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Successful use of extracorporeal membrane oxygenation for acute respiratory failure in a patient with chronic granulomatous disease^{☆,☆☆,★}

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Abstract

A 9-year-old boy presented with pneumonia, bilateral pulmonary lesions, and fulminant respiratory failure requiring support with extracorporeal membrane oxygenation (ECMO). Open lung biopsy and subsequent bronchoscopy identified *Nocardia cyriacigeorgica* and *Burkholderia cepacia* pneumonia. Chronic granulomatous disease (CGD) was diagnosed by an abnormal neutrophil oxidative burst assay. An aggressive diagnostic and therapeutic strategy, which included ECMO, allowed for patient survival and return to baseline function. No ECMO survivors with CGD have previously been reported. It is now recognized that several forms of CGD exist, and some forms maybe compatible with long-term survival. Therefore, the diagnosis of CGD should not necessarily be considered a contraindication to ECMO. This is the first known survivor of CGD-related acute respiratory failure supported by ECMO.

Keywords

Extracorporeal membrane oxygenation; Immunocompromised; Pediatric; Nocardia; Chronic granulomatous disease; Respiratory failure

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency characterized by absent or markedly reduced neutrophil oxidative burst activity. Affected patients are susceptible to severe infections with catalase-producing organisms including *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia*, *Nocardia* spp, and *Aspergillus* spp, which can produce life-threatening pneumonia and respiratory failure [1,2].

Primary respiratory failure is one of the indications for extracorporeal membrane oxygenation (ECMO). The survival rates for pediatric patients with respiratory failure requiring extracorporeal life support have been recently reviewed based on data from the Extracorporeal Life Support Organization registry. Survival rates for children with acquired or inherited immune compromise ranged from 34.6% (recipients with solid organ transplant) to 0% (recipients with bone marrow transplant) [3]. Zabrocki et al [4] reported that an immunocompromised state was a major predictor of mortality in pediatric patients treated with ECMO for respiratory failure. They did not specifically include patients with CGD in their review. Using PubMed, MEDLINE, and the Extracorporeal Life Support Organization registry, we could not identify any patients with CGD and respiratory failure supported with ECMO who had survived [5,6]. Herein, we present a patient with CGD and acute respiratory failure who was successfully managed using ECMO.

1. Case presentation

A 9-year-old boy was hospitalized with a 2-week history of high fever and cough. His medical history was significant for recurrent skin granulomas since age 5 years and a prolonged febrile illness of unclear origin that had resolved 1 year before admission. Admission computed tomographic (CT) scan demonstrated a cavitating abscess in the right lower lobe, round nodular lesions in both lungs, and lymphadenopathy. Pleural fluid analyses were negative for malignancy and for autoimmune disease. Routine sputum cultures were negative for bacterial, fungal, and acid-fast pathogens. A respiratory burst assay by dihydrorhodamine-123 fluorescence was sent as an initial evaluation for CGD. The patient failed to improve on broad-spectrum antibiotics (clindamycin and ceftriaxone), and a second CT scan demonstrated progression of the lesions. A lung biopsy was subsequently performed on hospital day 7 for diagnosis.

Postoperatively, the patient experienced respiratory and hemodynamic failure. He failed to improve with conventional mechanical ventilator support and was transitioned to high-frequency oscillatory ventilation (HFOV). The patient's hemodynamics improved after initiating HFOV, and he was weaned off vasopressors. He continued to have worsening oxygenation as measured by a rising oxygenation index (OI), despite medical interventions. Medical interventions included changing his antimicrobial regimen to meropenem, vancomycin, gentamicin, and voriconazole. Chronic granulomatous disease was suspected after identifying granulomas on the lung biopsy and from the results of the dihydrorhodamine-123 fluorescence assay, which suggested autosomal recessive CGD. As a result, vancomycin was changed to linezolid to cover for possible actinomycetes, and high-dose trimethoprim-sulfamethoxazole was added to cover for possible *Nocardia*. Methylprednisolone ($1 \text{ mg kg}^{-1} \text{ d}^{-1}$) was started based on experimental evidence that significant morbidity in CGD results not only from failure to eradicate pathogens but from

excessive inflammation [7,8]. Similarly, interferon- γ was withheld to avoid possible proinflammatory effects of this medication [9]. On hospital day 11, pathology and culture results of the lung biopsy demonstrated *Nocardia cyriacigeorgica* resistant to meropenem, prompting adjustment in antibiotic coverage. Despite these measures, the patient continued to deteriorate, and ECMO was considered.

Previous studies of pediatric patients with respiratory failure suggest that an OI greater than 20 coupled with failure to improve on HFOV predicts a high mortality [10]. On hospital day 13, our patient's OI had increased to 65 from 25 on intensive care unit admission. Although there were no known survivors of CGD-associated respiratory failure requiring ECMO, his good health before this admission argued for initiation of ECMO support as a means to gain the needed time for medical therapies to take effect. Thus, the patient was cannulated via the internal jugular and femoral vein for venovenous ECMO support. He was converted to venoarterial ECMO because of inadequate flows on venovenous ECMO. On venoarterial ECMO, increased flows allowed ventilator weaning to achieve lung rest.

While on ECMO, steroids were continued, and a total of 3 granulocyte transfusions were given. γ -Interferon therapy was withheld in an effort to avoid any potential proinflammatory effects of the drug as well as potential hematoma formation from the subcutaneous injections. On day 8 of the ECMO run, the patient failed a weaning trial, and the decision to perform a therapeutic and diagnostic flexible bronchoscopy was made. The patient benefited from the removal of extensive secretions and subsequent identification of resistant *B. cepacia*. However, bronchoscopy was complicated by a left pneumothorax that required placement of a chest tube. The following 2 days were complicated by increasing hemorrhage from the cannulation sites and the right hemithorax, which required continuous infusion of packed red blood cells. On ECMO day 10, the patient tolerated a rapid ECMO wean and was decannulated. The bleeding stopped after decannulation, and he transitioned successfully to conventional mechanical ventilation.

The patient was extubated on hospital day 29. Steroids were tapered and then stopped after 1 month of therapy. He was discharged home on hospital day 47 without supplemental oxygen and on maintenance γ -interferon therapy. He completed 8 weeks of intravenous therapy with linezolid, levofloxacin, voriconazole, and trimethoprim-sulfamethoxazole. At 3-year follow-up, he has returned to normal activities including sports without any respiratory limitations. A recent CT scan demonstrated multiple stable bilateral calcified lung nodules.

2. Discussion

Chronic granulomatous disease was once thought to be a universally fatal childhood disease. Improvements in medical care, antibiotics, and antifungals have allowed many affected individuals to live into adulthood [2]. It is also now known that certain genotype variants may present later in life and follow a more indolent course. Bender et al [1] described such a series of patients, including the subject of this case report, who were diagnosed with variant X-linked CGD. As did others in that report, our patient had an intermediate dihydrorhodamine fluorescence profile, which initially incorrectly suggested autosomal

recessive CGD. The definitive diagnosis was found using high-resolution scanning followed by targeted sequencing for precise genetic analysis of the mutation.

We found 3 published cases of patients with respiratory failure and CGD requiring ECMO, all of whom died [5,6]. It is now recognized that illness severity is variable in CGD, however, and that some genetic variants may be compatible with long-term survival. When CGD is diagnosed, especially the variant X-linked CGD, it should not be thought of as a contraindication to ECMO. Our patient's survival is likely caused by the aggressive nature of the diagnostic workup and respiratory support using ECMO, which allowed time for the medical treatment to take effect.

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