Title

Bleomycin-induced lung injury treated with venovenous extracorporeal membrane oxygenation (ECMO) and ultra-protective ventilator settings

Journal

BMJ Case Reports, 13(11)

ISSN

1757-790X

Authors

Odish, Mazen Faris

McGuire, William Cameron

Thistlethwaite, Patricia

et al.

Publication Date

2020-11-01

DOI

10.1136/bcr-2020-236474

Peer reviewed

Bleomycin-induced lung injury treated with venovenous extracorporeal membrane oxygenation (ECMO) and ultra-protective ventilator settings

Mazen Faris Odish ,[1] William Cameron McGuire,[1] Patricia Thistlethwaite,[2] Laura E Crotty Alexander[1]

[1]Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, California, USA
[2]Surgery, Division of Cardiovascular and Thoracic Surgery, University of California San Diego, La Jolla, California, USA

Correspondence to
Dr Mazen Faris Odish; modish@health.ucsd.edu

Accepted 30 October 2020

To cite: Odish MF, McGuire WC, Thistlethwaite P, *et al*. *BMJ Case Rep* 2020;**13**:e236474. doi:10.1136/bcr-2020-236474

SUMMARY

Bleomycin treats malignancies, such as germ cell tumours and Hodgkin lymphoma. While efficacious, it can cause severe drug-induced lung injury. We present a 42-year-old patient with stage IIB seminoma treated with radical orchiectomy followed by adjuvant chemotherapy with bleomycin, etoposide and cisplatin. His postbleomycin course was complicated by the rapid onset of hypoxic respiratory failure, progressing to acute respiratory distress syndrome and requiring venovenous extracorporeal membrane oxygenation (VV-ECMO) support. Although the patient was treated with high dose systemic steroids and ultra-protective ventilator strategies to minimise ventilator-induced lung injury while on VV-ECMO, his lung injury failed to improve. Care was withdrawn 29 days later. Lung autopsy revealed diffuse organising pneumonia. We found six case reports (including this one) of bleomycin-induced lung injury requiring VV-ECMO with a cumulative survival of 33% (2/6). While VV-ECMO may be used to bridge patients to recovery or lung transplant, the mortality is high.

BACKGROUND

Bleomycin is a chemotherapy agent used to treat malignancies such as germ cell tumours and Hodgkin lymphoma. While efficacious, a feared side effect is bleomycin-induced lung injury. This lung injury occurs in 10%–40% of patients receiving bleomycin, with mortality from pulmonary toxicity in about 0%–4% of patients. However, some studies have found a 25% mortality rate.[1] Bleomycin's mechanism of action is DNA damage by strand scission causing single or double-strand breaks with reactive oxygen species. The lung has a relative deficiency of the bleomycin-inactivating enzyme, bleomycin hydrolase, likely contributing to lung injury and its associated pulmonary fibrosis.

Bleomycin-induced lung injury includes pulmonary fibrosis, interstitial pneumonitis, organising pneumonia and hypersensitivity pneumonitis. In fact, bleomycin is a common drug used to induce lung fibrosis in animals.[2] Risk factors for bleomycin-induced lung injury include older age, concurrent cisplatin or gemcitabine, history of thoracic radiation and exposure to higher inspired oxygen (F_iO_2).[3] Patients often present with dyspnoea, cough and hypoxemia; however, they can also present with an asymptomatic, subclinical disease defined by a decrease in their diffusing capacity for carbon monoxide even up to 6 months after drug exposure. The mainstay of treatment includes bleomycin discontinuation, respiratory support, avoidance of high F_iO_2 and systemic steroids.[4] We present a patient who died of acute respiratory distress syndrome (ARDS) from organising pneumonia due to bleomycin-induced lung injury despite high dose systemic steroids, antifibrotic therapy, venovenous extracorporeal membrane oxygenation (VV-ECMO) and ultra-lung protective ventilator settings.

CASE PRESENTATION

A 42-year-old man with stage IIB seminoma treated with radical orchiectomy and adjuvant chemotherapy had completed his last cycle of bleomycin, etoposide and cisplatin 2 weeks prior to presentation when he was admitted to an outside hospital for neutropenic fever. His family and social history were unremarkable. His infectious workup for neutropenic fever was negative. On hospital day 7, he became increasingly hypoxemic. CT chest showed ground glass and nodular consolidation with subpleural sparing consistent with organising pneumonia due to drug injury.

INVESTIGATIONS

The patient's infectious workup was negative which included bronchoalveolar cultures (bacterial, fungal and acid-fast bacteria), aspergillosis galactomannan antigen of blood and bronchoalveolar fluid, respiratory viral panel PCR (BioFire), coccidioidomycosis antibody screen, cryptococcal antigen screen and blood cultures. The patient's CT chest was consistent with drug-induced organising pneumonia, see figure 1.

