Central Extracorporeal Membrane Oxygenation Support for Blastomycosis-Induced Septic Shock

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Abstract

Keywords

- ▶ central extracorporeal membrane oxygenation
- ▶ fungal infection
- ▶ septic shock
- ▶ *Blastomyces dermatitidis*
- ▶ pediatric

Blastomyces dermatitidis, a rare fungus endemic to the central North America, has the potential to cause respiratory dysfunction in both immunocompromised and immunocompetent hosts. Blastomycosis infections can progress to severe respiratory failure and multisystem organ failure. Extracorporeal membrane oxygenation (ECMO) can be used as a temporary support device to allow time for a patient's organs to recover. Central ECMO has proven to be a successful treatment option for high-output septic shock. This case report describes a 12-year-old girl, erroneously diagnosed with juvenile idiopathic arthritis and treated with immunosuppressives, afflicted with blastomycosis-induced septic shock. High-flow central ECMO was used to reverse her lactic acidosis by increasing oxygen delivery. Unfortunately, continued lung deterioration secondary to the *B. dermatitidis* infection caused irreversible damage to the lung parenchyma. This is the second pediatric ECMO case report for severe respiratory failure related to blastomycosis and the first case report on central ECMO support for high-output septic shock from blastomycosis.

Introduction

Blastomycosis is most commonly found in North America, extending from Canada through parts of Central America. In the United States, blastomycosis is endemic to the Great Lakes Basin, extending southeast into the central Appalachian Mountains and southwest to the Mississippi River Valley (▶ Fig. 1). Unlike other fungal infections, it typically infects immunocompetent middle-aged men exposed to moist soil involved in outdoor recreational activity. In endemic areas, the yearly incidence of blastomycosis is ~1 to 2 cases per 100,000 people and it is estimated ~10% of patients reported with blastomycosis are children.^{1,2} Blastomycosis most commonly infects patients through the lungs, skin, and bone. However, the central nervous

system, joints, liver, spleen, pericardium, thyroid, gastrointestinal tract, and adrenal glands can also be involved.³ Case-fatality rates of 4 to 22% have been reported with blastomycosis.³ Immunocompromised patients with extensive pulmonary involvement and extrapulmonary infections carry an even higher mortality rate (25–54%).³

When patients are stricken with potentially reversible severe lung disease, septic shock, or cardiac dysfunction, extracorporeal membrane oxygenation (ECMO) can be a potential life-saving bridge to recovery. Estimated survival rates are <50% when ECMO is used for children with septic shock.⁴ Septic shock from fungal disease is known to increase the mortality risk in ECMO patients as circulating fungal organisms may adhere to the ECMO circuit and subsequently be challenging to eliminate.⁵ However, despite

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Fig. 1 Geographic distribution of areas endemic with blastomycosis.

this increased mortality risk, fungal disease associated with ECMO is survivable.⁶ The following case report summarizes a patient with blastomycosis-induced high-output septic shock supported with central ECMO followed by a discussion related to the treatment and ECMO course of the patient.

Case Report

A 12-year-old African American girl presented to a rheumatologist with a 1-month history of bilateral ankle and right wrist pain associated with swelling. The patient was subsequently started on methotrexate and prednisone for the presumed diagnosis of juvenile idiopathic arthritis and later received intra-articular injections corticosteroids. Afterward, she presented to an emergency department in respiratory distress with painful swelling of the right wrist and bilateral ankles and was admitted to the pediatric intensive care unit. On initial exam, her vital signs demonstrated a temperature of 36.8°C, pulse of 122, respiratory rate of 37, and a blood pressure of 137/78 mm Hg. Significant physical exam findings revealed a distressed patient with tachycardia, decreased breath sounds bilaterally, and tachypnea. It was noted her right wrist had an effusion, was warm, and had restricted motion especially at the radial head. Her right elbow was in a flexed position with warmth and restriction and pain on extension. Both ankles were notably swollen with obscured medial and lateral malleoli. Diagnostically, chest radiograph demonstrated extensive air-space disease which had a nodular quality most suggestive of overwhelming pneumonia (► **Fig. 2**). Trimethoprim/sulfamethoxazole and naproxen were started for suspected *Pneumocystis jiroveci* and for the history of juvenile idiopathic arthritis. With worsening respiratory distress, heated high-flow nasal cannula was initiated and escalated to 25 L/min. On day 2 of admission, the patient was intubated secondary

to continued respiratory deterioration, and mechanical ventilation was instituted with synchronized intermittent mandatory ventilation/pressure-regulated volume control, fraction of inspired oxygen concentration (FiO_2) of 80%, peak end-expiratory pressure of 10, tidal volume of 360 mL, and respiratory rate of 14. A bronchial alveolar lavage (BAL) demonstrated broad-based fungal organisms, and the aspirate of the right wrist effusion was consistent with blastomycosis. Amphotericin B was added to the treatment regimen. At this time, the patient's arterial partial pressure of oxygen in the blood was 88 torr, mean airway pressure 13 cm H_2O , FiO_2 75%, and oxygen index (OI) calculated to be 11. The patient soon experienced hypotension with her blood pressure dropping from 104/45 to 60/35 mm Hg. Epinephrine was initiated for hypotension in the setting of septic shock unresponsive to fluid boluses and escalated to 0.7 $\mu\text{g}/\text{kg}/\text{min}$ over

Fig. 2 Initial chest radiograph in emergency department demonstrating diffuse nodular pneumonia.

