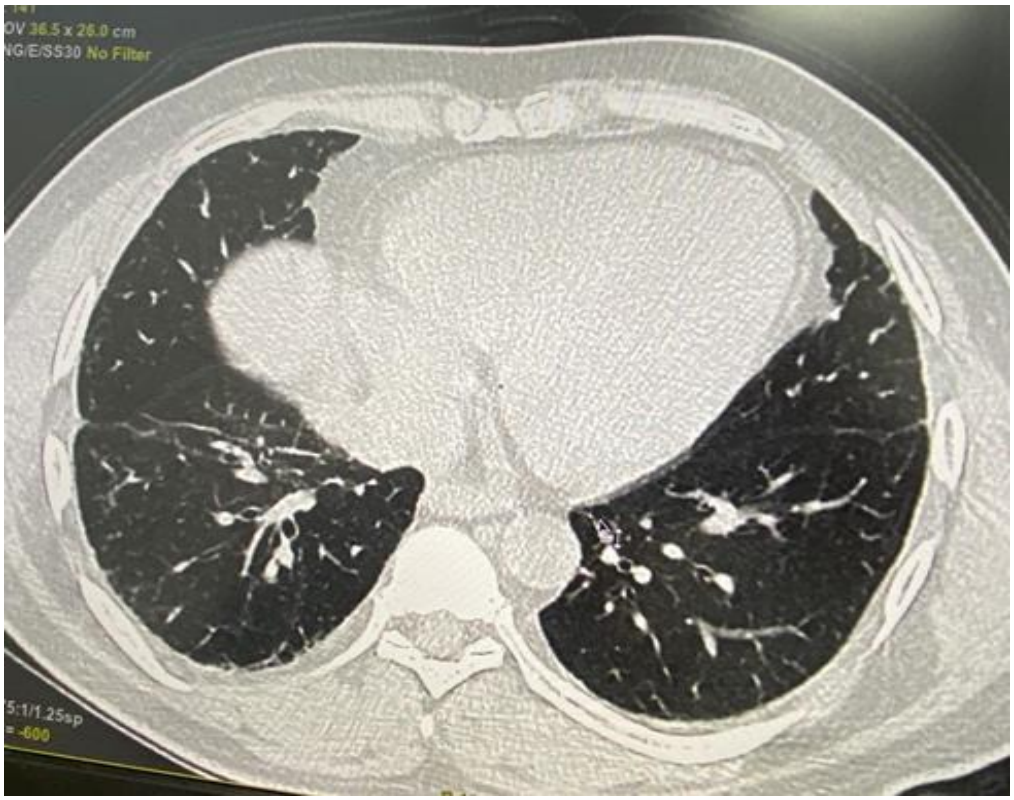

Image 3. *HRCT showing septal thickening, bronchiectasis, and fibrotic opacities.(Right> Left)*

Discussions

Any chemotherapy can cause a wide range of side effects. Drug-induced injuries may be organ-specific or involve the deterioration of multiple organs' functions, potentially leading to multi-organ failure. Even a single dose infusion or cumulative dose may result in adverse events and possibly cause treatment interruption. This typically occurs when the injury exceeds the body's total physiological compensation, leading to signs and symptoms. The spectrum of pulmonary toxicity induced by drugs ranges from diffuse alveolar damage to non-specific interstitial pneumonitis (NSIP) and Cryptogenic organising pneumonia (COP).[4] Bleomycin is included in various chemotherapy regimens, such as ABVD for Hodgkin's lymphoma, as seen in our patients' cases (cases 1 and 2), as well as in BEP (as in our 3rd patient), and in chemotherapy protocols for germ cell tumours.

Bleomycin accounts for approximately 3-18% of cases of pulmonary toxicity.[5] Chest X-rays often fail to provide a definitive diagnosis, whereas HRCT offers superior imaging for confirmation. Nevertheless, drug-induced lung toxicity remains a diagnosis of exclusion and depends heavily on patient history. The lungs are primarily affected because high concentrations of the drug can persist up to 24 hours after infusion.[6] Factors contributing to drug injury include the use of granulocyte-colony stimulating factor (G-CSF), advanced age, concurrent radiation therapy, renal failure, and smoking.[7] Lung tissue is particularly vulnerable due to its low levels of bleomycin hydrolase, leading to slow metabolism, increased exposure, and toxicity. Bleomycin

also stimulates the production of pro-fibrotic cytokines, making the lung parenchyma more prone to damage. Additionally, the presence of abundant oxygen facilitates the formation of oxygen-free radicals, causing DNA breaks and halting DNA synthesis, which explains its effects. The injury mechanism involves direct damage to the lung endothelium or through the action of cytokines, such as tumour necrosis factor-alpha. Activation of TNF-alpha results in fibrosis and permanent endothelial damage.[8][9]

