SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2023; 40 (3); e2023030 DOI: 10.36141/svdld.v40i3.14385

Bleomycin and perioperative care: A case report

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Abstract. Bleomycin is associated with pulmonary toxicity ranging from pneumonitis, pulmonary fibrosis, to fatal acute respiratory distress syndrome. Oxygen administration can potentiate or precipitate bleomycin pulmonary toxicity, and the most common setting of oxygen exposure is during anesthesia. We report here the successful management and perioperative care of a patient with documented bleomycin pulmonary toxicity who had to undergo an eight hour long retroperitoneal surgery. With proper preoperative assessment, chest physiotherapy, inhaled steroids and bronchodilators, antibiotics, perioperative restriction of oxygen and fluids and good postoperative care no further pulmonary insult was inflicted.

Key words: bleomycin, cancer, oxygen, perioperative care, pulmonary toxicity

Introduction

Bleomycin is an antitumor antibiotic that was isolated from a strain of *Streptomyces verticillus* in 1966 and is being used to treat a variety of malignancies, predominantly germ cell tumors and Hodgkin lymphoma. Bleomycin is known to be associated with pulmonary toxicity ranging from pneumonitis and pulmonary fibrosis to fatal acute respiratory distress syndrome. Bleomycin-induced pneumonitis (BIP) incidence vary widely, between 2% and 42% (1). Risk factors include high total bleomycin dose (>300 U), impaired renal function, use of granulocyte-colony stimulating factor, cigarette smoking, tumor stage IV and older age (1). Moreover, a genetic predisposition to BIP exists depending on the activity levels of the enzyme bleomycin hydroxylase in the lungs (2). It is known that oxygen administration can potentiate or precipitate bleomycin pulmonary toxicity and the most common setting of oxygen exposure is during anesthesia. Development of acute respiratory distress syndrome (ARDS) after surgery in patients who received bleomycin was reported in 1978 (3). The first five patients died from ARDS, but the next 12 did not have a similar mortality as they changed to a lower fraction of inspired oxygen (FiO2) and preferential use of colloids protocol. However, the role of oxygen in inducing bleomycin lung injury is not clear as a few other studies have reported no harm. A study on 47 patients who received bleomycin less than 6 months before surgery showed that strict intraoperative maintenance of an inspiratory 30% oxygen concentration resulted in lower than expected postoperative respiratory complications (2). The dosage of oxygen and the duration of exposure to increase the risk of toxicity have not been well described.

Most of the reports concentrate on preventing bleomycin toxicity in patients undergoing surgery. The outcomes of patients with lung involvement and the steps needed to prevent further worsening have not been studied well. In this report, we describe the

Received: 1 March 2023
Accepted: 15 July 2023
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perioperative management of a patient with documented bleomycin pneumonitis who underwent an 8 hour long retroperitoneal surgery along with a clear plan for assessment and management.

Case report

A 32-year-old male with a history of 30 pack-years smoking, hepatitis C infection, drug abuse and uncontrolled diabetes was found to have a retroperitoneal mass (7.7 x 5 cm), partially encasing the aorta, inferior venacava, proximal jejunum, duodenum and stomach with displacement of the proximal jejunum and irregular mucosal outlines suggestive of invasion. Computed tomography (CT) guided biopsy of the mass showed features of embryonal carcinoma. Tumor markers including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (bHCG) and lactate dehydrogenase (LDH) were negative. Ultrasound showed a 10 mm lesion in the right testis. Right inguinal orchiectomy was done and the pathology showed a focus of prepubertal teratoma, which was unlikely to be the primary to the retroperitoneal germ cell tumor. With a final diagnosis of extragonadal non-seminomatous germ cell tumor with retroperitoneal mass, the patient was treated with 4 cycles of BEP (bleomycin, etoposide and cisplatin) chemotherapy. Pretreatment chest radiograph or CT chest did not show any lung parenchymal changes. During this period patient was monitored for bleomycin pulmonary toxicity by respiratory symptoms, clinical examination and periodic chest radiographs. Restaging CT done after 2 weeks of stopping bleomycin showed features of pulmonary involvement thus establishing a diagnosis of bleomycin induced lung involvement. This CT also showed a good response to chemotherapy with the regression of retroperitoneal mass. Since the patient responded to chemotherapy the multidisciplinary team decision was to go for total removal of the tumor.

