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Case Series

Pharmacology Section

Pulmonary Toxicity of Bleomycin – A Case Series from a Tertiary Care Center in Southern India

NAVIN PATIL[1], RINZ MATHEW PAULOSE[2], KARTHIK SUBRAMANYA UDUPA[3], NARAYANAN RAMAKRISHNA[4], TALHA AHMED[5]

ABSTRACT

Hodgkin's lymphoma is one of the curable cancers and the standard treatment regimen involves combination chemotherapy involving bleomycin. One of the fatal side effect of bleomycin is pulmonary toxicity. Here we present three cases of Hodgkin's lymphoma treated with ABVD chemotherapy who had pulmonary toxicity. All three developed bleomycin induced pulmonary toxicity in the form of pulmonary fibrosis during treatment of the disease. Mode of treatment, severity of the condition and the treatment outcome varied among the three. Two recovered following treatment and one patient died due to irreversible pulmonary damage. Causality assessment using Naranjo's scale gave a score of 7 for case one and three and a score of 6 for case two, both indicating the adverse drug reaction to be a probable bleomycin induced Lung fibrosis.

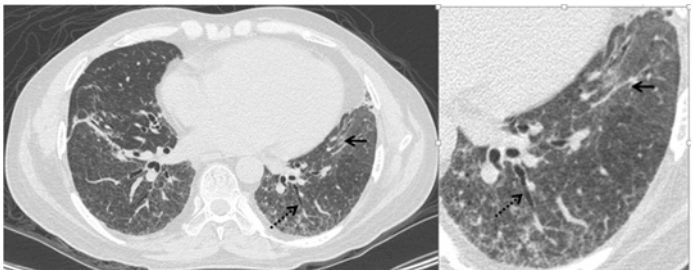
Keywords: Fibrosis, Lymphoma, Naranjo's scale

CASE SERIES

CASE 1

A 22-year-old male who presented with complaints of swelling in the right side of neck and cough with mucoid expectoration was diagnosed to have Hodgkin's lymphoma, stage 2B and was started on 6 cycles of ABVD (Adriamycin, Bleomycin, Vincristine, Dacarbazine) regimen from January 2004 to June 2004, followed by IFRT (Involved Field Radiotherapy). Patient was in complete remission post radiotherapy and was kept under regular follow up.

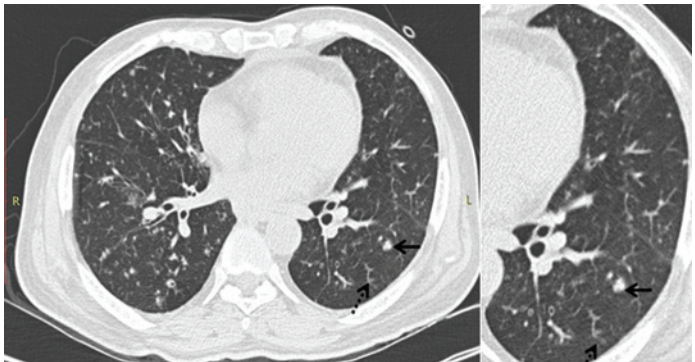
After 10 years, he again presented with right inguinal lymphadenopathy and biopsy was suggestive of Hodgkin's lymphoma. Staging evaluation showed involvement of bone marrow and hence was diagnosed as having relapsed Hodgkin's lymphoma stage 4A. He was started on COPP/ABV regimen (Cyclophosphamide, Oncovin, Prednisone, Procarbazine, Adriamycin, Bleomycin, Vinblastine) with the dose of the offending drug Bleomycin being 15 IU in 100ml 0.9% normal saline. Two weeks after the last chemotherapy cycle 4, patient presented with complaints of breathlessness on exertion which was insidious and progressive and hence was admitted in intensive care unit. High Resolution Computed Tomography (HRCT) thorax showed septal thickening with interspersed areas of ground glass attenuation predominantly in basal and pleural aspects with an associated impression of interstitial lung disease [Table/Fig-1]. In view of above presentation and computed tomography (CT) findings and drop in saturation, patient was started on non-invasive ventilation, steroids and acyclovir. Patient responded to treatment and was weaned on ventilation after one month and steroids were stopped after 6 weeks. Subsequent cycles was planned by stopping Bleomycin and continuing with COPP/AD regimen and on repeating a Computed Tomography (CT) scan there was a regression and resolution of pulmonary fibrosis. Hence according to Naranjo's algorithm, the score was 7 indicating the causality assessment to be probable.



[Table/Fig-1]: High resolution computed tomography (HRCT), showing late stage of Bleomycin induced pulmonary toxicity, showing architectural distortion (black arrow) and traction bronchiectasis (black dashed arrow) in both lungs predominantly in the lower lobes, suggesting fibrosis.

