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Original Research Article

A Bleomycin Induced Lung Injury Case Studies

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Abstract:

The relative absence of immunosuppression and myelosuppression with bleomycin makes it an indispensable component of chemotherapy in Hodgkin lymphoma (HL) and germ cell tumours (GCT) However, bleomycin induced pulmonary toxicity (BIP) is a significant limitation and may affect treatment outcomes in cancer patients in absence of any approved standard treatment. We reviewed the imaging findings of five patients with bleomycin toxicity from the radiology database, who presented to our hospital from January to July 2019. The index cases were aged between 5 to 63years. Three of the patients had Hodgkin lymphoma, one patient had anaplastic non-Hodgkin lymphoma (NHL) and one patient was diagnosed with nonseminomatous germ cell tumour(NSGCT). They received ABVD (Adriamycin, bleomycin, vincristine and dacarbazine) for lymphoma and BEP (Bleomycin, etoposide and cisplatin) chemotherapy regimen for NSGCT. All patients underwent CTimaging. Additional ultrasound was performed for two patients. Four of the patients developed clinical features of drug toxicity with corroborative HRCT appearances during the course of treatment. Bleomycin was withheld from the subsequent drug regimens and no recurrence of the pulmonary symptoms was noted. One patient showed HRCT evidence of BIP after completion of his chemotherapy, albeit without clinical correlate. This suggested subclinical toxicity and did not significantly affect the patient's performance status. Bleomycin induced pulmonary toxicity affects the clinical course of patients with Hodgkin lymphoma and germ-cell tumour and can be fatal in 2-3% of the cases. Imaging plays an adjunctive role in the diagnosis of this condition and can prompt further clinical evaluation in subclinical cases.

Keywords: Bleomycin, diffuse alveolar damage, organizing pneumonia, High-Resolution Computed Tomography, Lung Injury.

Introduction

Bleomycin, a chemotherapeutic agent, plays a pivotal role in treating lymphomas, germ cell tumors, and squamous cell carcinomas of the cervix and head and neck [1]. These malignancies predominantly afflict young individuals, offering the prospect of extended survival. However, the clinical utility of bleomycin is tempered by a significant drawback—bleomycin-induced lung injury, a complication with a notable impact on patient outcomes [2]. According to recent studies, this adverse effect occurs in approximately 10% of patients treated with bleomycin [3,4].

The adverse effects of bleomycin-induced lung injury pose a considerable challenge, both in terms of prevalence and severity, underscoring its clinical relevance and necessitating a nuanced understanding of its implications [5]. In fact, a retrospective analysis reported that this complication occurs more frequently in elderly patients, those with impaired renal function, and individuals receiving cumulative doses exceeding 400 units or concomitant treatment with other toxic chemotherapeutic agents, GM-CSF, or thoracic irradiation [6].

Bleomycin-induced lung injury, with its non-specific clinicoradiological profile [7], further complicates the clinical landscape. The challenges in diagnosing this adverse effect are substantial, prompting the need for a more detailed examination of the diagnostic hurdles in the identification of bleomycin-induced lung injury. A recent study highlighted the diagnostic challenges, emphasizing the need for prompt diagnosis by exclusion of other mimics and immediate cessation of the offending drug to prevent long-term debilitating consequences [8]. As we embark on a journey to explore bleomycin-induced lung injury, it is imperative to acknowledge the existing gaps in the literature concerning its management and diagnosis. A comprehensive review by underscored the need for further research to address the gaps in our understanding of bleomycin-induced