2 hours because of continued hypotension. The lactic acid trended from 4.9 to 12.1 mmol/L during this time and Noninvasive Ultrasonic Cardiac Output Monitor demonstrated a cardiac output of 8.4 L with a systemic vascular resistance of 428 dyne s/cm⁵. At this time, the OI remained 11. Secondary to high output, warm septic shock unresponsive to the α -1 effects of high-dose epinephrine, and poor oxygen delivery evidenced by a rising lactate, ECMO was entertained. Venoarterial ECMO through the chest was chosen secondary to the current poor oxygen delivery despite the patient's elevated cardiac output. It was reasoned that the patient would require extremely high ECMO flow rates to provide a greater cardiac output than currently measured to improve oxygen delivery. ECMO was initiated and the patient was cannulated via sternotomy for central ECMO with a 7-mm (21 FR) Sarns aortic cannula and a 28 FR/38 FR two-stage venous cannula into the right atrium. The sternum was left open, but the incision was closed around the cannulas and drains.

Initial ECMO settings included blender FiO_2 of 60%, sweep flow of 0.5 L/min, and an ECMO flow rate of 5.6 L (111 mL/kg/min). Rest ventilator settings included FiO_2 21%, peak end-expiratory pressure 10, tidal volume 200 mL, and respiratory rate 10. Lactic acid fell to a level of 6 mmol/L within 7 hours after ECMO initiation. The patient's widened pulse pressure narrowed and epinephrine was able to be weaned to 0.1 $\mu\text{g/kg/min}$. The patient's chest was explored twice for bleeding within 24 hours. During one exploration, the 7-mm Sarns aortic cannula was removed and replaced with an 8-mm (24 FR) Sarns aortic cannula. High flow rates continued with a maximum flow of 6.8 L (135 mL/kg/min). The patient remained on low-dose epinephrine until day 7. Following resolution of the hypotension and lactic acidosis, ECMO flow rates were weaned. However, the patient's respiratory status worsened and ECMO was then continued for respiratory support. A repeat BAL again reconfirmed *Blastomyces*, and on day 8, sedation was lifted demonstrating the patient's ability to follow commands and respond to questions. By day 11, adjunctive inhaled amphotericin was added to the antifungal regimen as another repeat BAL confirmed *Blastomyces*. The liposomal amphotericin B was changed to amphotericin B lipid complex as the patient's phosphate began to rise and for a theoretical mechanism of improved tissue penetration.⁷ A computerized tomography (CT) of the head was repeated and was within normal limits. Ultimately, on day 16 another chest CT demonstrated irreversible damage to the lung parenchyma ($\rightarrow$ Figs. 3 and 4). The grave prognosis was discussed with the family and care was withdrawn. The autopsy showed extensive necrosis of both lungs parenchyma but without signs of other organ involvement ($\rightarrow$ Fig. 5).

Discussion

To the authors' knowledge, this case report represents the third overall case report and second pediatric case report of fulminant *Blastomyces dermatitidis* requiring ECMO.^{5,8} However, our case differs in that our pediatric patient initially

Fig. 3 Chest radiograph on day 16 demonstrating evolution of disease process when compared with day 1 chest radiograph.

Fig. 4 Computerized tomography chest on day 16 of hospital stay demonstrating significant lung tissue damage.

Fig. 5 Gross lung tissue specimen visualized during autopsy.

required ECMO for severe septic shock and not acute respiratory distress syndrome. Moreover, like the previous two ECMO cases in the literature, our patient eventually expired secondary to irreversible lung disease. As illustrated by this patient, high-output septic shock from *B. dermatitidis* can be successfully supported with central ECMO. Unfortunately, the described patient developed progressive lung disease that was not survivable. In patients with severe lung disease, some physicians monitor the OI and consider ECMO when the OI is greater than 40. The use of ECMO in high-output septic shock has historically been limited secondary to the inability to achieve extremely high ECMO flow rates related to limited venous return. However, MacLaren et al⁹ reported the successful use of central ECMO in refractory septic shock with a 74% survival rate to hospital discharge in 23 patients. Our patient also met the inclusion criteria that MacLaren et al⁹ used in their study. Our patient was cannulated centrally secondary to a noninvasive cardiac output of 8.4 L/min. Despite placing a 28 FR/38 FR two-stage venous cannula into the right atrium, venous flow was still limited and the maximal ECMO flow rate achieved was 6.8 L (135 mL/kg/min). However, this seemed to be adequate as the patient's lactate decreased, pulse pressure narrowed, and epinephrine was weaned successfully. Goal ECMO flow rates by MacLaren et al⁹ were >2.4 L/min/m² in septic shock patients over 10 kg. This goal was overachieved in the described patient who was ~ 1.5 m² with ECMO flow rates consistently over 6 L/min during the period of support for high-output septic shock. However, we felt our patient required the higher amount of flow secondary to the persistence of poor oxygen delivery manifested by the persistent lactic acidosis. As MacLaren et al⁹ eluded to in their paper, patients require an individualized, goal-directed approach when using ECMO for septic shock.

