CASE REPORT

Drug induced lung injury – a case of fatal bleomycin interstitial pneumonitis

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Abstract

Bleomycin is an antineoplastic agent that is known for its potential for fatal lung toxicity. Cell injury occurs through the formation of free radicals.
Timely detection of bleomycin-induced pneumonitis (BIP) can be difficult and it is vital to keep a low index of suspicion in patients receiving bleomycin. We describe a patient with Hodgkin's lymphoma who died of bleomycin-induced lung injury in our intensive care unit. We discuss treatment options and review the literature.

Introduction

With the knowledge that the prognosis of patients with haematological malignancies in the ICU has been improved in the past decades[1], dealing with life-threatening conditions in these patients forms a major challenge for the ICU clinician. Usually, respiratory failure and /or sepsis are the main reasons for ICU admission.
Less often we are involved in the treatment of toxicity of chemotherapy in patients cured of haematological malignancy. We report a patient with Hodgkin's lymphoma who died in our ICU due to a complication of bleomycin-containing chemotherapy.

Case description

A 74-year old patient was transferred from the haematology-oncology department to our ICU because of respiratory failure.
He had been diagnosed with M. Hodgkin stage IVB with cervical, mediastinal and retroperitineal localisations and was treated with six courses of adriamycine, bleomycine, vinblastine and dacarbazine in a 4-weekly schedule. His previous medical history included a myocardial infarction and CABG at the age of 55. For the past 54 years he had smoked one pack of cigarettes per day, and never managed to quit despite counselling. Pulmonary function tests performed before the initiation of chemotherapy showed COPD GOLD stadium II, without reversibility and without complaints (*table 1*).
After the first two rounds of chemotherapy, however, the patient complained of rhinitis, an irritable cough and dyspnoea on exertion. CT thorax at that point showed no intrapulmonary abnormalities, and pulmonary function tests were stable (*table 1*). Treatment for an upper respiratory tract infection was given, and chemotherapy continued as scheduled. Chest X-ray and pulmonary function tests were repeated after the fourth month of chemotherapy, and again there were only minor changes and as his symptoms had not worsened, chemotherapy continued (*table 1*).
After the sixth ABVD-course, the patient underwent a FDG-PET-scan, and as staff members noticed considerable dyspnoea, he was referred to the haematology-oncology department for admission afterwards. Progressive dyspnoea and cough had developed since his last round of chemotherapy three weeks earlier.
On examination the patient was not acutely ill, but mildly distressed with a respiratory rate of 16 breaths per minute, reaching a PaO_2 of 8.2 kPa and an oxygen saturation of 92%. The temperature was 37.3 °C. Laboratory analysis showed: ESR 21 mm/hr, C-reactive protein 29 mg/l, haemoglobin 7.5 mmol/l, LDH 544 mmol/l, creatinine 61 mmol/l. The PET-CT thorax revealed diffuse ground glass opacities

Table 1. Pulmonary function tests during chemotherapy

	VC max [L]	VC [% of predicted]	FEV-1 [L]	FEV-1 [% of predicted]	TLC-He [L]	TLC-He [% of predicted]	DLCOc [mmol/min/kPa]
Baseline	3.98	93	2.30	73	6.90	95	5.62
Two months	3.94	92	2.38	76	6.90	94	7.12
Four months	3.56	83	2.02	65	6.91	95	6.34

and thickening of intra- and interlobular septa (*figure 1*), but no new localisations of Hodgkin's lymphoma.

Given the subacute onset of dyspnoea after administration of bleomycin, the absence of fever and relatively low inflammation markers, the working diagnosis was bleomycin interstitial pneumonitis rather than pneumonia. However, as the patient was immunocompromised, bacterial (super)infection or an opportunistic infection (especially Pneumocystis jirovecii pneumonia) had to be considered as well. Therefore, treatment with prednisone (100 mg/day), cefuroxime and high-dose cotrimoxazole was commenced. Administration of oxygen was kept to a minimum, aiming for an oxygen saturation level of 90%. The consulting pulmonologist decided to review the patient shortly after admission in order to schedule a broncho-alveolar lavage for further diagnostic steps.