Preoperative evaluation

Computed tomography of the chest showed a picture of nonspecific interstitial pneumonia (NSIP) with reticular and fibrotic shadows on both sides and diffuse ground glass opacities bilaterally. (Figure 1). Pulmonary function test showed a mild restrictive defect with moderate impairment of diffusion {Forced vital capacity (FVC)- 3.03L, 72%; Forced expiratory volume in 1 second (FEV1)-2.46L,70%; FEVI/FVC- 81%; Total lung capacity (TLC)-4.80L ,72%; Diffusing capacity for carbon monoxide (DLCO)-44%}. Arterial blood gases (ABG) showed normal values. (pH -7.43, PaCO2- 46.1 mmHg, PaO2-85.3 mmHg, HCO3- 30.0 mmol/L, and Lactate 0.8 mmol/L). The patient did not have any clear respiratory symptoms and was not breathless at rest or during routine activities.

The patient had bleomycin induced lung changes, nonspecific interstitial pneumonia, with diffuse ground glass opacities and focal reticular changes. Pulmonary function was acceptable with only a mild restriction and moderate diffusion impairment with preservation of oxygen saturation. With this lung reserve we did not anticipate any intraoperative or immediate post-operative pulmonary issues. The concern was the threat of ARDS in the perioperative period, especially with the use of oxygen. In view of the ground glass opacities and history of smoking he was started on nebulized salbutamol and budesonide as well as antibiotics preoperatively. Chest physiotherapy was also begun a day before surgery.

Intraoperative measures

Retroperitoneal lymph nodes dissection and excision of residual mass was done under combined general anesthesia and thoracic epidural analgesia. Epidural anesthesia was given with preservative free morphine 2mg followed by an infusion of 0.125% levobupivacaine 5-8ml/hour intraoperatively. Anesthesia was completed in 7 minutes with propofol (2 mg/kg), fentanyl (2 μg/kg) and rocuronium (0.6 mg/kg) and was maintained with sevoflurane. During induction, 100% oxygen was given for 3 minutes. The FiO2 after induction was maintained at just around 30% during surgery, accepting a saturation around 94%. End tidal carbon dioxide (ETCO2) was maintained between 37-42 mm Hg and the positive end expiratory pressure (PEEP) at 5mmHg. Two hourly ABG values are given in figure 2. The surgery lasted for 7 hours and 15 minutes.

Both crystalloid and colloid administration was kept to a minimum guided by a goal-directed approach to fluid management. The intake was 2600 ml and the output 1000 ml. Only 100 cc of 20% albumin was given during this period. No diuretics