TREATMENT

Due to concerns for bleomycin-induced lung injury, the patient was started on 1 g of methylprednisolone daily on hospital day 9. On hospital day 17, the patient was intubated for worsening hypoxic respiratory failure. Despite typical severe ARDS management, the patient's PaO_2/FiO_2 ratio (P:F) continued to worsen even with prone positioning and neuromuscular blockade with cisatracurium. Because of a low P:F ratio of 58, high plateau pressures of 36 cm of H_2O and poor lung compliance, the patient was transferred to our institution on hospital day 19 and cannulated for VV-ECMO.

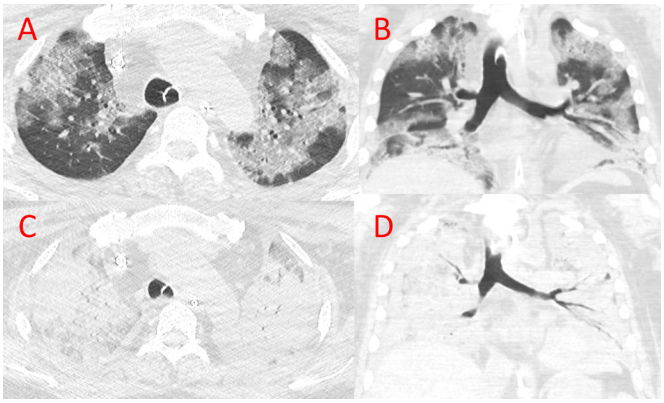

Figure 1 (A and B) CT chest on hospital day 19 demonstrating extensive, relatively symmetric crazy paving pattern of opacities with ground-glass, intralobular and interlobular septal thickening and multifocal areas of lobular sparing. These findings are present throughout all lobes of both lungs with more confluent consolidative opacities in the lung bases. These findings are consistent with evolving lung injury characterised by probable organising pneumonia in the early fibrotic phase. (C and D) Interval CT chest on hospital day 25, demonstrating near complete consolidation of all five lobes. Interval increase in size of small bilateral pleural effusions.

The VV-ECMO venous drainage cannula was placed in the right femoral vein, with the infusion cannula in the right internal jugular vein, achieving flows of 3.5 L/min. Prior to ECMO, he was ventilated with lung-protective ventilator strategies; tidal volume (TV) of 400 mL (6 mL/kg of ideal body weight), respiratory rate of 24/min, positive end-expiratory pressure (PEEP) of 15 cm of H_2O, requiring an F_iO_2 of 80% to maintain saturation >88%. VV-ECMO allowed for an ultra-protective ventilator strategy; TV of 115 mL (2 mL/kg of ideal body weight), respiratory rate of 10/min and a PEEP of 10 cm of H_2O. After VV-ECMO initiation, the patient's F_iO_2 was able to be decreased from 80% to 35% and the driving pressure was decreased from 28 cm to 10 cm of H_2O. VV-ECMO was continued 10 days without any improvement in his chest imaging (see figure 1) or pulmonary compliance despite ultra-protective ventilator settings, conservative fluid management and high dose steroids (6 mg/kg). Prior to transfer to our institution, n-acetylcysteine was trialled in an attempt to scavage for radical oxygen species. Pirfenidone was also tried for a progressive, fibrotic lung disease.

OUTCOME AND FOLLOW-UP

The patient died on hospital day 29, after the family transitioned to comfort care and VV-ECMO and other supportive therapies were discontinued. The autopsy was consistent with bleomycin-induced lung injury with diffuse organising pneumonia in all lobes and pneumocytes with metaplastic squamous changes, see figure 2. No viral inclusions, bacterial organisms or fungal hyphae were found on autopsy.

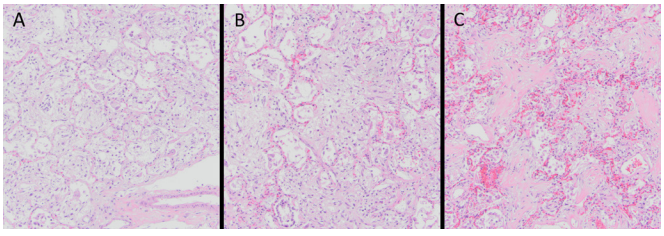

Figure 2 Lung pathology at 100x magnification, H&E sections. (A) Left upper lobe (LUL), and earlier phase of organisation, with large reactive pneumocytes. (B) Right middle lobe, organisation at a stage between LUL and left lower lobe (LLL). (C) LLL, shows more advanced fibrosis with denser collagen.

