CASE REPORT

Acute fibrinous and organising pneumonia: a rare histopathological variant of chemotherapy-induced lung injury

Arjun Gupta,¹ Shiraj Sen,² Harris Naina¹

¹University of Texas Southwestern Medical Center, Dallas, Texas, USA

²University of Texas MD Anderson Cancer Center, Houston, TX

Correspondence to
Dr Arjun Gupta,
guptaarjun90@gmail.com

Accepted 19 March 2016

SUMMARY

Bleomycin-induced lung injury is the most common chemotherapy-associated lung disease, and is linked with several histopathological patterns. Acute fibrinous and organising pneumonia (AFOP) is a relatively new and rare histological pattern of diffuse lung injury. We report the first known case of bleomycin-induced AFOP. A 36-year-old man with metastatic testicular cancer received three cycles of bleomycin, etoposide and cisplatin, before being transitioned to paclitaxel, ifosfamide and cisplatin. He subsequently presented with exertional dyspnoea, cough and pleuritic chest pain. CT of the chest demonstrated bilateral ground glass opacities with peribronchovascular distribution and pulmonary function tests demonstrated a restrictive pattern of lung disease with impaired diffusion. Transbronchial biopsy revealed intra-alveolar fibrin deposits with organising pneumonia, consisting of intraluminal loose connective tissue consistent with AFOP. The patient received high-dose corticosteroids with symptomatic and radiographic improvement. AFOP should be recognised as a histopathological variant of bleomycin-induced lung injury.

BACKGROUND

Bleomycin is an antitumour antibiotic used to treat a spectrum of malignancies including squamous cell cancers, germ cell tumours and lymphoma. Unfortunately, 10–15% of patients receiving the drug develop pulmonary fibrosis, which can be life-threatening. Specific histological patterns of lung injury, including non-specific interstitial pneumonia, diffuse alveolar damage, organising pneumonia and hypersensitivity pneumonitis, are also recognised.^{1 2}

Acute fibrinous organising pneumonia (AFOP) is a relatively new pathological entity described in association with autoimmune disorders, infection and drug and occupational exposure.³ We describe the first case report of bleomycin-induced AFOP and discuss its clinical presentation, management, therapy and outcomes.

CASE PRESENTATION

A 36-year-old man with metastatic testicular seminoma underwent treatment with BEP chemotherapy (bleomycin 30 units days 1, 8, 15, etoposide 100 mg/m²/day for days 1–5 and cisplatin 20 mg/m²/day for days 1–5) every 3 weeks for a total of 3 cycles. Baseline chest X-ray (CXR), CT of the chest and pulmonary function tests (PFTs) were

unremarkable. The patient thus received a total of 270 units of bleomycin over 9 weeks, with significant tumour response. His bleomycin dose approached our institution's lifetime limit of 300 units; he was transitioned to paclitaxel, ifosfamide and cisplatin (TIP). He received three cycles of TIP without complication. Six weeks later, he presented with a dry cough, exertional dyspnoea and pleuritic chest pain. He denied smoking and drug use, and drank alcohol occasionally. He also denied both recent travel and sick contacts. No exposure to toxic chemicals or fumes was reported. Vital signs on presentation included heart rate 84 bpm, respiratory rate 22/min, blood pressure 128/76 mm Hg and temperature 98.8°F. The patient's oxygen saturation on room air was 94%. Neither cyanosis, clubbing nor oedema was noted, but respiratory examination revealed faint crackles in bilateral lung fields without signs of respiratory distress.