In our first case, the patient presented with an acute onset of dyspnea during chemotherapy. He had been receiving Bleomycin for the last three cycles, and current exposure to the drug may have triggered acute toxicity. Although the cumulative dose did not exceed 400 mg, as documented in many cases, it was responsible for lung toxicity.[10] Cardiac toxicities are also associated with Bleomycin, but an immediate 2D echo, along with normal troponin and pro-BNP levels, ruled out acute cardiac toxicity. Further HRCT images showed non-cardiogenic pulmonary oedema, which resolved with corticosteroids and discontinuation of the drug. This supports the diagnosis of non-cardiogenic pulmonary oedema (NCPE), a known phenomenon.[11][12] In our second case, the patient experienced grade II mMRC dyspnea after ABVD chemotherapy, with a decline in PFT parameters from baseline. HRCT chest revealed new fibrotic parenchymal opacities and reduced DLCO in a non-smoker with a history of drug exposure. The absence of fibrotic opacity in previous imaging pointed towards drug-induced lung toxicity. Our patient had poor stem cell mobilisation; hence, bone marrow transplantation was aborted; however, on relapse, response with an anti-PD1 inhibitor resulted in remission. Similar findings are also observed in other studies after receiving Pembrolizumab.[13][14] There is debate about whether this toxicity is reversible or irreversible, with many case reports suggesting reversibility; however, lung fibrosis has also been documented with Bleomycin, causing permanent disability or death.[12][15] In our case, we stopped the offending agent and started pulmonary rehabilitation, which resolved the patient's symptoms. In our third patient, dyspnea occurred after BEP chemotherapy, and subsequent HRCT findings confirmed parenchymal fibrotic opacities. With no other factors contributing to lung toxicity, bleomycin-induced toxicity becomes more likely. We enrolled this patient in pulmonary rehabilitation, and he is currently free from any respiratory issues.

The management of bleomycin-induced lung toxicity includes corticosteroids, imatinib, or infliximab. [16] The decision to start early anti-fibrotic therapy with pirfenidone or nintedanib remains subject to debate; however, existing literature shows promising results. [17] Our first case involved a 4-year-old boy, and the safety of pirfenidone at this age has not been definitively established. Steroids are the primary treatment. We began therapy with methylprednisolone and empirical antibiotics (Inj. Cefoperazone + Sulbactam and Inj. Amikacin), and the patient slowly recovered from respiratory failure. Although various case reports suggest that steroids can be helpful in treating lung toxicity, there are no consensus guidelines, and treatment mainly depends on individual case experiences.

Hodgkin's lymphoma exhibits a bimodal age distribution. Our first case involved a four-year-old, while the second was a 53-year-old. Literature indicates that drug toxicity tends to increase with age. [7] However, in our cases, the first patient had a fulminant course in hospital, requiring ICU admission and invasive ventilation. The RATHL trial showed no reduction in efficacy when bleomycin was omitted after two cycles of ABVD. [2] A prospective single-centre study from Hungary also found that patients not receiving bleomycin experienced less pulmonary toxicity compared to those continuing with ABVD chemotherapy. The same study further suggests that there is no increased risk of pulmonary toxicity in patients receiving ABVD with concurrent Involved Field Radiotherapy (IFR) for bulky disease. [18] Nonetheless, less toxic protocols such as Nivolumab–AVD or BV-AVD are not cost-effective from an Indian perspective. Therefore, ABVD remains a promising and affordable option.

Author Contributions: Conceptualisation- all authors; Investigation- all authors; Writing – Original Draft- all authors; Writing – Review & Editing- all authors; Funding Acquisition- None; Supervision- NG, PS, AY, HM

Ethical Considerations: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

Conflict of interest: We certify that we do not have any financial or personal relationships that might bias the content of this work.

Availability of data and materials: The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies."

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