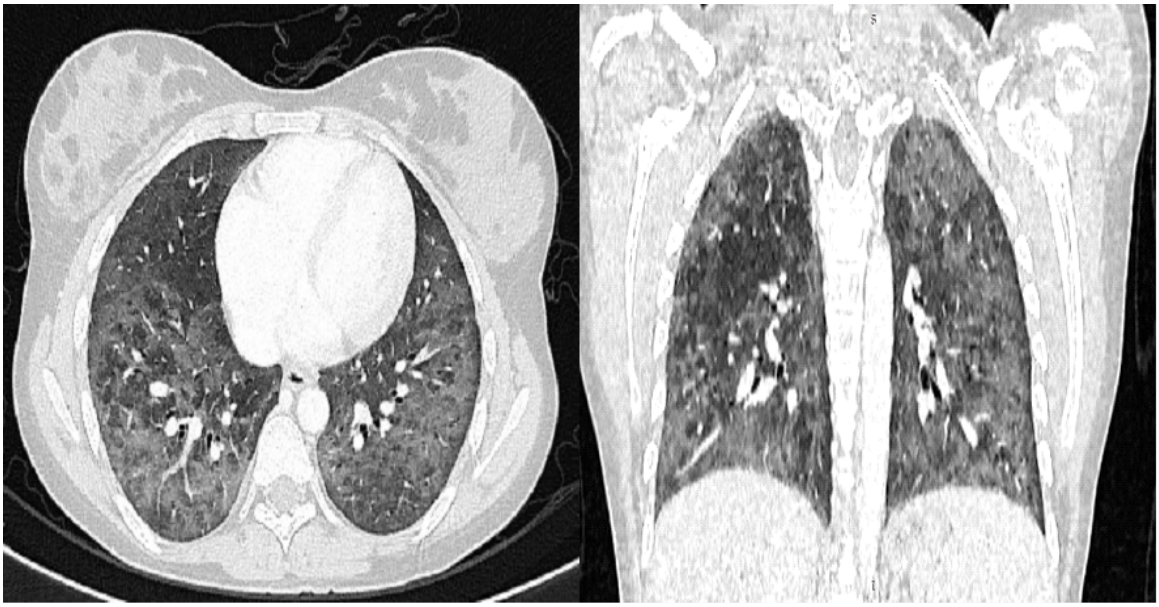
pulmonary toxicity, emphasizing the importance of tailored diagnostic approaches and effective management strategies [9].While we delve into the complexities of bleomycin-induced lung injury, it is essential to recognize the broader impact of this adverse effect on patient outcomes. Recent study demonstrated that patients who experienced bleomycin-induced lung injury had a significantly higher risk of long-term respiratory complications, emphasizing the critical need for early detection and intervention to mitigate these consequences [10].To augment the scientific depth of the introduction, a brief discussion on the mechanisms underlying bleomycin-induced lung injury is warranted. According to recent study bleomycin induces the formation of oxygen free radicals, DNA damage, and the release of cytokines by alveolar macrophages, leading to subsequent epithelial and endothelial damage with fibroblastic proliferation [11]. By providing readers with insights into the pathophysiology, we can foster a more profound understanding of the processes at play, setting the stage for the subsequent case series to explore these mechanisms in real-world clinical scenarios.

Case Series

Case 1

A 21-year-old female presented to our hospital with complaints of swelling on the right side of the neck and was diagnosed with classical Hodgkin lymphoma stage IIB. She underwent 4 cycles of ABVD, with the dose of the offending drug, bleomycin, being 12 mg per cycle. Approximately 1 week after the last cycle of chemotherapy, she developed exertional breathlessness and a drop in oxygen saturation.

Contrast-enhanced computed tomography (CECT) of the chest revealed ground glass opacities diffusely involving both lungs (Figure 1). The patient received non-invasive ventilation (NIV), steroids, N-acetylcysteine (NAC), and antifibrotic agents. Bleomycin was withheld from subsequent cycles, and follow-up HRCT showed regression of pulmonary opacities. According to the casualty assessment by Naranjo's algorithm, the score was 5, indicating probable bleomycin toxicity.



A B

Figure 1: (1A and 1B) CECT chest shows diffuse GGOs in bilateral lungs with slight lower lobe predominance

Case 2

A 5-year-old male complained of fever and shortness of breath and was diagnosed with mediastinal Hodgkin lymphoma stage IIIB. The patient underwent 6 cycles of AVBD and GM-CSF, with 8.5 mg of bleomycin administered per cycle. Concomitant involved field radiotherapy (IFRT) was also given. After the third cycle, the patient developed acute breathlessness and tachycardia. HRCT of the chest revealed non-specific ground glass opacities (GGOs) in bilateral lower lobes (Figure 2). Viral/Pneumocystis jiroveci pneumonia (PJP) and acute bleomycin toxicity were considered.

The patient did not respond to antibiotics but showed improvement on steroids and oxygen therapy, leading to the removal of bleomycin from the regimen. HRCT changes reversed on follow-up scans, with no recurrence of pulmonary symptoms.

Naranjo's score was 4, indicating possible bleomycin toxicity.