Fungal disease is not an absolute contraindication for ECMO use. However, since systemic fungal organisms presumably bind to the ECMO circuit and are challenging to remove, it may be difficult to clear a fungal infection, especially if the fungus is located in the blood. ECMO patients with fungal infections continue to have an increased risk of mortality, possibly due to the previously mentioned challenges related to ECMO.¹⁰ Our patient had *B. dermatitidis* isolated from the sputum, but not the blood. The ECMO circuit and our patient did not produce any positive fungal blood cultures for the entire hospital admission.

The patient was left on venoarterial ECMO through the chest for the length of her hospital stay after ECMO initiation. Conversion to venovenous ECMO was not performed because of the continued deterioration of the lungs and inadequate oxygenation with circuit clamping. In addition, because of the extensive air-space disease, it was felt that the patient would have elevated pulmonary pressures, making it difficult to achieve adequate flow across her pulmonary bed for the necessary left ventricular preload. This was evidenced by hypotension with circuit clamping, increased right ventricle dilation on echocardiogram when clamped, and by enlarged pulmonary arteries on chest CT. The patient was at an increased risk of mediastinitis due to the central cannulation;

however, our patient did not experience a known infection because of the central cannulation. It was also felt that a continued venoarterial ECMO bridge to pulmonary transplantation was not feasible.

During high-flow and prolonged centrifugal ECMO, hemolysis is always a concern. This patient was at risk secondary to the use of a Quadrox oxygenator and the high ECMO flow rate.¹¹ Hemolysis, in these situations, is routinely evaluated with plasma-free hemoglobin levels. Unfortunately, plasma-free hemoglobin was not available as an in-house laboratory test during this patient's ECMO period. However, we did find evidence of hemolysis in the form of a lactic dehydrogenase level of 1555 U/L (313–618 U/L) and a haptoglobin level of 8 mg/dL (16–200 mg/dL). Clinically, the patient did not have evidence of renal insufficiency. Serum creatinine remained low (maximum was 0.8 mg/dL) and the patient had good urine output throughout the hospitalization. Since we did not see renal toxicity and the circuit remained without blood clots, the circuit was not changed during the 350 hours of ECMO.

In our patient, we hoped ECMO would improve oxygen delivery and allow time for septic shock resolution. This was accomplished in ~ 3 to 4 days. Following resolution of septic shock, our attention turned to the lung function. Pulmonary support with ECMO was continued with the hope of limiting further iatrogenic lung injury from mechanical ventilation while allowing time for the antifungals to take action. Liposomal amphotericin B was continued and later transition to amphotericin B lipid complex for improved lung penetration. It has been shown that ECMO circuit tubing does not decrease amphotericin B levels in serum.⁵ Our patient never had blastomycosis isolated from the serum, despite 16 blood cultures being drawn. Possible explanations as to why little response to antifungal medication was noted could be attributed to the slightly late implementation of antifungals with prior immunosuppression in an immunocompetent patient. Also, running high ECMO flow rates and bypassing the lungs could have possibly limited pulmonary antifungal delivery. Dalton et al,⁵ in a previous case report, ran ECMO flow rates low to maintain pulmonary blood flow on ECMO for blastomycosis-induced respiratory failure. Our patient had adequate pulmonary blood flow as demonstrated by lower flow rates after day 3 of ECMO and resolution of septic shock. However, in both our patient and the patient described by Dalton et al,⁵ lung function did not improve and the patients did not survive.

In conclusion, blastomycosis rarely produces severe symptoms; however, on rare occasion, it can be an extremely virulent disease process that can infect immunocompetent and immunocompromised hosts. In the case presented, central ECMO facilitated resolution of septic shock and continues to be a reasonable option for high cardiac output septic shock. When cases of disseminated blastomycosis are identified, aggressive management with antifungals, bronchoscopy, and mechanical ventilation may be used. Early recognition and institution of appropriate antifungal treatment remain important factors for survival and the prevention of fungal pneumonia-associated chronic pulmonary disease. ECMO may offer an opportunity to

prolong survival and allow time for resolution of the fungal disease. However, at this time, survival from ECMO-related blastomycosis-induced respiratory failure or septic shock has not occurred.

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