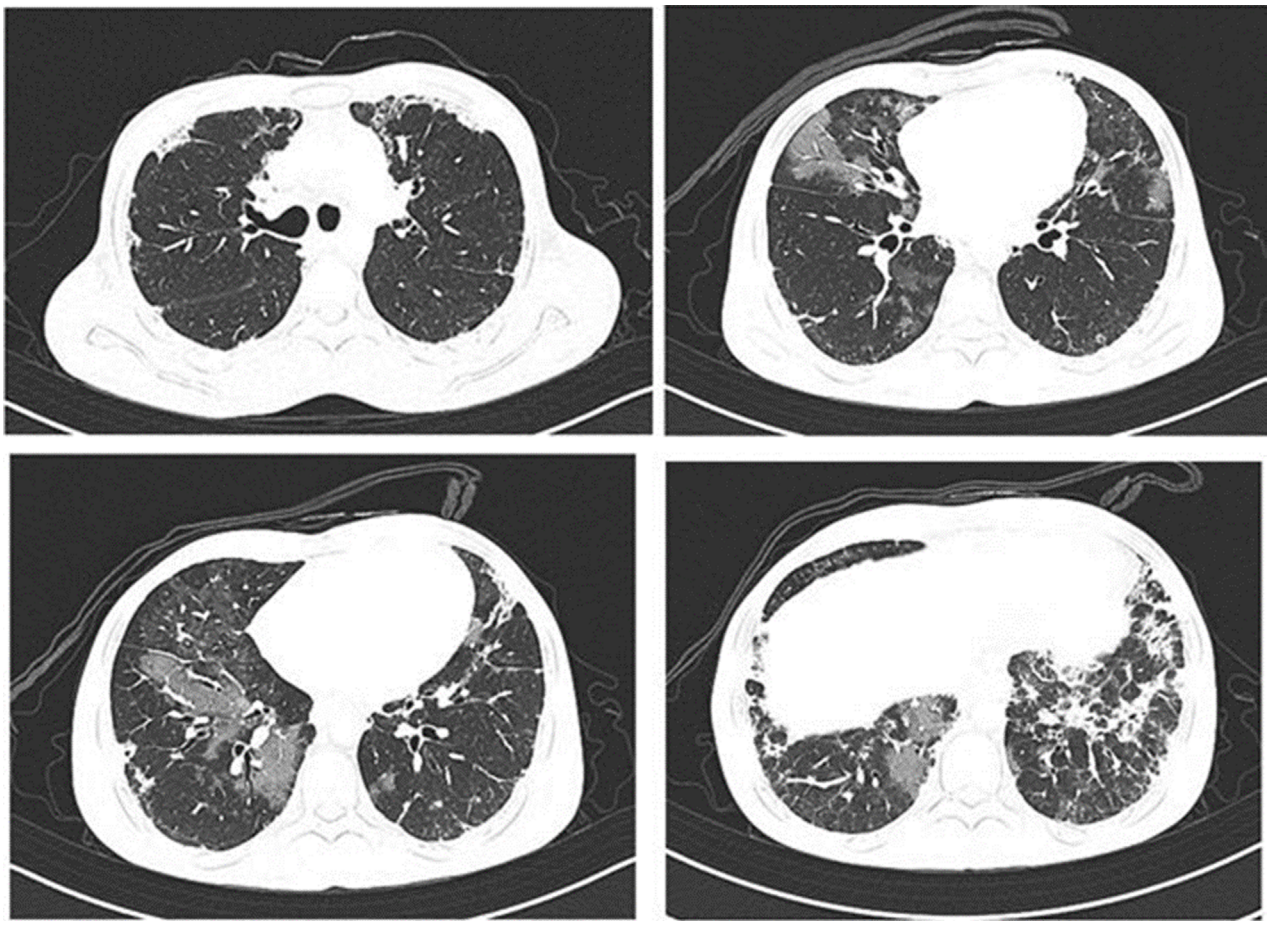

Figure 1. Computed tomography of the chest showing lower zone predominant reticular and fibrotic shadows on both sides with diffuse ground glass opacities bilaterally.

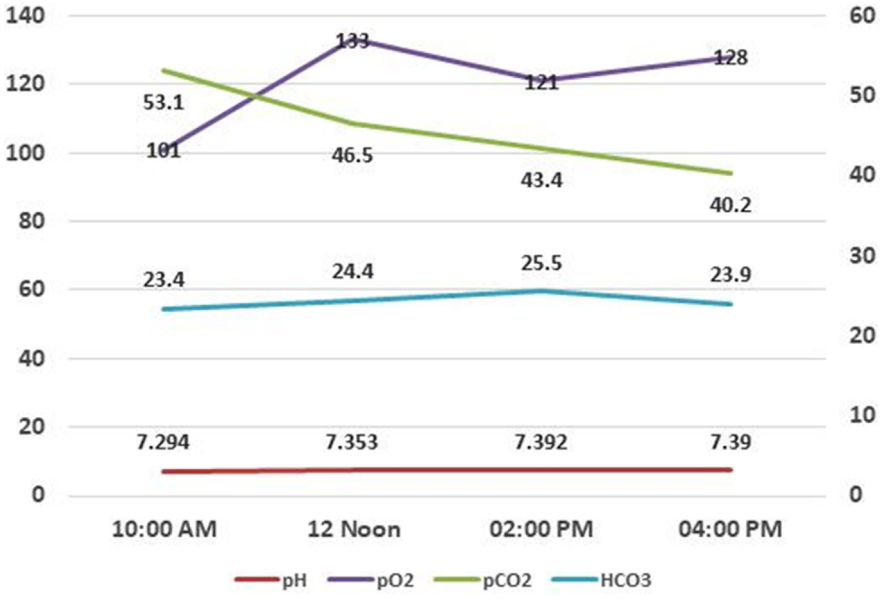

Figure 2. Two hourly arterial blood gas values during the intraoperative period.

were administered considering the possible major fluid shifts in this case where the surgery was prolonged and open with exposure of bowels. Estimated blood loss was only 150 ml and so no blood transfusions were given. In addition, patient received paracetamol, cefazolin, dexamethasone, tranexamic acid, granisetron and dexmedetomidine.