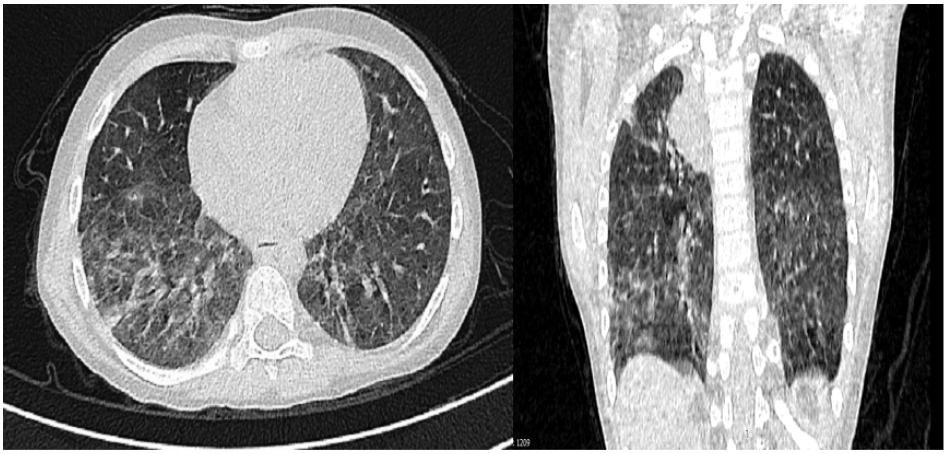


Figure 2: (2A and 2B) HRCT chest shows patchy GGOs in bilateral lower lobes

Case 3

A 25-year-old male presented with right testicular swelling, abdominal lump, and raised serum markers (beta-hCG, LDH). Ultrasound revealed a large heterogeneous testicular mass with bulky retroperitoneal nodal metastasis, encasing bilateral ureters with upstream hydroureteronephrosis. Due to deranged renal function, a non-contrast CT scan showed similar findings. Non-seminomatous germ cell tumor (NSGCT) was diagnosed on histopathology. A single cycle of chemotherapy (BEP) excluded Bleomycin due to renal impairment. Post bilateral percutaneous nephrostomy (PCN) insertion, renal parameters improved, and subsequent chemotherapeutic regimens (BEP) were administered at a full dose, with 20 mg per cycle for bleomycin. The patient showed a good clinical response, and follow-up imaging revealed new ground glass opacities with interspersed septal thickening in subpleural regions of the upper and lower lobes of bilateral lungs, raising a possibility of bleomycin-induced pulmonary toxicity radiologically (Figure 3).

Evaluation indicated no significant functional impairment; however, his DLCO was reduced, suggesting subclinical pulmonary disease. Based on Naranjo's scale, he was a possible case with a score of 4.

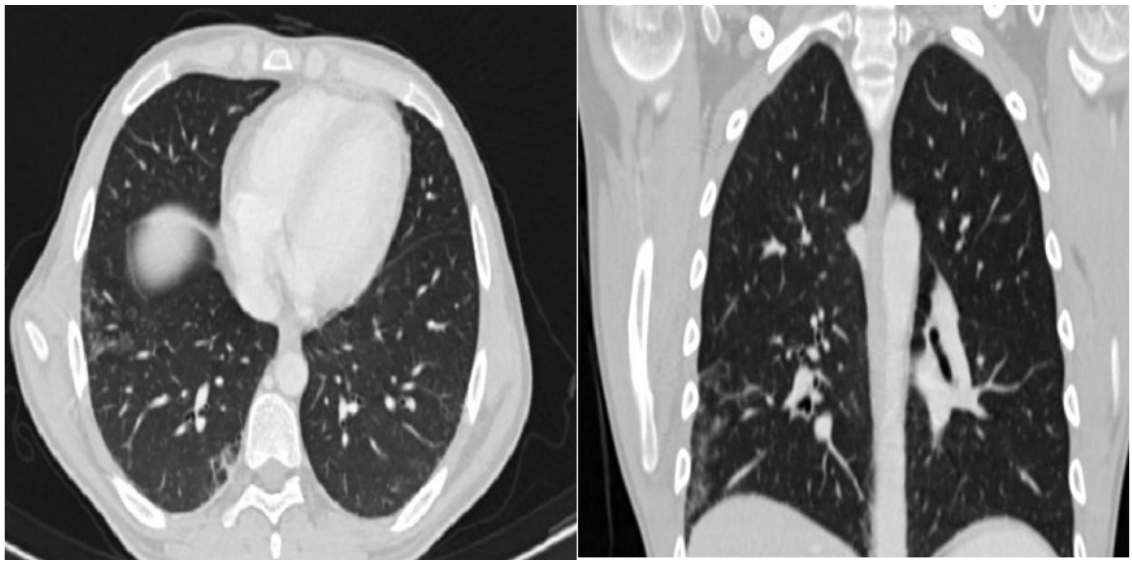


Figure 3: (3 A and 3 B) HRCT chest reveals patchy GGOs and septal thickening in subpleural distribution in bilateral upper and lower lobes