During admission, however, the patient's clinical condition deteriorated rapidly with major changes in behaviour, and progressive hypoxaemia.

On day 2 of hospital admission, the ICU's rapid response team was called to the haematology-oncology ward to assess the patient. We saw a distressed, restless and at times aggressive patient who responded to verbal stimuli. His airway was clear. With 22 breaths per minute and administration of 2 L O_2/min by nose prong, his SpO_2 was 80%. On auscultation bilateral crackles were heard. His blood pressure was 135/80 mmHg, with a sinus tachycardia of 110 beats per minute, and a temperature of 37.4°C. Further examination was unremarkable.

Blood gas analysis at that point showed: pH 7.46; pCO_2 3,7 kPa; bicarbonate 20 mmol/l; base excess -3.6; pO_2 4.8; O_2 saturation 65%. Further lab results were: Haemoglobin 6.5 mmol/l; leucocytes 12.4 *10^9/l, thrombocytes 132*10^9/l, CRP 38 mg/l, LDH 570 U/l. A CXR showed bilateral consolidations (*figure 2*).

We transferred the patient to the ICU where high flow oxygen through nasal cannulae (Optiflow™) was given, aiming for an oxygen saturation of 88-90%. Morphine and sedatives were administered for comfort.

Figure 1. CT thorax: Bilateral airspace consolidation and ground glass opacities

Figure 2. Chest X-ray with bibasal consolidations

We considered bleomycin interstitial pneumonitis to be the most likely diagnosis, but were also concerned about possible PJP-infection. Alternative diagnoses (atypical pneumonia, acute lung injury due to a different, unknown cause) were considered much less likely. Therefore high-dose prednisolone and cotrimoxazole were continued and to include *Pseudomonas aeruginosa* coverage, ceftazidim was substituted for cefuroxim.

We discussed intubation and mechanical ventilation of the patient in order to perform a broncho-alveolar lavage. But considering the fact that bleomycin toxicity was the most likely diagnosis, given the subacute onset and slowly progressive course coupled with a relatively low CRP, we decided against intubation. Treatment with Optiflow™ had the main advantage of the patient being able to communicate with his relatives. Over the next two days, the patient's condition was poor but stable. His CRP-level dropped slightly, and consolidations on CXR barely improved. He remained strictly dependent on Optiflow (FiO_2 55%, 50L/min), with oxygen saturation levels between 85-94% and had considerable respiratory distress on incidental removal of the Optiflow™ cannulae. Academic institutions were consulted for their opinion regarding the benefit of mechanical ventilation, e.g. extracorporeal membrane oxygenation (ECMO) or other experimental therapies. However, as lung damage was severe, and no short-term improvement was to be expected, they advised continuing the conservative treatment.

We informed the patient and his relatives of the prognosis, with a very poor chance of survival in an acceptable condition. They agreed to withhold further active treatment. Patient comfort was ensured by continuous administration of morphine and midazolam. The patient died a few hours after cessation of therapy.

Permission for autopsy was obtained, and findings were as follows: Both lungs were heavy and solid, with white-yellow to grey discolorations. Microscopic examination revealed areas of

congestion and haemorrhage in alveolar septa (*figure 3 and 4*) and fibroblast-plugging in alveoli (*figure 5*). Macrophages in alveoli were noted as well as a few hyaline membranes. These findings are consistent with diffuse alveolar damage and organizing pneumonia, which are both known patterns of lung reaction to toxic drugs, like bleomycin. Additional PAS and Grocott-stain of the lungs did not reveal any micro-organisms, and culture for *Aspergillus* was negative. There was mediastinal lymphadenopathy but on microscopy no atypical lymphoid cells were found.