DISCUSSION

We present a case of bleomycin-induced lung injury requiring VV-ECMO support who died after 22 days with severe ARDS due to diffuse organising pneumonia. We have found five previous case reports of using ECMO support for bleomycin-induced lung injury. Shah *et al* used protective mechanical ventilator settings with a bicaval dual-lumen, single cannula ECMO strategy with the patient ultimately surviving.[5 6] Scherrer and Bechir similarly used a protective ventilation strategy with VV-ECMO support for their patient, who unfortunately died.[7] Galcaianu *et al* similarly treated a patient with VV-ECMO, systemic steroids and cyclophosphamide, but he unfortunately also died due to diffuse alveolar damage on autopsy.[8] VV-ECMO has been used to support patients for recovery and eventual

Patient's perspective

Father of patient:

One of the hardest things for me to wrap my mind around is the number of patients who get treated with bleomycin who don't develop this complication only for my son to develop it after all of his chemotherapy was over and we thought he was in the clear. And then he continued to get worse despite everything everyone was doing. It was really hard watching him have more and more trouble breathing as his lungs got worse.

When it came to putting [patient's name] on ECMO, there wasn't really a question. I would have tried anything to bring my son back. The fact that ECMO had even a chance of success made it worth it. The chance to rest his lungs and give them an opportunity to recover was explained to us before he was transferred for ECMO cannulation. I wasn't sure if it would work or not, but I figured it was the logical choice. Having said that, I didn't go in to his transfer from the VA to UCSD for ECMO with the assumption that he would go on the machine and then come out of it 100%. I don't think of myself as a pessimist, but I'm a realist and I didn't go in thinking there was a very good chance of success or that he would come out of this process unscathed.

Throughout [patient's name]'s nine days on ECMO, we did not want to have to make the decision to stop life support. As it was becoming clear that he was not getting better, the need to make a decision about continuing ECMO versus stopping weighed heavier and heavier on our minds. Ultimately, having to decide to stop ECMO was the hardest part of the entire process. It felt like we were admitting defeat and letting our son die. And no parent ever wants to do that.

Since he passed away, the family is pulling through the experience of losing [patient's name]. The holidays were the hardest on everyone. He spent a lot of time with his mother and they were basically inseparable, so she has been taking this the hardest. But, we have all been dealing with it and developing our own different coping mechanisms. For me personally, the hope that someone somewhere can learn something from [patient's name]'s case is what I hang on to. Learning something from [patient's name]'s death is why I gave permission for an autopsy and am giving permission for this journal article.

Learning points

- Six case reports of patients requiring extracorporeal membrane oxygenation (ECMO) for bleomycin-induced lung injury have a cumulative survival of 33% (2/6).
- Patients with bleomycin-induced lung injury may be supported with ECMO as a bridge to recovery with lung-protective ventilator settings to minimise ventilator-induced lung injury, systemic steroids and possibly further steroid-sparing immunosuppression.
- Patients with bleomycin-induced lung injury with a decision to initiate ECMO should concurrently be evaluated for lung transplantation. This requires close consultation with the patient's oncologists to determine likelihood of cure of the underlying malignancy.
- If ECMO is initiated as a bridge to lung transplantation, mobility while on ECMO is essential to help prevent deconditioning.

transplant. Narayan *et al* described a case where a patient was on VV-ECMO for 139 days, until lung transplantation.[9] Mailman and Levine describe the use of VV-ECMO initially with the addition of venoarterial ECMO for severe right ventricular failure and refractory hypoxemia for a patient as a bridge to transplant, who unfortunately died prior to transplantation.[10] Overall, the six case reports (including this one) of bleomycin-induced lung injury requiring ECMO support had 33% (2/6) survival.

In retrospect, we would have initiated ECMO earlier in this patient's disease course given the ultimate diagnosis and outcome; this may have prevented further hyperoxic damage. However, this did not happen for two reasons. First, the ultimate diagnosis was not clear initally as imaging and symptoms were both consistent with a possible infectious aetiology. Second, initiation of VV-ECMO prior to attempting evidence-based therapies for ARDS is not standard of care and not typically pursued at the referring institution. Ultimately, we placed our patient on VV-ECMO as a bridge to recovery or transplant. Our three main goals with VV-ECMO were to minimise ventilator-induced lung injury (VILI) by targeting ultra-protective ventilator settings; minimise F_iO_2 to maintain a P_aO_2 of 60–80 mm Hg to decrease hyperoxic free radical damage; and provide respiratory support with systemic steroids as a bridge to recovery or lung transplantation if necessary. Amato *et al* showed that lower ventilator driving pressure and survival are directly related with no lower limit to the driving pressure (or TVs) and improved outcomes.[11] The majority of ECMO centres attempt to minimise ventilator settings and thus VILI.[12] As discussed in our background, reactive oxygen species may contribute to bleomycin lung injury, thus our rationale for minimising F_iO_2 and keeping a P_aO_2 around 60–80 mm Hg while on VV-ECMO.