Case 4

A 63-year-old female complained of dysphagia and weight loss and was diagnosed with anaplastic large cell NHL on histopathology. A CT scan showed involvement of both tonsils, nasopharynx, and hypopharynx up to the level of the vocal cord with bilateral cervical lymphadenopathy (stage IIIB). The patient underwent 6 cycles of AVBD

with bleomycin given in the dose of 12 units per cycle. However, after the fourth cycle, the patient developed new-onset breathlessness.

HRCT of the chest0 showed peribronchial and subpleural GGOs and consolidations in bilateral lungs with basal preponderance (Figure 4). The patient was treated with steroids, bronchial dilators, and steam inhalation. Bleomycin was omitted from the drug regimen thereafter, on suspicion of bleomycin-induced pneumonitis (BIP). Follow-up CT scans showed mild improvement in lung findings, and the patient continued to maintain oxygen saturation of over 95%. A possible score of 4 was given on the Naranjo scale.

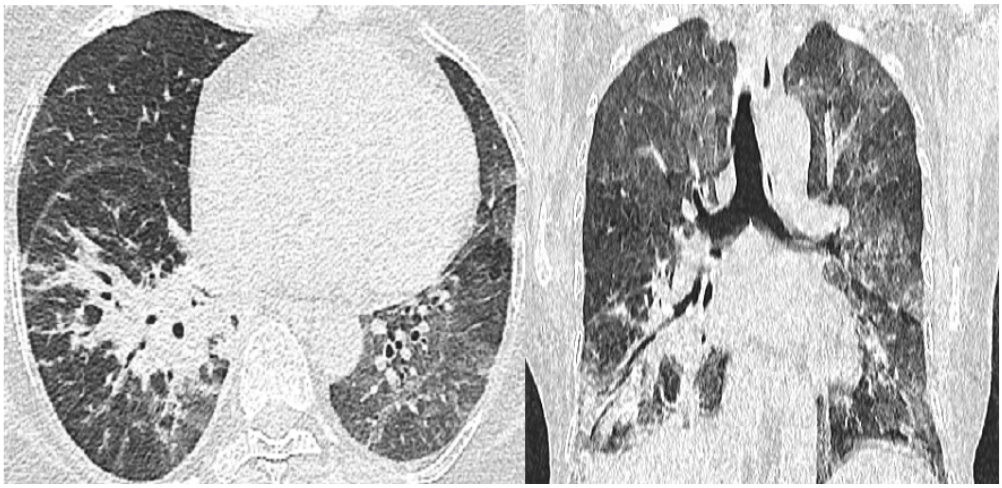


Figure 4: (4A and 4B) HRCT chest shows peribronchial consolidation in right lower lobe and patchy areas of GGOs and septal thickening in peribronchial and subpleural distribution in bilateral lungs

Case 5

A 53-year-old female presented to our hospital with complaints of fever and neck pain. Ultrasound showed bilateral cervical nodes, sampled and yielded a diagnosis of Hodgkin lymphoma. On staging CT scan, there were enlarged bilateral cervical, mediastinal, and retroperitoneal nodes (Stage IIIB). Three cycles of chemotherapy (ABVD) were administered uneventfully, with bleomycin being 14 units per cycle. However, after the fourth cycle, the patient complained of exertional dyspnea and cough. CT chest showed subpleural septal thickening with GGOs in bilateral lungs - organizing pneumonia pattern (Figure 5).

Steroids were administered, and bleomycin was subsequently omitted from the chemotherapeutic regimen. Thus, bleomycin toxicity was a possibility according to the Naranjo scale, with a score of 4.

