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Extracorporeal Membrane Oxygenation for Hemophagocytic Lymphohistiocytosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Male, 21
Final Diagnosis: Hemophagocytic Lymphohistiocytosis
Symptoms: Acute respiratory insufficiency • anemia • thrombocytopenia
Medication: —
Clinical Procedure: Extracorporeal membrane oxygenation
Specialty: Hematology

Objective: Rare disease

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare hematological disease characterized by an excessive inflammatory response to various triggers, resulting in rapid multi-organ failure. Its incidence may be underestimated due to its rarity, its variable clinical presentation, and its high mortality rate prior to diagnosis. Oftentimes, HLH is mistaken for refractory sepsis and improperly treated as such. Left untreated, the disease is universally fatal. With treatment, case series of adults with HLH report a 30-day mortality of up to 44% and an overall mortality of up to 75%.

Case Report: We describe the use of extracorporeal membrane oxygenation (ECMO) in a previously healthy young man with HLH and acute respiratory distress syndrome (ARDS), a common sequela of HLH. ECMO was employed to provide temporary hemodynamic support, allowing for recovery of pulmonary function compromised during the initial cytokine storm. Additionally, and perhaps more importantly, implementation of ECMO provided the time necessary for the eventual diagnosis and treatment of HLH.

Conclusions: Although limited case reports and case series suggest that the use of ECMO in pediatric patients with HLH is associated with high mortality, our experience suggests that ECMO should not be rejected as a supportive modality in adults with HLH who have potentially recoverable cardiopulmonary function. We believe that ECMO may be appropriately instituted in select patients with HLH, or in rapidly deteriorating patients with an unknown illness refractory to conventional therapy, to allow for end-organ recovery, to reach a diagnosis, and to administer appropriate therapy.

MeSH Keywords: Diagnosis, Differential • Extracorporeal Membrane Oxygenation • Lymphohistiocytosis, Hemophagocytic

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/899460

Background

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by the inappropriate prolonged activation of lymphocytes and macrophages [1], usually triggered by an underlying infectious illness or inflammatory process such as autoimmune conditions or malignancy [2]. The incidence of HLH is poorly characterized, as the symptoms of HLH closely resemble those of sepsis and oftentimes death occurs prior to diagnosis.

HLH is classified as one of the "cytokine storm" syndromes, as uncontrolled proliferation of lymphocytes and macrophages secretes excessive inflammatory cytokines. This results in rapid multi-organ failure. The term "hemophagocytic lymphohistiocytosis" describes the characteristic pathologic finding of macrophages engulfing blood cells in marrow, lymph nodes, spleen, and liver on biopsy; therefore, tissue biopsy aids in diagnosis. Diagnosis of HLH requires a minimum of five of eight characteristic findings: fever, splenomegaly, at least two peripheral cytopenias, hypertriglyceridemia or hypofibrinoginemia, elevated ferritin levels (as ferritin is secreted by macrophages), documented hemophagocytosis on bone marrow or lymphatic tissue biopsy, depressed natural killer cell function, and elevated CD25 levels [1]. Early diagnosis is essential, as treatment differs significantly from that of sepsis, and rapid deterioration and demise is almost universal if untreated.

Case Report

A previously healthy 21-year-old male with a recent exposure to infectious mononucleosis presented to an outside hospital with a 5-day history of lethargy, myalgia, anorexia, fever, sore throat, nonproductive cough, shortness of breath, and diarrhea. He reported testicular pain and fullness for two days. He had been treating himself with over-the-counter nonsteroidal anti-inflammatory medications with minimal relief.

Upon presentation to the outside hospital, he was intubated on admission day 1 secondary to worsening hypoxemia and chest imaging findings consistent with acute respiratory distress syndrome (ARDS). Workup at the time was negative for infectious mononucleosis, influenza A and B, group A streptococcus, as well as a 17-virus respiratory panel by polymerase chain reaction (PCR). Serologies for hepatitis A, B, and C and human immunodeficiency virus (HIV) were negative. Echocardiogram demonstrated mildly reduced left ventricular ejection fraction (50–55%) with mild inferior wall hypokinesis, trace mitral and tricuspid regurgitation, and mild dilation of the right ventricle. Venovenous (VV) extracorporeal membrane oxygenation (ECMO) was initiated three days after presentation secondary to worsening chest radiograph findings and refractory hypoxemia despite elevated fraction of inspired oxygen, muscle relaxation, and inhaled epoprostenol (Figure 1). ECMO was employed to provide adequate oxygenation in the setting of ARDS and to allow time for discovery of the underlying pathology responsible for his rapid deterioration. The patient was cannulated for VV ECMO via the right internal jugular vein and the right femoral vein using single bore cannulae appropriate to patient habitus. CARDIOHELP system™ (Maquet Getinge Group; Rasttat, Germany), a third generation Maquet pump, was employed. The system was equipped with a HLS Set Advanced 7.0 (Maquet Getinge Group; Rasttat, Germany) single use cartridge. Standard circuit was used to connect the pump to the cannulae without a bridge connector.