INVESTIGATIONS

Laboratory studies revealed a white cell count of $8000 \times 10^9/L$ with a normal differential. Blood and sputum cultures remained negative. Nasal swab for influenza and a respiratory virus panel PCR did not detect any organisms. CXR showed bilateral reticular infiltrates, worse at the bases, and chest CT demonstrated ground glass opacities with peribronchovascular distribution, reticulations, subpleural lines and interstitial thickening bilaterally (figure 1). PFTs revealed a restrictive pattern with reduced forced expiratory volume in 1 s 48%, forced vital capacity 47% and total lung capacity 57%, compared to baseline, and diffusing capacity of carbon monoxide impaired to 33%. Bronchoscopy with lavage revealed clear fluid with 130 nucleated cells (86% macrophages). Infectious studies including Gram stain, cultures, acid-fast bacilli stain and *Pneumocystis* stains returned negative for infectious pathology. A transbronchial biopsy revealed benign bronchial mucosa and alveolar parenchyma. Several groups of alveolar spaces were filled with fibrin aggregates (fibrin balls) without significant fibroblast proliferation (figure 2). Reactive alveolar pneumocytes were noted.

DIFFERENTIAL DIAGNOSIS

The presentation was initially concerning for pneumonia. The absence of fever and presence of diffuse lung disease on imaging was concerning for an atypical infectious process. Bronchoscopy with

CrossMark

To cite: Gupta A, Sen S, Naina H. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214721

Figure 1 CT of the chest demonstrating ground glass, reticulations, subpleural lines and interstitial thickening seen in both lungs.

lavage also did not identify an infectious aetiology—nor did it indicate any other classic pulmonary process. Given the history of bleomycin use, concern for bleomycin-induced lung damage was considered. The histopathological pattern seen on transbronchial biopsy was consistent with AFOP.

TREATMENT

The patient initially received supportive therapy with oxygen and bronchodilators as needed. Empiric therapy for healthcare-associated pneumonia (given frequent clinic visits and chemotherapy administration) was initiated but discontinued after 48 h when cultures returned negative. A high-dose corticosteroid (intravenous methylprednisone 125 mg every 6 h) was administered and transitioned to oral prednisone 60 mg/day with extended taper over 24 weeks once the diagnosis of AFOP was made.

OUTCOME AND FOLLOW-UP

At last follow-up 48 months later, the patient had symptomatically and radiographically improved without any recurrences. Bleomycin was never re-initiated.

Figure 2 H&E stained section (×200) of the transbronchial biopsy demonstrating alveolar parenchyma with both intra-alveolar fibrin aggregates (short arrow) and a focal fibroblastic plug (long arrow).

DISCUSSION

AFOP is a histopathological pattern of lung injury characterised by the patchy presence of intra-alveolar fibrin ‘balls’, organising pneumonia and interstitial lymphocytic infiltrates, and was initially described in 2002.³

AFOP has been described in patients with malignancy, infection, stem cell transplant, autoimmune disease and various environmental exposures. Drugs such as amiodarone, trimethoprim-sulfamethoxazole and abacavir, have been known to cause AFOP as well. However, bleomycin has not previously been associated with AFOP. Our patient received multiple chemotherapeutic agents, including bleomycin, etoposide, paclitaxel and cisplatin. Although, theoretically, any one of these may have caused the AFOP, it is very likely that bleomycin was the culprit given its propensity of causing lung dysfunction.

Bleomycin can cause several types of lung toxicity including subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organising pneumonia and an acute chest pain syndrome during rapid infusion. Inflammatory cytokines and alveolar macrophages are central to the pathogenesis of lung injury. Risk factors for bleomycin-induced lung toxicity include age, prior and concurrent radiotherapy,⁴ and renal insufficiency.^{5–6} While administration of higher doses of bleomycin (>400 units) clearly increases the risk of lung injury, injury can occur at doses less than 50 units.⁷ Concurrent administration of cisplatin and colony stimulating factors may increase the risk of pulmonary toxicity.⁸

The onset of clinical manifestations usually occurs subacutely between 1 and 6 months after bleomycin treatment, but may occur during therapy or more than 6 months following the administration of bleomycin.^{9–10} Symptoms and signs of bleomycin-induced lung toxicity include non-productive cough, dyspnoea, pleuritic or substernal chest pain, fever, tachypnoea, pulmonary crackles, lung restriction and hypoxaemia. The clinical course of patients with AFOP is dichotomous; in the original cohort study, 9/17 patients died after a sudden and severe illness, while 8/17 had a subacute illness with ultimate recovery of function.³