If VV-ECMO is used as a bridge to recovery or transplantation, mobilisation during therapy is essential to minimise deconditioning for potential lung transplant. Ambulation while on VV-ECMO can now be done with bicaval dual-lumen single cannulas (Crescent, Avalon, etc), but also with two cannula configurations.[13] Discussion with the patient's oncologists is essential in determining if the patient's malignancy is likely cured prior to lung transplant listing. Our patient was evaluated by the lung transplant team and deemed not a suitable candidate due to pre-morbid psychiatric history, deconditioning and concerns that his underlying malignancy was not cured.

Patients with bleomycin-induced lung injury with severe ARDS should be treated with respiratory support, systemic corticosteroids and consideration can be made for steroid-sparing immunosuppression and lung transplantation. VV-ECMO may be used to help support patients with bleomycin-induced lung injury as a bridge to recovery or lung transplantation, although the evidence is mixed and limited to case reports that have a 33% survival rate.

Acknowledgements The authors would like to thank the following people and groups. Dr Robert Owens for his expertise in ARDS and ECMO. Dr Travis Pollema and Cassia Yi as the UC San Diego ECMO medical director and ECMO coordinator. Dr Ann Tipps, our expert pathologist who reviewed our patients pathology. ECMO specialists at our institution including ICU nurses, perfusionists, respiratory therapists and physical and occupational therapy. Finally, we would like to thank all the medical teams that took care of our patient.

Contributors All authors made individual contributions to the writing of this case report, and approved the final version submitted. MFO contributed to the abstract, summary, figures, background, case presentation and discussion. WCMG contributed to the abstract, case presentation, discussion and patient perspective. PT contributed to the case presentation and discussion. LCA contributed to the abstract, summary, background, case presentation and discussion.

Funding This study was funded by National Institute of General Medical Sciences.

Competing interests None declared.

Patient consent for publication Parents/Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Mazen Faris Odish http://orcid.org/0000-0003-1247-1371

REFERENCES

1 Evens AM, Helenowski I, Ramsdale E, *et al*. A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era. *Blood* 2012;119:692–5.
2 Della Latta V, Cecchettini A, Del Ry S, *et al*. Bleomycin in the setting of lung fibrosis induction: from biological mechanisms to counteractions. *Pharmacol Res* 2015;97:122–30.
3 Gupta R, Ettinger NA. Beyond conventional therapy: role of pulse steroids in bleomycin induced lung injury. *Respir Care* 2014;59:e9–12.
4 White DA, Stover DE. Severe bleomycin-induced pneumonitis. clinical features and response to corticosteroids. *Chest* 1984;86:723–8.
5 Shah A, Pasrija C, Kronfli A, *et al*. Veno-Venous extracorporeal membrane oxygenation use in the treatment of bleomycin pulmonary toxicity. *Innovations* 2017;12:144–6.
6 Kronfli A, Pasrija C, Shah A, *et al*. Thrombosis of the right internal jugular vein is not a contraindication to ambulatory Veno-Venous extracorporeal membrane oxygenation with a Bicaval Dual-Lumen, single cannula system. *Heart Surg Forum* 2016;19:282–3.
7 Scherrer M. Bechir M extracorporeal membrane oxygenation in presence of severe chemotherapy-induced (bleomycin, Etoposid and Efosfomid) interstitial fibrosis. *SOJ Anesthesiol Pain Manag* 2004;1:1–4.
8 Galcaianu G, Calcaianu M, Gschwend A, *et al*. Fatal bleomycin-induced pulmonary fibrosis in case of seminoma open. *Journal of clinical and medical case reports* 2016;2:2379–1039.
9 Narayan V, Deshpande C, Bermudez CA, *et al*. Bilateral lung transplantation for Bleomycin-Associated lung injury. *Oncologist* 2017;22:620–2.
10 Mailman J, Levine A. 1603.. *Crit Care Med* 2016;44:476.
11 Amato MBP, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015.
12 Schmidt M, Pham T, Arcadipane A, *et al*. Mechanical ventilation management during ECMO for ARDS: an international multicenter prospective cohort. *Am J Respir Crit Care Med* 2019.
13 Colclough E, Ramsey S, Barrett P, *et al*. Mobilization of ECMO patients with various cannulation configurations. *J Heart Lung Transplant* 2018;37:S59–60.