Post-operative course

Patient was extubated in the theatre and was managed in the postoperative high dependency care unit (HDU) for next three days. He was maintaining a saturation of 97-98% on room air and no supplemental oxygen was given. He received intravenous balanced crystalloids at 1ml/kg/hour for 3 days. The approach is more conservative as usually a higher volume is given in the immediate post-operative period in such prolonged surgeries. Epidural analgesia was continued with levobupivacaine (0.125%) infusion @ 6ml/hour with fentanyl (2mcg/ml) for 3 days. He had an uneventful postoperative course and was discharged in a stable state on the 11th day.

Follow up

Histopathology of the mass showed matted lymph nodes with adjacent fibro-fatty tissue exhibiting marked necrosis, fibrosis, hemorrhage, vascular congestion and edema with sheets of foamy histiocytes and multinucleated giant cells suggestive of noticeable treatment effect. There were no discernible viable tumor cells in the mass nor the regional lymph nodes. When reviewed in the clinic a month later he was doing fine, maintaining good exercise tolerance and normal oxygen saturation. Repeat CT showed striking improvement in the ground glass and the reticular opacities.

Discussion

We successfully managed a patient with documented bleomycin pulmonary toxicity who had to undergo an eight hour long retroperitoneal surgery. With proper preoperative assessment, chest physiotherapy, inhaled steroids and bronchodilators, antibiotics, perioperative restriction of oxygen and fluids and good postoperative care no further pulmonary insult was inflicted.

The association between bleomycin and ARDS after surgery was noted when five deaths attributed to oxygen toxicity and notably, to the liberal use of crystalloids was reported in late 70's (3). The mechanism of bleomycin-induced lung injury is not well understood, but may include oxidative damage, genetic deficiency of the deactivating enzyme bleomycin hydrolase and release of inflammatory cytokines. The presence of large amount of free oxygen radicals maybe responsible for accelerating bleomycin pulmonary toxicity during oxygen administration as well as an inability of bleomycin-injured lung tissue to scavenge released oxygen radicals (4). Moreover, high inspired oxygen concentrations, even many years following exposure to bleomycin, has also been reported to increase the risk for pulmonary toxicity

The most common scenario of oxygen exposure is during anesthesia. But, the effect of inspired oxygen on bleomycin lung injury are not always consistent nor do we know the dosage of oxygen which can result in toxicity. Even a modest increase in FiO2 to 0.32 or 0.45, during surgery, has resulted in lung toxicity and death (3). Gilson et al report the development of ARDS, even when the FiO2 was kept around 0.33, in a patient who had a favorable response to corticosteroids for bleomycin pulmonary toxicity a few months before (4). At the same time, only 7 patients developed ARDS out of 316 bleomycin treated patients who underwent a surgical procedure lasting greater than one hour (5). In a study over an 8-year period, no correlation was noted between perioperative oxygen restriction and postoperative pulmonary morbidity among 77 patients undergoing major surgery following bleomycin (6). Another study reports that enrichened inspired oxygen is not hazardous in testicular cancer patients who were exposed to bleomycin and suggest that oxygen should not be restricted (7).

If not preoxygenated, desaturations to the mid-70 to 80 % lasting 30 to 45 seconds are not uncommon during induction of anesthesia and intubation. Administration of 100% oxygen for 1-4 minutes during induction of anesthesia and maintaining a FiO2 < 30% during surgery was found to be safe (2,8). Case reports suggest pre-treatment with corticosteroids may be of benefit, especially in those cases where a higher need for FiO2 is anticipated (9). Risk factors for pulmonary toxicity like; high total bleomycin dose (>300 U), impaired renal function, use of granulocyte-colony stimulating factor,

cigarette smoking, tumor stage IV and older age have to be evaluated. Lower preoperative FVC was found to be a significant predictor of postoperative pulmonary morbidity in these patients (6). Pre-existing pulmonary damage from bleomycin and prior exposure to bleomycin within a 1 to 2-month period also increases the chances of pulmonary toxicity. A low DLCO during PFT is probably the most sensitive indicator of subclinical damage. It is known that the patients with established interstitial lung disease (ILD) experience an increased risk of postoperative pulmonary complications when undergoing both pulmonary and non-pulmonary surgery (10). Our patient had already developed pulmonary toxicity, was a smoker, received a higher bleomycin dose and had low DLCO and was thus at a greater risk for oxygen induced lung damage.