Figure 3. Diffuse alveolar damage: acute and organising pattern. Congestion of alveolar capillaries in the alveolar septal wall (left) and rupture of this wall by young organizing fibrine, fibroblasts and type II pneumocytes (right)
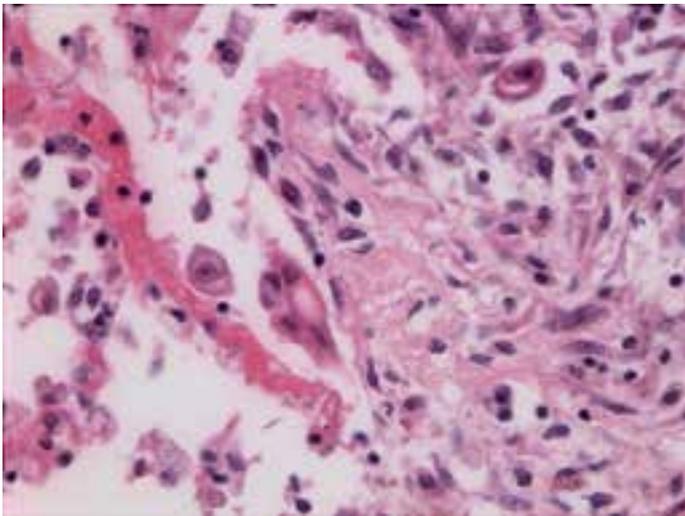

Figure 4. Diffuse alveolar damage: acute and organizing patterns. Erythrocyte extravasation in alveolar spaces (upper left), congestion of erythrocytes in septal capillary (right below) and fibrosis in alveolar septal wall consisting of loose organizing type of connective tissue. Prominent hyperplastic type 2 pneumocytes line the alveolar walls
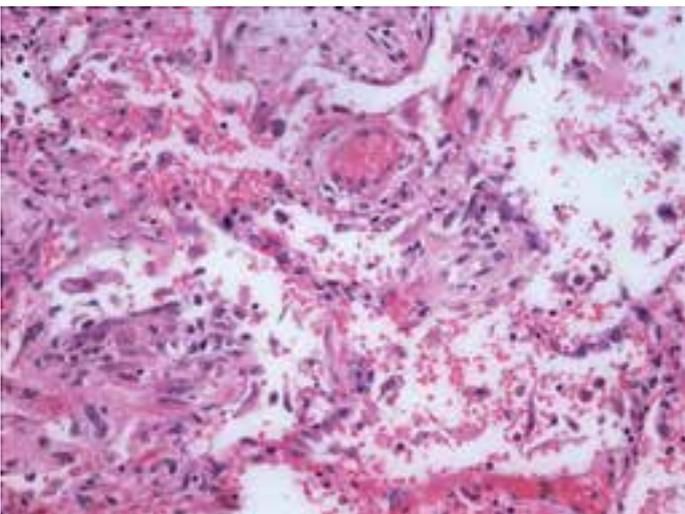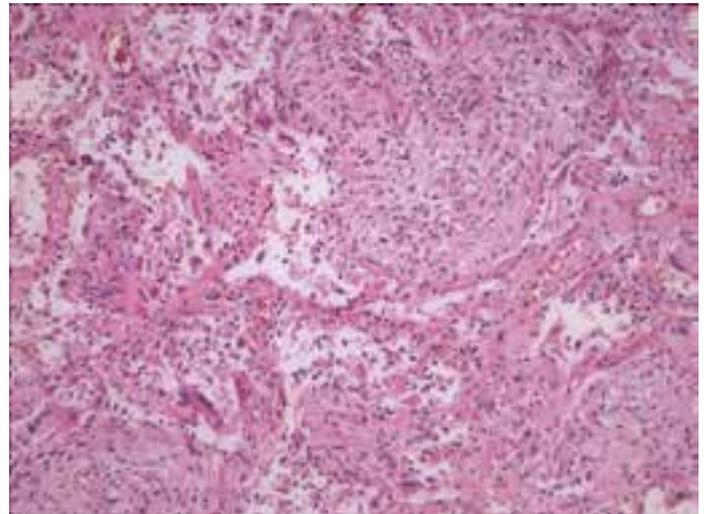

Figure 5. Diffuse alveolar damage: Late phase of organizing pattern with intra-alveolar plugs, and dense connective tissue

In conclusion, there was diffuse alveolar damage and organizing pneumonia, consistent with bleomycin pulmonary toxicity, but no evidence of an opportunistic infection or recurrence of the Hodgkin's lymphoma.