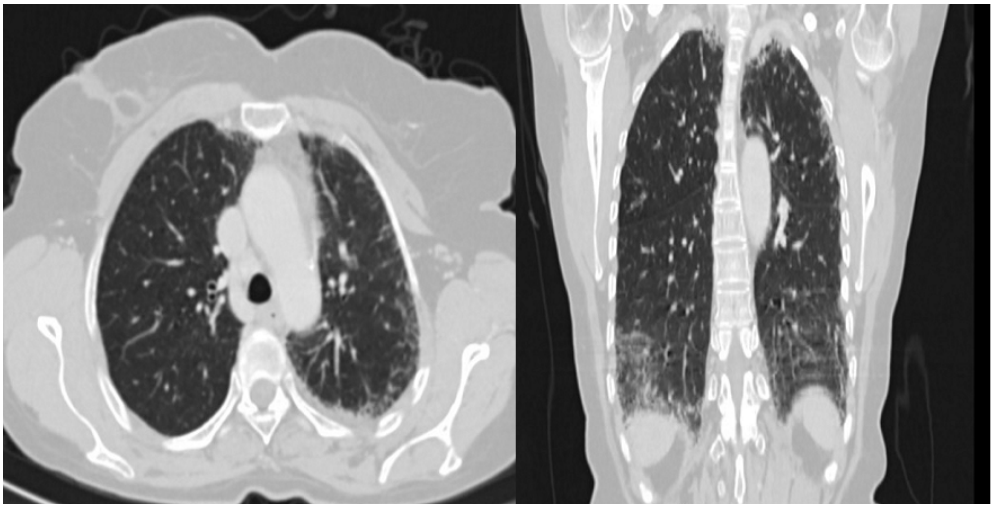


Figure 5: (5A and 5B) HRCT chest shows subpleural septal thickening with GGOs in bilateral lungs

Discussion

Pulmonary toxicity is a challenging side effect associated with bleomycin therapy, affecting approximately 10% of treated patients [10,12,13,14]. The occurrence of pulmonary toxicity is contingent on the dosage, primarily manifesting with doses surpassing 400,000 IU [15]. Additional risk factors encompass renal

impairment, advanced age, exposure to supplementary oxygen, bolus infusion administration, the extent of lung metastases, and pre-existing lung conditions [7,15].

The production of pro-collagen by fibroblasts emerges as a crucial mechanism in Bleomycin-induced fibrosis. However, recent findings underscore the significance of proinflammatory cytokines such as IL-18 and IL-1 beta, along with scaffold proteins like caveolin-1, in the injury mechanism [11,16,17]. Subsequently, fibroblasts, both directly and indirectly prompted by Bleomycin, contribute to collagen deposition [17]. The breakdown of Bleomycin is facilitated by Bleomycin Hydrolase, an enzyme present in most tissues [16,17]. Manifestations encompass nonproductive cough, dyspnea, pleuritic or substernal chest pain, fever, tachypnea, crackles, bibasal inspiratory crepitations, lung restriction, and hypoxemia. Chest X-ray commonly reveals bibasilar infiltrates and interstitial thickening. Typically, clinical signs emerge gradually within one to six months post-treatment initiation, persisting for more than six months after treatment cessation in some cases.The most frequent High-Resolution Computed Tomography (HRCT) pattern is diffuse alveolar damage (DAD), presenting as airspace consolidation and ground glass opacities [8]. Depending on the extent of injury, it may significantly improve or progress to extensive lung fibrosis [4]. Organizing pneumonia (OP) manifests as subpleural and peribronchial areas of patchy, sometimes nodular consolidation, ground glass opacities, and septal thickening [9,10,11]. In contrast to DAD, patients with Bronchiolitis Obliterans Organizing Pneumonia (BOOP) may be entirely asymptomatic and show a good response to corticosteroids [10]. Pulmonary edema, non-specific interstitial pneumonitis (NSIP), and hypersensitivity pneumonitis pattern can also be encountered occasionally [3] (Table 1). Rarely, air leaks such as pneumomediastinum and pneumothorax have been reported [1].The initial indication of Bleomycin-Induced Lung Injury (BILI) is often dyspnea coupled with a decrease in the Diffusing Capacity for Carbon Monoxide (DLCO) [18]. Clinical guidelines and the U.S. Food and Drug Administration (FDA) advocate for pulmonary function tests (PFTs) both at the beginning and monthly or following each new treatment cycle [19]. If a reduction in Diffusing Capacity for Carbon Monoxide (DLCO) exceeds 30-35%, healthcare providers are recommended to halt bleomycin administration, even in asymptomatic cases, owing to the potential risk of Bleomycin-Induced Lung Injury (BILI). However, a recent randomized phase III trial has raised questions about the efficacy of routine PFTs, as it revealed that the presence of cough had a stronger correlation with BILI than changes in PFTs [20].