Inhaled steroids or antibiotics are not generally used prophylactically in the perioperative period. But there are reports advocating the use of airway preparation with drug therapy including antibiotics, inhaled steroids, bronchodilators, and mucolytic agents combined with physical rehabilitation to prevent perioperative pulmonary complications in high respiratory-risk surgeries (11,12). So, in our patient with an established lung involvement and smoking history who was at risk for oxygen induced further lung injury, we followed good perioperative airway preparation and chest physiotherapy measures.

Conclusion

With a proper perioperative care, our patient with bleomycin lung toxicity underwent a lengthy surgical procedure without any worsening in his respiratory status. The care of these patients should begin with an extensive preoperative evaluation. Computed tomography and pulmonary function test should be done to identify the early involvement. The need as well as the risks of oxygen administration should be considered on an individual basis, depending on presence of preexisting lung involvement, total bleomycin dose as well as the timing of the last dose and the presence of risk factors. Patients with no documented pulmonary toxicity or major risk factors may not deteriorate from hyperoxia. Those with major risk factors or documented pulmonary involvement should be maintained on lowest FiO2 to maintain SpO2>90% during anesthesia and postoperative care. In addition, preferring colloids over crystalloids, restrictive fluid strategies and lung protective ventilation can further reduce the risk of pulmonary toxicity.

Declaration of Conflicting Interests: The Authors declare that there is no conflict of interest.

Informed Consent: Written informed consent was obtained for publication of the submitted article and accompanying images from the patient

Funding Information: No grant was received from any agency in the public, commercial or not-for-profit sectors.

References

1. Stephens M, Murphy T, Hendry D. Anaesthesia for retroperitoneal lymph node dissection in the treatment of testicular cancer. BJA Educ. 2019;19:283–9.
2. Wuethrich PY, Burkhard FC. No Perioperative pulmonary complications after restricted oxygen exposition in bleomycin-treated patients: A short report. ISRN Anesthesiol. 2011;2011:1–3.
3. Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland WS. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. Br Med J. 1978 ;1 (6128):1664–7.
4. Gilson AJ, Sahn SA. Reactivation of bleomycin lung toxicity following oxygen administration. Chest. 1985;88:304–6.
5. Aakre BM, Efem RI, Wilson GA, Kor DJ, Eisenach JH. Postoperative acute respiratory distress syndrome in patients with previous exposure to bleomycin. Mayo Clin Proc. 2014;89:181–9.
6. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? J Urol. 1998;160:1347–52.
7. LaMantia KR, Glick JH, Marshall BE. Supplemental oxygen does not cause respiratory failure in bleomycin-treated surgical patients. Anesthesiology. 1984;60:65–6.
8. Waid-Jones MI, Coursin DB. Perioperative considerations for patients treated with bleomycin. Chest. 1991;99:993–9.
9. Ingrassia TS, Ryu JH, Trastek VF, Rosenow EC. Oxygen-exacerbated bleomycin pulmonary toxicity. Mayo Clin Proc. 1991;66:173–8.
10. Patel NM, Kulkarni T, Dilling D, Scholand MB, Gupta N, Strek M, et al. Preoperative evaluation of patients with interstitial lung disease. Chest. 2019;156:826–33.
11. Gao S, Barello S, Chen L, Chen C, Che G, Cai K, et al. Clinical guidelines on perioperative management strategies for enhanced recovery after lung surgery. Transl Lung Cancer Res. 2019;8:1174–87.
12. Zhu X, Zhang P, Lou C, Wu J. Perioperative inhaled corticosteroids treatment is associated with decreased length-of-stay and direct medical costs in high-respiratory-risk surgeries. J Med Econ. 2020;23:280–6.