The patient's physical examination was remarkable for erythematous conjunctiva, dark discoloration and desquamation of the tips of the ears bilaterally, a macular truncal rash, petechiae on the upper extremities, and bilateral scrotal swelling and ecchymosis. Labs were remarkable for a white blood cell count of 6.9 thousand cells/mL, hemoglobin of 8.7 mg/dL, platelet count of 59 thousand cells/mL, ferritin of 13,548 ng/mL (reference 30–400 ng/mL), fibrinogen of 107 mg/dL (reference 170–410 mg/dL), total bilirubin of 4.6 mg/dL (indirect bilirubin of 3.5 mg/dL, direct bilirubin of 1.2 mg/dL), aspartate transaminase of 356 U/L, alanine transaminase of 251 U/L, and creatinine of 1.33 mg/dL. Beta-2 microglobulin levels were elevated, a finding consistent with lymphoma or multiple myeloma. Blood cultures did not grow bacteria, mycobacteria, or fungus after a total of four weeks of incubation, nor were parasites seen on blood smear.

Skin and bone marrow biopsies were performed in order to aid in diagnosis. Pathology of skin biopsies of his rash showed hyperkeratosis, spongiosis, and perivascular lymphocytic infiltrates, all nonspecific findings consistent with dermatomyositis and several other pathologies. A bone marrow biopsy showed hemophagocytosis and atypia. It also showed hyperplasia and cytologic atypia of the erythroid and megakaryocyte lineages, findings suggestive of an underlying myelodysplastic syndrome. Flow cytometry was negative for overt evidence of leukemia or lymphoproliferative disease.

At this point, the patient met five of eight criteria for diagnosis of HLH, including fever, at least two peripheral cytopenias, decreased fibrinogen levels, elevated ferritin levels, and hemophagocytosis on bone marrow biopsy. Intravenous (IV) dexamethasone therapy 20 mg was initiated. Progressive recovery was demonstrated by improvement in chest radiography, pulmonary compliance, and arterial oxyhemoglobin saturation on minimal ECMO settings (Figure 2). The patient was decannulated from ECMO four days after initiation of dexamethasone therapy and extubated two days thereafter. Treatment with chemotherapeutics or other immune-modulating medications was not employed given the patient's rapid improvement with

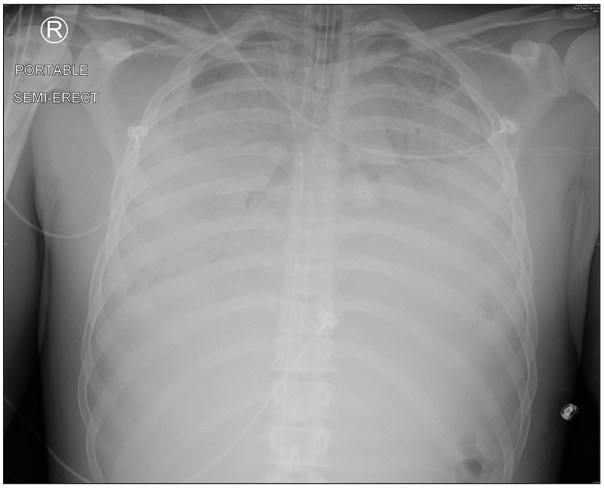

Figure 1. Chest radiograph at the time of ECMO cannulation demonstrating near complete opacification of both lungs and bilateral pleural effusions, consistent with severe ARDS.