AFOP is best diagnosed with open-lung biopsy (or video-assisted thoracic surgery biopsy), given the risk of under-sampling, in which one may miss areas of hyaline membranes that would be characteristic of diffuse alveolar damage (DAD). This patient underwent transbronchial biopsy; however, his subacute clinical course was not compatible with DAD, which is associated with acute respiratory distress syndrome and a high mortality rate. Organising pneumonia might present with a less fulminant course, but the presence of intra-alveolar fibrin aggregates throughout multiple samples from this patient's transbronchial biopsy is not a characteristic feature. The patchy distribution of lesions, presence of intra-alveolar fibrin, and absence of eosinophils and hyaline membranes, suggest AFOP defined as a distinct histological pattern, as seen in our patient. In the absence of other known offending agents, bleomycin is believed to be the aetiology of this patient's lung injury.

In cases of drug-induced AFOP, discontinuation of the offending drug and introduction of corticosteroids lead to improvement of AFOP.³ Similarly in our patient, oral steroids (prednisone 60 mg/day), tapered over 24 weeks and discontinuation of bleomycin, led to symptomatic and radiographic improvement.

Our case highlights the importance of recognising AFOP as a histopathological variant of bleomycin-induced lung injury.

Learning points

- ▶ Acute fibrinous and organising pneumonia (AFOP) is a relatively new and rare histological pattern of diffuse lung injury usually associated with infection, autoimmune disease, malignancy and drug use.
- ▶ It is characterised by intra-alveolar fibrin aggregates with a background of organising pneumonia.
- ▶ Bleomycin is associated with several patterns of lung toxicity—it can also lead to AFOP.
- ▶ Therapy for drug-induced AFOP includes discontinuation of the offending drug, with introduction of steroids and supportive care, usually with good outcomes.

Contributors AG, SS and HN were involved in the conception and design, acquisition and analysis of data, drafting the article or revising it critically for important intellectual content and gave final approval of the version published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Jules-Elysee K, White DA. Bleomycin-induced pulmonary toxicity. *Clin Chest Med* 1990;11:1–20.
- 2 Silva CI, Müller NL. Drug-induced lung diseases: most common reaction patterns and corresponding high-resolution CT manifestations. *Semin Ultrasound CT MR* 2006;27:111–16.
- 3 Beasley MB, Franks TJ, Galvin JR, *et al.* Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. *Arch Pathol Lab Med* 2002;126:1064–70.
- 4 Samuels ML, Johnson DE, Holoye PY, *et al.* Large-dose bleomycin therapy and pulmonary toxicity. A possible role of prior radiotherapy. *JAMA* 1976;235:1117–20.
- 5 Dalglish AG, Woods RL, Levi JA. Bleomycin pulmonary toxicity: its relationship to renal dysfunction. *Med Pediatr Oncol* 1984;12:313–17.
- 6 O'Sullivan JM, Huddart RA, *et al.* Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol* 2003;14:91–6.
- 7 McLeod BF, Lawrence HJ, Smith DW, *et al.* Fatal bleomycin toxicity from a low cumulative dose in a patient with renal insufficiency. *Cancer* 1987;60:2617–20.
- 8 Rabinowits M, Souhami L, Gil RA, *et al.* Increased pulmonary toxicity with bleomycin and cisplatin chemotherapy combinations. *Am J Clin Oncol* 1990;13:132–8.
- 9 Chen J, Stubbe J. Bleomycins: towards better therapeutics. *Nat Rev Cancer* 2005;5:102–12.
- 10 Uzel I, Ozguroglu M, Uzel B, *et al.* Delayed onset bleomycin-induced pneumonitis. *Urology* 2005;66:195.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow