

Case Report

SPONTANEOUS PNEUMOMEDIASTINUM CAUSED BY BLEOMYCIN-INDUCED PNEUMONITIS

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ABSTRACT

We report the case of a 24-yr-old woman treated for lymphoma who developed bleomycin-induced interstitial pneumonia. This interstitial pneumonia was complicated by spontaneous pneumomediastinum. Pneumomediastinum is an unfrequent side effect of high dose bleomycin-induced pneumonitis (BIP) and we describe the first case occurring with low-dose of bleomycin.

Key words: pneumomediastinum, Bleomycin, interstitial pneumonia

CLINICAL REPORT

A 24-yr-old woman was investigated for acrocyanosis and chest, axillary and abdominal lymph nodes. An anaplastic large B cell non-Hodgkin's lymphoma was diagnosed by biopsy of a left axillary node and was treated by 4 courses of ACVBP chemotherapy (adriamycin, cyclophosphamide, vindesin, bleomycine, methylprednisolone and intrathecal methotrexate) with a total amount of 80 mg of bleomycin over eight weeks. A complete tumour response was achieved. Two months later, she developed dyspnea and a non-respiratory dependent left chest pain limiting progressively her physical activities. Functional respiratory assessment showed a restrictive pattern (forced vital capacity (FVC) 1.79 L, (46% of the predicted value (PV)), *diffusion capacity* of the lung for carbon monoxide at 32% of the predicted value, total lung capacity (TLC) 3.26 L (61% PV). Chest computed tomography (CT) showed a pneumomediastinum and parietal emphysema with multifocal interstitial infiltrations predominant in the left lower lobe (Figure 1). Bronchoalveolar lavage was not contributive (140 white blood cells per mm³ with 6% of neutrophils, 3% of lymphocytes and 86% of macrophages). Lung surgical biopsy refuted infectious or

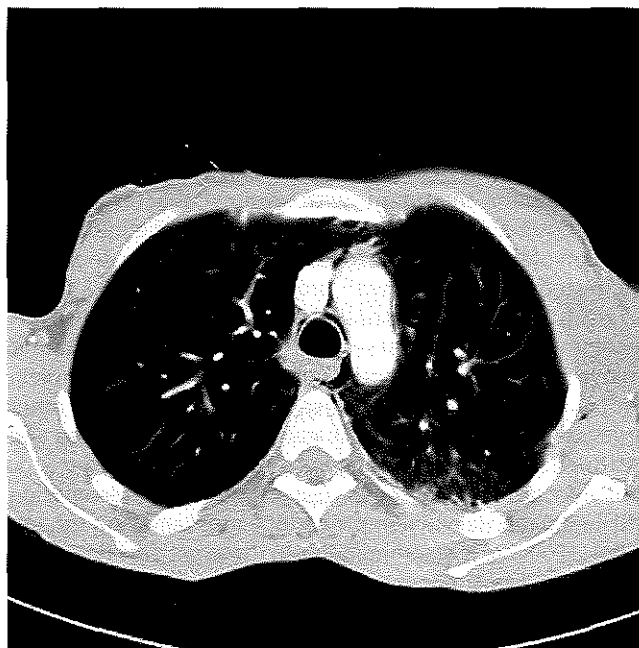


Figure 1: Chest computed tomography (CT) showing a pneumomediastinum and parietal emphysema with multifocal interstitial infiltrations predominant in the left lower lobe.

neoplastic aetiologies but confirmed an interstitial pneumonia due to bleomycin (Figure 2). Bleomycin was stopped and systemic corticotherapy begun. Seven months later, FVC and TLC had improved (2.50 liters, 64% PV and 3.93 liters, 74% PV, respectively) with clinical and radiological recovery (Figure 3).

DISCUSSION

Bleomycin is an antibiotic drug with antitumoural activity used for the treatment of germ cell tumours and Hodgkin's and non-Hodgkin's lymphoma. Bleomycin is inactivated by

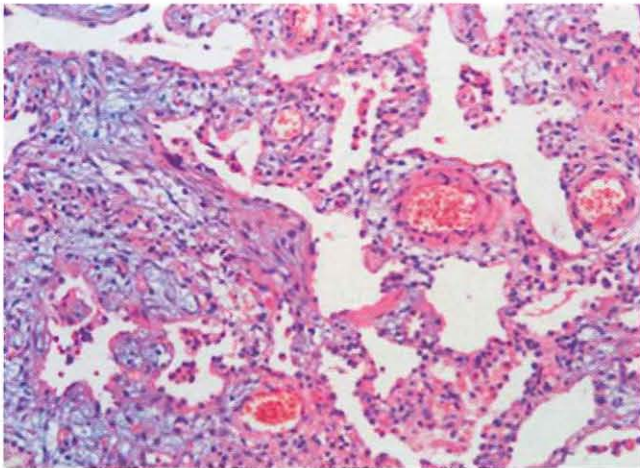


Figure 2: Lung surgical biopsy confirms an interstitial pneumonia.

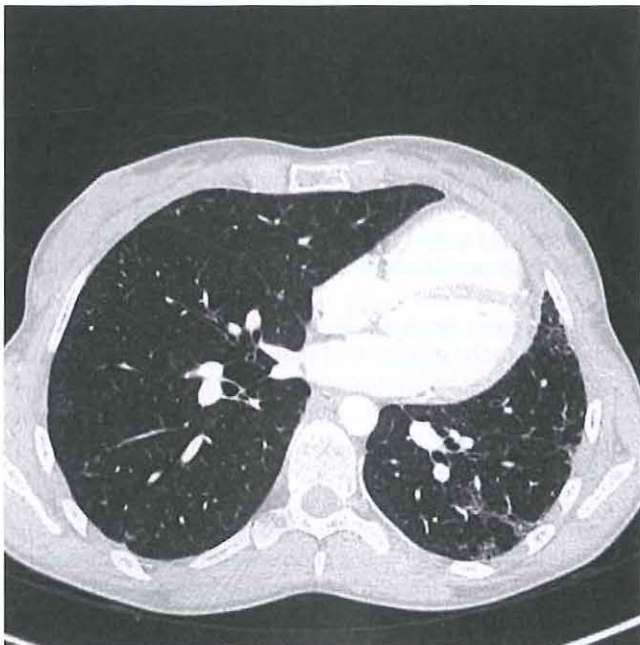


Figure 3: Radiological recovery with improved chest computed tomography images when bleomycin is stopped.

bleomycin hydrolase, but this enzyme is not found in the lung and the skin which might explain the high toxicity of the drug on these organs. Bleomycin can induce cell damage through lipid peroxidation. In the lung it can cause alveolar cell destruction leading to pulmonary inflammation. Pulmonary toxicity of bleomycin is the most feared side-effect of this medication. Several pulmonary diseases have been associated with the use of bleomycin, such as cryptogenic organising pneumonia, eosinophilic hypersensitivity and interstitial pneumonitis(1).

Ngeow et al published a prospective study of 184 patients treated for Hodgkin's lymphoma by adriamycin, bleomycin, vinblastine and dacarbazine (2). Bleomycin-induced pneumonitis (BIP) developed in 15% of the patients. The mortality rate of BIP is close to 3%. Pulmonary toxicity of bleomycin is a dose-dependent effect, and has been described at cumulative dose higher than 100 mg. Only two cases of pneumomediastinum

have been described with BIP and in these cases, the patients received high dose of bleomycin (225 mg and 300 mg, respectively) (3). We postulate that oxidative alveolar damages caused by bleomycin lead to pneumomediastinum by air leakage in the mediastinum.

Patients older than 70 years have a higher risk to develop BIP. Bleomycin is excreted by the kidney. Sleijfer et al showed that the incidence of BIP is correlated with the decrease of renal function (4). Lei et al have demonstrated that Granulocyte Colony-Stimulating Factor (G-CSF) used during bleomycin based chemotherapy enhanced the risk of respiratory failure. Bleomycin lung toxicity is partially due to the production of oxidants and G-CSF exacerbates this phenomenon by increasing superoxide release by neutrophils in response to stimuli (5). Administration of high inspired oxygen fraction could exacerbate the production of oxidants and so increase the risk of BIP.

In a review of 10 patients suffering from BIP White et al. found that dyspnea, dry cough, tachypnea and cyanosis were the presenting symptoms in nine patients; one was asymptomatic (6). Radiographic presentation of BIP is a bibasal reticular or fine nodular infiltrates. Findings are similar but are detected earlier on CT scan and impose to exclude other diagnoses such as metastasis or infectious pneumonitis. Decreasing FVC is more in relationship with bleomycin toxicity than TLCO (3).

In the series of ten patients described above, White et al. showed the efficacy of corticosteroids for the treatment of BIP (6). Seven patients were treated by corticosteroids and initially improved. After lowering the dose, 5 patients had a relapse of BIP. By contrast the 3 untreated patients died quickly. To the best of our knowledge there is no other published study that supports the efficacy of corticosteroids in BIP. But in patients with BIP, the most important is to avoid further bleomycin administration. Extensive architectural distortion seen in BIP can lead to a pneumomediastinum.

CONCLUSION

Our case highlights the occurrence of BIP after low-dose bleomycin. The absence of a risk factor must remind us that BIP can occur during bleomycin treatment in any patient and that we should follow FVC during such therapy. Furthermore, this is the first case in which a pneumomediastinum without associated pneumothorax was reported with low dose of bleomycin.

CONFLICT OF INTEREST: None.

REFERENCES

1. S. Sleijfer. Bleomycin-induced pneumonitis. *Chest* 2001; 120: 617-624.
2. Ngeow J, Tan IB, Kanesvaran R, et al. Prognostic impact of bleomycin-induced pneumonitis on the outcome of Hodgkin's lymphoma. *Ann Hematol* 2011; 90: 67-72.
3. T. Skidar, D Macvivar, J E Husband. *The British Journal of Radiology* 1998; 71: 1202-1204.
4. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. *Eur J Cancer* 1996; 32A(3): 550-552.
5. Lei KI, Leung WT, Johnson PJ. Serious pulmonary complications in patients receiving recombinant granulocyte colony-stimulating factor during BACOP chemotherapy for aggressive non-hodgkin's lymphoma. *Br J Cancer* 1994; 70: 1009-1013.
6. White DA, Stover DE. Severe Bleomycin-induced pneumonitis. Clinical features and response to corticosteroids. *Chest* 1984; 86(5): 723-728.