CASE 2

Patient aged 47-year-old came with complaints of fever with chills and rigors with associated lymphadenopathy. Lab tests showed low haemoglobin and high Erythrocyte Sedimentation Rate (ESR). Upon histopathological examination of lymph node and Contrast Enhanced Computed Tomography (CECT) thorax, patient was diagnosed with Hodgkin's lymphoma stage 3B. Hence patient was started on ABVD regimen with the dose of the offending drug bleomycin being 15 IU in 100ml 0.9% normal saline. Complete chemotherapy was given in 8 cycles for a period of 28 weeks from January 2014 to August 2014. The first chemotherapy cycle was started on 5/1/2014 and 28/1/2014 (day 1 and 15 of cycle 1) and last cycle being given on 26/6/2014 and 14/7/2014 respectively (day 1 and 15 of cycle 8). Following completion of the final cycle 8, patient got admitted with complaints of dry cough and exertional breathlessness. On examination he was tachypnoeic with coarse

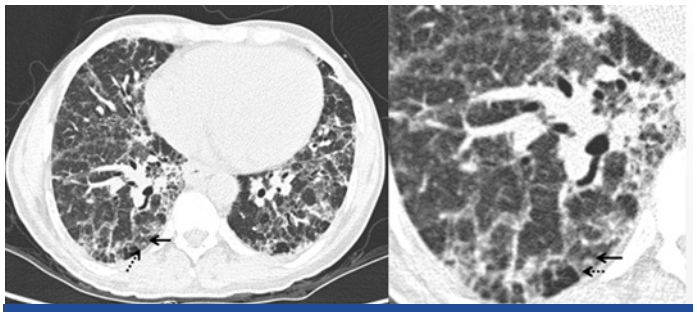


[Table/Fig-2]: A unique manifestation of bleomycin-related pulmonary toxicity. High resolution Computed tomography (HRCT) showing multiple pulmonary nodules scattered in both lungs (Black arrow). Also, note the interlobular septal thickening (black dashed arrow).

crepitations. High-Resolution Computed Tomography (HRCT) thorax was done which showed multiple ill-defined nodules scattered in both lungs with interlobular septal thickening [Table/Fig-2]. Hence diagnosis of Bleomycin induced pulmonary fibrosis with superimposed lower respiratory tract infection was made. Patient was started on antibiotic (tablets co-trimoxazole and cefepime) and steroids (tablet prednisolone). But despite above measures, his condition deteriorated and was shifted to ICU and was started on non invasive ventilation, but he did not show any improvement in his general condition and expired one week after his admission. Based on Naranjo's scale, the score was 6 and hence being a probable case.

CASE 3

A 52-year-old patient with complaints of fever with chills, scanty mucoid expectoration, cervical and supraclavicular lymphadenopathy was evaluated and lymph node biopsy was suggestive of Hodgkin's lymphoma stage 3B. Hence was started on Adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy containing bleomycin 15 IU in 100ml of 0.9% normal saline over 15 minutes from 28th December 2013 (1st cycle) to 4th February 2014 (3rd cycle). Following cycle 3, patient complained of shortness of breath and thereby a Computed Tomography (CT) scan was done which showed interlobar septal thickening and ground glass attenuation predominantly in the basal and pleural aspect of both lungs [Table/Fig-3] wherein he was diagnosed to have bleomycin induced lung disease. He was given 2 week course of oral steroid (tablet prednisolone) following which his breathlessness improved. His subsequent cycles of chemotherapy were continued without bleomycin. Presently the patient is in remission with no complaints of breathlessness. The following case showed a score of 7 based on Naranjo assessment and thereby its causality was considered to be probable.



[Table/Fig-3]: Bleomycin-induced Diffuse Alveolar Damage [DAD] in a 52-year old man with a Hodgkin disease. High-resolution CT scan shows scattered areas of ground-glass opacity (black arrow) and thickening of interlobular septa (dashed black arrow).

DISCUSSION

Pulmonary fibrosis has been considered to be a common problem in relation to an end-stage of a lung disease caused by radiation, environmental toxins, or chemotherapy treatments for cancer or even secondary to chronic inflammatory diseases [1]. The overall incidence of pulmonary toxicity is as immense as 10% and it is mortal in 1-2% [2].

Drug induced pulmonary toxicity is more commonly being diagnosed as a cause of acute and chronic lung disease. The most common manifestation of pulmonary drug toxicity is Diffuse Alveolar Damage (DAD). Various cytotoxic and non-cytotoxic drugs have been known to cause such toxicity [3]. Some of the risk factors associated with bleomycin induced lung fibrosis include: repeated systemic administration of bleomycin [4], total cumulative dose more than 450 units, elderly and in patients receiving oxygen therapy, those with a history of previous thoracic irradiation, or in whom therapy is re-instituted within 6 months of cessation [5], radiation, renal insufficiency, smoking history and any underlying lung disease [6]. It has also been understood that supplementation of adjuvant G-CSF plays an important role in aggravating toxicity. Although the exact mechanism is unknown, bleomycin-induced cell injury in the lung prompts an inflammatory response with recruitment of inflammatory cells and an increase in cytokine production. Granulocyte – colony stimulating factor (G-CSF) has been shown to augment these effects in animal models [4]. Other mechanisms leading to this side effect is mostly due to excess production of mature collagen fibrils, decrease in Nicotinamide Adenine Dinucleotide (NAD) and Adenosine Triphosphate (ATP) and enhanced concentration of reactive oxygen species [7].