Discussion

Drug-induced lung injury is an important cause of respiratory failure, but presentation is usually non-specific. In patients treated with antineoplastic agents, differentiation between drug toxicity and other causes of lung injury like (opportunistic) infection, cardiovascular disease or progression of primary disease can be difficult.

Bleomycin is an antineoplastic agent that is known for its potential for fatal lung toxicity[2]. This toxicity can present in several distinct patterns, including eosinophilic hypersensitivity, organizing pneumonia and bronchiolitis obliterans and interstitial pneumonitis (BIP), which may eventually progress to pulmonary fibrosis[2]. The incidence of BIP increases with cumulative dose up to 18% in patients who receive a dose of over 360 units of bleomycin[3], but it can occur even with doses < 50 units. Fatal toxicity has been reported in 0-3% of all patients receiving bleomycin-containing chemotherapy[4,5]. Patients surviving the acute phase of BIP, however, usually recover completely with total recovery of all lung function parameters after two years[6].

The main indications for bleomycin are disseminated germ cell tumours and Hodgkin's disease. Omission of bleomycin from the standard treatment for germ cell tumours has been shown to decrease the disease free survival[4]. In patients at high risk for BIP, however, alternative chemotherapeutic regimens can be used.

The antineoplastic effect of bleomycin occurs by inducing cell-death through induction of free radicals. Bleomycin binds to Fe(II), which is oxidized to Fe(III), resulting in free radicals formation. These free

radicals cause single- and double-strand breaks in DNA (scission), leading to cell-death. The enzyme bleomycine hydrolase deactivates the drug, but as this enzyme has low activity in the skin and the lungs, these organs are most susceptible to bleomycin toxicity[2].

Bleomycin causes activation of alveolar macrophages by an unknown mechanism, resulting in release of inflammatory, profibrotic cytokines[7]. Tumour necrosis factor α, transforming growth factor β and platelet-derived growth factor receptor α are believed to play a role in formation of fibrosis[8].

Bleomycin interstitial pneumonitis typically (but not exclusively) develops subacutely during treatment, up to six months afterwards[2]. Symptoms are nonspecific and include dyspnoea on exertion, dry cough, tachypnoea and fever. On examination, bibasilar fine crepitations and hypoxaemia can be noted.

Pulmonary function tests (PFTs) are usually obtained before initiation of bleomycin. Subsequent PFTs are usually performed as clinically indicated. Diffusing capacity of the lung for carbon monoxide (DLCO) decreases in most patients on bleomycin, but also decreases in patients receiving non-bleomycin-containing chemotherapy[9]. Deterioration of vital capacity (VC) or total lung capacity (TLC) also occurs in patients on bleomycin and is more specific for BIP[9].

Diagnosis is by exclusion. Cultures including viral and PCRs on blood, sputum or broncho-alveolar lavage (BAL) fluid can be done to rule out infection including opportunistic. Usually empiric antibiotic treatment is started pending culture results. BAL-fluid can also be checked for malignant cells.

Chest radiographic findings can be normal, but typically bibasilar infiltrates, progressing to diffuse alveolar or interstitial consolidation are found. Rarely, pneumothorax and pneumomediastinum have been reported in BIP[10]. On high resolution computed tomography (HRCT) abnormalities may be detected earlier than on plain chest radiography. HRCT is useful in characterizing the pattern and distribution of abnormalities. HRCT findings vary with underlying histopathologic pattern (*table 2*)[11]. Rarely, organizing pneumonia due to bleomycin presents with subpleural nodules, which should not be mistaken for progression of primary disease.

Lung biopsy can be obtained for histopathological examination, but findings may be nonspecific. Histopathologic patterns of bleomycin-induced lung injury include diffuse alveolar damage (DAD), nonspecific interstitial pneumonia, cryptogenic organizing pneumonia (COP) and bronchiolitis obliterans and eosinophilic pneumonia[12]. DAD, which was also found in our patient, is the most common form but is nonspecific. It is also the most common histopathologic pattern seen in ARDS[13]. It is characterized by diffuse alveolar septal thickening, patchy or diffuse airspace organization and focal or diffuse hyaline membranes, in the absence of signs of infection (including viral), granulomas and prominent eosinophils or neutrophils[14].