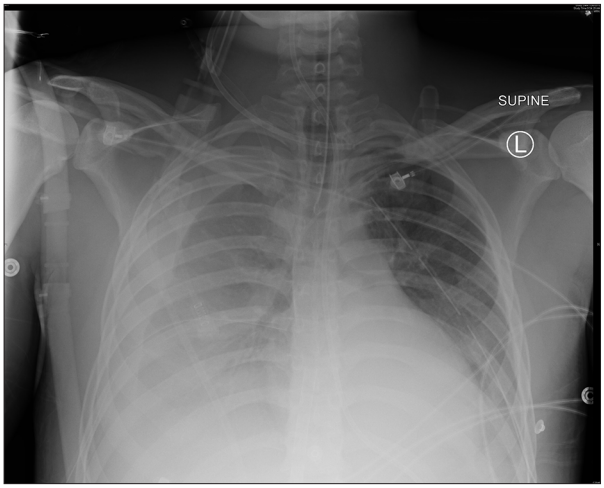

Figure 2. Chest radiograph at the time of ECMO decannulation.

dexamethasone therapy alone. He was transitioned from IV dexamethasone therapy to an oral prednisone taper, and eventually discharged from the hospital on oral prednisone until evaluated by an HLH specialist. The underlying trigger for HLH remains unclear. His exposure to infectious mononucleosis is an unlikely culprit, as laboratory testing for Epstein-Barr virus quantitation by PCR was negative.

Discussion

HLH is characterized as "primary" or "secondary" depending on the patient's age of presentation and family history of similar symptoms. As is the case of the patient described here, the secondary or acquired variant is seen in adolescents and adults without a clear family history of the disease.

With treatment, case series of adults with HLH report a 30-day mortality of 20–44% and an overall mortality of 50–75% [3–8]. Treatment of HLH is primarily supportive and includes immunemodulating therapies. Treatment protocols have been designed for HLH, and agents used individually or in combination include podophyllotoxin derivatives, glucocorticoids, etoposide, and cyclosporine [1]. It should be noted, however, that the use of chemotherapeutics, steroids, or other immunosuppressants such as those mentioned above may be extremely risky without the absolute exclusion of a pathogen-driven process. The immunosuppression that inevitably follows the administration of these agents may result in an unchecked propagation of the underlying infection if a pathogen-driven process is at play.

ECMO is a plausible strategy aimed at providing temporary support to victims of HLH, allowing them to recover the cardiac and/or pulmonary function compromised during the initial cytokine storm. This storm may be waited out and/or the aforementioned therapies may be implemented. There are few reports discussing the use of ECMO as a mechanism of supportive care in HLH, and the few that exist involve exclusively the pediatric population. Dharia and Noe [9] describe a case of a 7-year-old boy with a history of juvenile idiopathic arthritis and HLH in remission after chemotherapy treatment, who subsequently developed pulmonary alveolar proteinosis. ECMO was instituted, but the patient never regained pulmonary function and care was ultimately withdrawn with demise of the patient. Lucchese et al. [10] describe a case in which venous-arterial ECMO and pulse therapy with dexamethasone were instituted in a 4-year-old boy with suspected viral myocarditis and encephalitis. The child was gradually weaned from ECMO given improvement in cardiac function, but died shortly thereafter secondary to grade III heart block followed by asystole. Upon autopsy, a diagnosis of HLH was made.

In a case series describing 30 pediatric patients with HLH on ECMO, it was demonstrated that pediatric HLH patients on ECMO had worse survival than pediatric patients without HLH on ECMO (27% in HLH patients *vs.* 63% in non-HLH patients) [11]. This may be attributed to the fact that ECMO is a potent immunostimulator in and of itself. Alternatively, HLH patients who are placed on ECMO likely have multiple organs irreversibly damaged, making recovery almost impossible. This underlies the notion that ECMO may have unpredictable effects in patients with HLH. Currently, it is difficult to assess how a patient with HLH will respond to implementation of ECMO.

Taking all of the aforementioned into account, we believe that the process of selecting HLH patients, or patients with an unknown illness refractory to conventional therapy, for ECMO should not differ from that of the general recommendations for employing ECMO. In the case described, ECMO provided

the support necessary to recover pulmonary function in the setting of ARDS while giving us time to perform diagnostic studies. We believe that our patient would have died from refractory respiratory failure before a diagnosis of HLH could be made had ECMO not been instituted.

Conclusions

A high index of suspicion for HLH should be raised in rapidly deteriorating patients with a sepsis-like picture for whom conventional therapies fail to elicit a clinical response. ECMO may be employed as a mechanism for supportive care in order to allow for cardiopulmonary recovery from the initial cytokine storm and to allow time for diagnosis of HLH. Thereafter, immune-modulating therapies such as chemotherapeutics, steroids, and/or other immunosuppressants may be employed for definitive treatment. Although the limited case reports and case series suggest that the use of ECMO in pediatric patients with HLH is associated with high mortality, our experience suggests that ECMO should not be rejected as a supportive modality in adults with HLH who have potentially recoverable cardiopulmonary function.

Statement

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