Table 1: HRCT manifestations of various histopathological patterns of bleomycin toxicity [10]

Histopathological patterns	HRCT manifestations
Diffuse alveolar damage	Bilateral airspace consolidation and GGOs involving dependent lung regions
Alveolar hemorrhage	Extensive bilateral ground glass opacities with or without superimposed inter-lobular linear opacities (crazy paving)
Hypersensitivity pneumonitis	Bilateral GGOs, small poorly defined centrilobular nodules, air trapping, mosa-ic attenuation
Nonspecific interstitial Pneumonia	Patchy bilateral GGOs with septal thickening mainly involving lower lung zones and subpleural regions
Organizing pneumonia	consolidation/GGOs in subpleural or peribronchial distribution. Rarely nodular pattern
Eosinophilic Pneumonia	Airspace consolidation and GGOs in predominantly peripheral distribution involving middle and upper zones (reverse batwing)

This series describes five patients with suspected bleomycin toxicity, encompassing three cases of Hodgkin lymphoma, one case of anaplastic NHL, and one case of NSGCT of the testis. Among these, three were young individuals, while the other two were elderly. All received a low cumulative dose of bleomycin ranging from 100-160 mg before the onset of toxicity. The HRCT patterns of pulmonary involvement included DAD, NSIP, and OP patterns in one, one, and three cases, respectively. Remarkably, one patient exhibited subclinical pulmonary toxicity after the conclusion of chemotherapy, presenting air space opacities in OP pattern on imaging with reduced DLCO. However, the patient remained asymptomatic, and subsequent lung opacities remained stable, requiring no specific treatment. In the remaining patients, omission of bleomycin and institution of steroids led to improvement. DAD pattern of involvement required additional antifibrotic therapy. Concurrent radiotherapy and GM–CSF administration in one patient, and altered renal function in another, may have increased their individual susceptibility to bleomycin toxicity (Table 2).

Table 2: Overview of the patients with suspected bleomycin toxicity

Age (in years)	Diagnosis	regimen	Pretoxiccumul-ative Dose (mg)	Risk Factor	HRCT pattern	treatment	outcome	Naranjo Score
21	HL IIB	4ABVD	96	-	DAD	Steroids Stop bleomy-cin NAC NIV	improved	5
5	HL IIIB	6ABVD+ GM-CSF+ IFRT	102	GM-CSF IFRT	NSIP	Steroids Stop bleomy-cin	regressed	4
25	NSGCT IIC	1EP+ 4BEP	160	Renal Failure	OP	-	stable	4
63	NHL IIIB	6ABVD	96	-	OP	Steroids Stop bleomy-cin	regressed	4
53	HL IIIB	6ABVD	112	-	OP	Steroids Stop bleomy-cin	stable	4

Bleomycin-Induced Lung Injury management entails the immediate cessation of all chemotherapeutic agents. Symptomatic patients receive corticosteroids, with the recommended prednisone dosage ranging from 0.75 to 1 mg/kg (based on ideal body weight) per day, capped at a maximum of 100 mg/day, over the initial four to six weeks, as supported by clinical data and case reports [21,22,23,24].

Clinical and radiographic amelioration is reported variably within 7 to 12 days when high-dose corticosteroid therapy is promptly initiated [22]. Notably, insufficient corticosteroid doses have been linked to two fatal cases of BILI, underscoring the necessity for an effective higher dose. While the majority of patients respond well to treatment, limited case reports have documented corticosteroid-refractory BILI, prompting exploration into off-label therapies. Recent case reports suggest variable success with imatinib, infliximab, and pirfenidone in treating BILI, even in cases resistant to corticosteroids; however, these alternative therapies necessitate prolonged durations for clinical success [25,26,27,28,29].

Recent data indicates that the overall risk of clinically apparent severe bleomycin-induced lung injury is low, and most patients experience reversible pulmonary toxicity without long-term consequences [30,31].