Bleomycin has been used as a principle chemotherapeutic agent because it does not cause major myelosuppression or immunosuppression unlike other cytotoxic drugs [8]. Bleomycin-containing chemotherapy regimens form the backbone in treating Hodgkin's Lymphoma and continue to be included into the newer regimens being proposed such as the Stanford V regimen which includes doxorubicin, vincristine, vinblastine, bleomycin, mechlorethamine, cyclophosphamide, etoposide, and prednisone and the BEACOPP regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. Although there is no approved standard treatment for Bleomycin induced pulmonary toxicity, some of the most common approaches until date include witholding bleomycin from subsequent chemotherapy, continuing with a non-bleomycin based regimen in relevant patients or corticosteroid treatment. The impact of this has on the result in HL remains ambiguous [5].

In our case series all three patients who developed bleomycin pulmonary toxicity developed the same while on treatment and were treated with oral steroids. Two among the three recovered from toxicity and subsequent cycles were delivered omitting bleomycin. Both these patients are in complete remission and are having no symptoms of shortness of breath. While the other patient even though was started on steroids (prednisolone 1 mg/kg) did not respond to treatment and died a week after admission.

Clinically, the most useful test for lung function is the diffusing capacity of the lungs for carbon monoxide (DLCO). The lungs capacity to transfer gas from inhaled air to the red blood cells in pulmonary capillaries is determined by the DLCO. It is an effortless and convenient test for the patient to perform. Diseases which hinder oxygen uptake cause a proportionate decrease in carbon monoxide uptake, as measured by the DLCO [9].

Decrease in DLCO is one of the earliest manifestations of bleomycin lung toxicity leading to determination of a subclinical pulmonary toxicity even though the sensitivity and reliability of the test is debatable [10] and hence we recommend DLCO after every cycle of ABVD chemotherapy. Careful interpretation of the results and omitting bleomycin if there is a significant drop in DLCO could probably be the best strategy available presently to prevent bleomycin lung toxicity [11].

CONCLUSION

Pulmonary toxicity due to bleomycin is one of the fatal side effect of this drug in the treatment of Hodgkin's lymphoma. Every physician should have high degree of suspicion in diagnosing this problem. DLCO is one of the easy methods available to diagnose this problem and we recommend DLCO after every cycle of ABVD chemotherapy which helps in early diagnosis of this unwanted side effect.

REFERENCES

[1] Azoulay E, Herigault S, Levame M, Brochard L, Schlemmer B, Harf A, et al. Effect of granulocyte colony-stimulating factor on bleomycin-induced acute lung injury and pulmonary fibrosis. *Crit Care Med.* 2003;31:1442-48.
[2] Reinert T, Baldotto CS, Nunes FAP, Scheliga AA. Bleomycin induced lung injury. *Journal of Cancer Research*. 2013;2013:1-9.
[3] Weerakkody Y, Radswiki, et al. Bleomycin lung toxicity. cited from http://radiopaedia.org/articles/bleomycin-lung-toxicity assessed on 10th March 2015.
[4] Martin GW, Ristow KM, Habermann MT, Colgan JP, Thomas EW, Stephen MA. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with hodgkin's lymphoma. *Journal of Clinical Oncology*. 2005;23:7614-20.

[5] Chen J, Ghorai KM, 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.
[6] Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity:radiologic and pathologic manifestations. *Radiographics*. 2000;20:1245-59.
[7] Husain JH, Zubairi ABS, Irfan M. Bleomycin induced pneumonitis: a case successfully managed with high-dose steroids. *Journal of Pakistan Medical Association*. 2007;57:91-92.
[8] Pilling D, Roife D, Wang M, Ronkainen DS, Crawford JR, Elizabeth LT, et al. Reduction of Bleomycin-Induced Pulmonary Fibrosis by Serum Amyloid P. *The Journal of Immunology*. 2007;179:4035-44.
[9] Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720-35.
[10] Bleomycin. cited from http://www.drugs.com/pro/bleomycin.html assessed on 29th February 2016
[11] Houghton BB, Grimison PS, Toner GC, Chatfield M, Thomson DB, Friedlander M, et al. cited from http://meetinglibrary.asco.org/content/72636-104assessed on 29th February 2016

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, KMC, Manipal, Karnataka, India.
2. Post Graduate Student, Department of Pharmacology, KMC, Manipal, Karnataka, India.
3. Assistant Professor, Department of Oncology, KMC, Manipal, Karnataka, India.
4. Assistant Professor, Department of Radiodiagnosis, KMC, Manipal, Karnataka, India.
5. Student, KMC, Manipal, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Karthik Subramanya Udupa,
Assistant Professor, Department of Oncology, KMC Manipal, ManipaL-576104, Karnataka, India.
E-mail: udupa.k@gmail.com

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