Risk factors for development of BIP have been identified (table 3)[2,15]. A previous history of pulmonary disease has not been reported as a risk factor, but the risk of dealing another blow to an already compromised organ seems obvious.

Table 2. High resolution computed tomography manifestations of different histopathological types associated with bleomycin toxicity[11]

Diffuse alveolar damage	Bilateral airspace consolidation and ground glass opacities involving dependent lung regions
Alveolar haemorrhage	Extensive bilateral ground glass opacities with or without superimposed interlobular linear opacities ('crazy paving')
Hypersensitivity pneumonitis	Bilateral ground glass opacities and/or small poorly defined centrilobular nodules. Air trapping
Nonspecific interstitial pneumonia	Patchy bilateral or diffuse ground glass opacities with associated reticular opacities. Mainly lower lung zones and subpleural regions involved
Cryptogenic organizing pneumonia and bronchiolitis obliterans	Ground glass opacities in bilateral random distribution. Airspace consolidation in subpleural or peribronchial distribution. Rarely solitary nodules
Eosinophilic pneumonia	Airspace consolidation and ground glass opacities in predominantly peripheral distribution, involving middle and upper lung zones

Table 3. Risk factors for bleomycine pulmonary toxicity[2,15]

Age
Renal insufficiency
Smoking
Radiation therapy
High fraction of inhaled oxygen
Concurrent use op granulocyte colony stimulating factor
Concurrent use of cisplatin

The role of high FiO2-administration is controversial. The pathogenetic mechanism (with a central role for formation of free radicals) suggests a possibly harmful effect of high FiO_2, which has been confirmed by most studies in animals. In humans, this is supported by reports of patients developing acute respiratory failure postoperatively after previous treatment with bleomycin. A major review article in 77 patients who received bleomycin, however, failed to show a correlation between FiO_2-restriction and postoperative pulmonary morbidity or survival[16]. Usual practise is to keep FiO_2 as low as possible. In hypoxemic patients, oxygen is supplemented as needed to reach an oxygen saturation of 89-92%.

Once BIP has been diagnosed, further bleomycin treatment should be withheld. Patients can be treated with glucocorticoids (for example, prednisone 0.75-1 mg/kg day up to 100 mg/day). There are no controlled studies of glucocorticoids, but observational studies have suggested a beneficial effect[5]. Response may vary according to histopathological pattern. Further treatment is mainly supportive. Shortly after we lost our patient, an interesting case report was published, describing a patient with life-threatening BIP, who was completely cured with imatinib-mesylate, after steroid treatment failed[17].

Our patient was at increased risk of bleomycin pulmonary toxicity due to his age, smoking status and COPD. In retrospect, he had already showed symptoms of BIP after the first two rounds of chemotherapy. His symptoms were given clinical attention, but unfortunately the treating physicians were lured into a false sense of

security by the normal findings on CT-scan and pulmonary function testing and bleomycin-containing chemotherapy was continued.

During ICU admission we were faced with the difficult decision regarding intubation or palliative treatment. Though the patient's chances seemed poor, there would have been a small chance of survival with aggressive management. The patient and his relatives, however, decided against this as they were afraid of prolonged suffering and a poor clinical and functional outcome.

Conclusion

Bleomycin treatment is often complicated by pulmonary toxicity, which can be severe. Screening tests (like radiographic imaging or pulmonary function tests) are unreliable, making it vital to keep a low index of suspicion especially in patients with risk factors. Withholding further bleomycin from patients with dyspnoea or a non-productive cough should be seriously considered, even in the absence of abnormalities on CT-scans or PFTs.

As establishing the diagnosis is mainly by exclusion and patients are also prone to infection whether opportunistic or not, this can be problematic. Once BIP is suspected, treatment with high-dose glucocorticoids should be started. Excess administration of oxygen is to be avoided, but in patients with respiratory failure, adequate tissue oxygenation should be maintained. Initiation of mechanical ventilation requires careful consideration as the effect on BIP is unknown. Treatment with high flow oxygen allows comfort and verbal communication. By admitting this severely hypoxaemic patient to the ICU we were able to gain some valuable time for him through good palliative treatment.

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