Findings from the Daugaard et al., and Lauritsen et al., suggest that only a minority of patients treated with bleomycin, including those who discontinued it due to a decrease in carbon monoxide diffusing capacity (DLCO), developed long-term restrictive or obstructive lung disease at the five-year follow-up [32,33]. Depending on clinical criteria and cumulative bleomycin dose, the incidence of bleomycin-induced pulmonary toxicity in adults undergoing ABVD for Hodgkin lymphoma ranges from 10 to 53%, with fatal pulmonary toxicity rates at 4 to 5% [34]. Additionally, long-term functional respiratory impairment is observed in approximately 15 to 18% of patients [35,36,37].

Conclusion

In conclusion, our case series underscores the significance of heightened awareness and vigilance regarding bleomycin-induced pulmonary toxicity, even at lower cumulative doses. The diverse high-resolution computed tomography (HRCT) patterns observed, primarily organizing pneumonia (OP), highlight the variability in clinical presentations, necessitating individualized management approaches. The observed lower toxic dose threshold prompts considerations for risk stratification and warrants further investigation into potential contributing factors. The prompt recognition, cessation of bleomycin, and judicious use of corticosteroids remain pivotal in managing this toxicity. The nuanced approach to pulmonary function testing, particularly in asymptomatic patients, challenges the routine reliance on PFTs alone for early detection. The discussion also highlights the potential impact of alternative therapies in corticosteroid-refractory cases, suggesting future research directions to optimize treatment strategies. Varied clinical outcomes and a relatively favorable prognosis, especially in cases with OP patterns, provide valuable insights for clinicians managing bleomycin-induced pulmonary toxicity. Given the challenges, ongoing surveillance and awareness among healthcare

providers are crucial for timely intervention and improved patient outcomes, contributing to the evolving understanding of this complex clinical entity.

References

1. Burman S, Das A, Gupta N. Atypical radiological presentation of bleomycin-induced lung injury: Case report and review of literature. Current Med Res Practice. 2020: 10(5):244-7.
2. Chen J, Ghorai MK, Kenney G, Stubbe J. Mechanistic studies on bleomycin-mediated DNA damage: multiple binding modes can result in double-stranded DNA cleavage. Nucleic Acids Res. 2008;36(11):3781-90.
3. Debnath J, Singh HP, George RA, et al. Reversible Bleomycin Toxicity. Med J Armed Forces India. 2010;66(3):290-1
4. Godoy MC, Nonaka D, Raphael BG, Vlahos I. Diffuse Ground-Glass Opacities in a Patient with Hodgkin Lymphoma and Progressive Respiratory Failure. Chest. 2008;134(1):207-12.
5. Madabhavi I, Modi G, Patel A, Anand A, Panchal H, Parikh S. Pulmonary toxicity following bleomycin use: A single-center experience. J Cancer Res Ther. 2017;13(3):466-70.
6. Ommurugan B, Priya A, Patil N, Thomas J. Bleomycin-Induced Reversible Acute Interstitial Pneumonia. Asian J Pharm Clin Res. 2017;10(5):6.
7. Patil N, Paulose RM, Udupa KS, Ramakrishna N, Ahmed T. Pulmonary Toxicity of Bleomycin - A Case Series from a Tertiary Care Center in Southern India. J Clin Diagn Res. 2016;10(4):FR01-R3.
8. McLeod B, Lawrence H, Smith D, Vogt P, Gandara D. Fatal bleomycin toxicity from a low cumulative dose in a patient with renal insufficiency. Cancer. 1987;60(11):2617-20.
9. Reinert T, Baldotto C, Nunes F, Scheliga A. Bleomycin-Induced Lung Injury. J Cancer Res. 2013;2013:1-9.
10. Rossi S, Erasmus J, McAdams H, Sporn T, Goodman P. Pulmonary Drug Toxicity: Radiologic and Pathologic Manifestations. Radiographics. 2000;20(5):1245-59.
11. Silva CI, Müller NL. Drug-induced lung diseases: most common reaction patterns and corresponding high-resolution CT manifestations. Semin Ultrasound CT MR. 2006;27(2):111-6.
12. Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001;120:617-24.
13. Azambuja E, Fleck JF, Batista RG, Menna Barreto SS. Bleomycin lung toxicity: who are the patients with increased risk? PulmPharmacol Ther. 2005;18:363-6.
14. O'Sullivan JM, Huddart RA, Norman AR, et al. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol. 2003;14:91-6.
15. Martin GW, Ristow KM, Habermann MT, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol. 2005;23:7614-20.
16. Hoshino T, Okamoto M, Sakazaki Y, et al. Role of proinflammatory cytokines IL-18 and IL-1beta in bleomycin-induced lung injury in humans and mice. Am J Respir Cell Mol Biol. 2009;41:661-70.
17. Kasper M, Barth K. Bleomycin and its role in inducing apoptosis and senescence in lung cells - modulating effects of caveolin-1. Curr Cancer Drug Targets. 2009;9:341-53.
18. Nippon Kayaku Co., Ltd. Blenoxane (bleomycin sulfate) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050443s036lbl.pdf. Revised April 2010. Accessed December30, 2023.
19. Watson RA, De La Peña H, et al. Development of a best-practice clinical guideline for the use of bleomycin in the treatment of germ cell tumours in the UK. Br J Cancer. 2018;119(9):1044-51.
20. Shamash J, Sarker SJ, Huddart R, et al. A randomized phase III study of 72 h infusional versus bolus bleomycin in BEP (bleomycin, etoposide and cisplatin) chemotherapy to treat IGCCCG good prognosis metastatic germ cell tumours (TE-3). Ann Oncol. 2017;28(6):1333-8.
21. Wang, X, Deng, J, Sothwal, A, Gordon, E, Patel, G. Bleomycin-Induced Pneumonitis Responds To Super-High-Dose Steroid and Monitored By LDH and PAO2/FIO2. Critical Care Med. 2016;44(12):558.
22. Ghalamkari M, Khatuni M, Toogeh G, Haghighi S, Taherkhani M. Reversible Acute Lung Injury due to Bleomycin. Tanaffos. 2022;21(2):253-6.
23. Gupta R, Ettinger NA. Beyond conventional therapy: role of pulse steroids in bleomycin induced lung injury. Respir Care. 2014;59(1):e9-12.
24. Rashid RS. Bleomycin lung: a case report. BMJ Case Rep. 2009;2009:bcr11.2008.1175.
25. Sakamoto K, Ito S, Hashimoto N, Hasegawa Y. Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma. BMC Cancer. 2017;17(1):526.
26. Banakh I, Lam A, Tiruvoipati R, Carney I, Botha J. Imatinib for bleomycin induced pulmonary toxicity: A case report and

evidence-base review. Clin Case Rep. 2016;4(5):486-90.
27. Aykaç N, Tecimer C. Imatinib Treatment for Bleomycin-Induced Pulmonary Toxicity. Turk Thorac J. 2020;21(6):457-60.
28. Carnevale-Schianca F, Gallo S, Rota-Scalabrini D, et al. Complete resolution of life-threatening bleomycin-induced pneumonitis after treatment with imatinib mesylate in a patient with Hodgkin's lymphoma: hope for severe chemotherapy-induced toxicity? J Clin Oncol. 2011;29(24):e691-3.
29. Ge V, Banakh I, Tiruvoipati R, Haji K. Bleomycin-induced pulmonary toxicity and treatment with infliximab: A case report. Clin Case Rep. 2018;6(10):2011-4.
30. Daugaard G, Kier MGG, Bandak M, et al. The Danish Testicular Database. Clin Epidemiol. 2016;8:703-7.
31. Lauritsen J, Kier MG, Bandak M, et al. Pulmonary function in patients with germ cell cancer treated with bleomycin, etoposide, and cisplatin. J Clin Oncol. 2016;34(13):1492-9.
32. Ranganath P, Kesler KA, Einhorn LH. Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. J Clin Oncol. 2016;34(36):4445-6.
33. Necchi A, Miceli R, Oualla K, et al. Effect of bleomycin administration on the development of pulmonary toxicity in patients with metastatic germ cell tumors receiving first-line chemotherapy: A meta-analysis of randomized studies. Clin Genitourin Cancer. 2017;15(3):e213-20.
34. Hirsch A, Vander Els N, Straus DJ, et al. Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin’s disease. J Clin Oncol. 1996;14(5):1297-305.
35. Avivi I, Hardak E, Shaham B, et al. Low incidence of long-term respiratory impairment in Hodgkin lymphoma survivors. Ann Hematol. 2012;91(2):215-21.
36. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin’s Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009;27(33):5390-6.
37. Jóna Á, Miltényi Z, Ujj Z, et al. Late pulmonary complications of treating Hodgkin lymphoma: bleomycin-induced toxicity. Expert Opin Drug Saf. 2014;13(10):1291-7.