Use of Extracorporeal Support in Hemophagocytic Lymphohistiocytosis Secondary to Ehrlichiosis

Amy Cheng, MD,[a] Feifei Williams, MD, FAAP,[a,b] James Fortenberry, MD, FAAP, MCCM,[a,b] Catherine Preissig, MD,[c] Steven Salinas, MS,[d] Pradip Kamat, MD, FAAP, MBA, FCCM[a,b]

Ehrlichiosis, caused by transmission of *Ehrlichia chaffeensis* to humans through the bite of an infected lone star tick, can lead to secondary hemophagocytic lymphohistiocytosis (HLH), a life-threatening condition caused by uncontrolled activation of the cellular immune system. We describe a child with HLH secondary to ehrlichiosis who developed multiorgan failure and was successfully managed with extracorporeal membrane oxygenation (ECMO). A 9-year-old boy developed headaches, fever, and sore throat after suspected tick exposure. He presented with pancytopenia, elevated ferritin, and soluble interleukin-2 receptor levels, all consistent with HLH. Bone marrow biopsy revealed hemophagocytosis. Polymerase chain reaction was positive for *E chaffeensis*. He developed acute kidney injury, coagulation failure, hepatic insufficiency, and progressive respiratory failure requiring intubation. Due to refractory hypoxemia, he was cannulated for veno-venous ECMO. Continuous veno-venous hemofiltration was used to manage acute kidney injury and fluid overload. He received doxycycline and dexamethasone/etoposide for treatment of ehrlichiosis and HLH, respectively. Plasma exchange was used for thrombocytopenia-associated multiple organ failure. The patient was decannulated after 140 hours of ECMO and subsequently transferred for inpatient rehabilitation after extubation. Review of the Extracorporeal Life Support Organization Registry database identified 6 patients with tickborne diseases who received ECMO for organ support (survival in 3 of 6); ehrlichiosis was not reported in any of these cases. ECMO likely allowed a platform for stabilization and additional therapeutic interventions in this patient.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease due to uncontrolled immune activation. HLH can be primary or secondary to an autoimmune process, immunodeficiency, malignancy, or infections. Isolated reports have described the development of HLH in patients with infection due to *Ehrlichia chaffeensis*, transmitted through the bite of an infected lone star tick.[1–3] The use of extracorporeal support to provide life-saving therapy in patients with multiple organ failure (MOF) due to *E chaffeensis*–induced HLH has not been previously reported. We describe the successful use of veno-venous (VV) extracorporeal membrane oxygenation (ECMO) in a child with MOF due to HLH secondary to *E chaffeensis*.

CASE REPORT

A previously well 9-year-old boy developed headache, fever (39°F),

[a]*Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia;* [b]*Department of Critical Care Medicine, Children's Healthcare of Atlanta at Egleston, Atlanta, Georgia;* [c]*Department of Critical Care Medicine, Children's Hospital Navicent Health, Macon, Georgia; and* [d]*University of Georgia, Athens, Georgia*

Dr Cheng drafted the initial manuscript and revised the manuscript; Drs Williams, Fortenberry, and Kamat critically reviewed and revised the manuscript; Dr Preissig reviewed and revised the manuscript and provided the pathology slides; Mr Salinas drafted the life cycle figure; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Amy Cheng, MD, Pediatric Emergency Medicine, Emory University School of Medicine, 1645 Tullie Circle, Atlanta, GA 30329. E-mail: aychen5@emory.edu

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chills, and sore throat after suspected tick exposure. He was taken for emergency care 4 days after the onset of symptoms. On presentation, he was lethargic, with pallor and hepatomegaly. Laboratory evaluation revealed pancytopenia (white count 2.7×10^9/L, hemoglobin 8.2 gm/dL, platelet 68×10^9/L), transaminitis (aspartate transaminase 1304 mg/dL, and alanine transaminase 183 mg/dL), coagulopathy (prothrombin time 20.4 seconds), hyperferritinemia (>40 000 ng/mL), elevated soluble interleukin-2 receptor (3022 pg/mL), high serum triglyceride (161 mg/dL), and decreased serum fibrinogen (138 mg/dL). Bone marrow biopsy revealed hemophagocytosis. He received intravenous (IV) vancomycin, ceftriaxone, and doxycycline for empirical antibiotic coverage. Polymerase chain reaction testing for *E chaffeensis* was positive. HLH was also suspected, as he met 5 of 8 criteria (Table 1), and dexamethasone was added for treatment. HLH genetic panel (perforin, Munc 13-4, and Munc 18-2) was subsequently negative, as were HIV-1 p24 antigen and HIV-1,2 antibodies. Polymerase chain reaction testing for adenovirus, cytomegalovirus, and Epstein-Barr virus were negative, and flow cytometry of peripheral blood did not reveal a clonal population suggestive of leukemia.

Despite aggressive support at an outlying facility, the patient required intubation for acute respiratory failure. He developed a severe coagulopathy, hepatic insufficiency, and acute kidney injury (AKI). On transfer to our quaternary care PICU, high-frequency oscillatory ventilation (HFOV) was initiated and quickly escalated to maximum settings. Inhaled nitric oxide was started due to profound hypoxemia. He was hypotensive and required an epinephrine infusion to maintain mean arterial pressure >60 mm Hg. Echocardiogram showed a structurally normal heart with mildly decreased left ventricular ejection function of 45%. Due to the patient's rapid escalation of oxygenation index from 51 to 102 and his inability to maintain oxygen saturation >88%, ECMO was recommended. He was cannulated for VV ECMO via the right internal jugular vein with a 27-French bicaval dual lumen cannula (Avalon Elite; Maquet Cardiovascular, Wayne, NJ). Echocardiogram was used to guide cannula position, with the arterial port flow jet directed toward the tricuspid valve.

TABLE 1 Diagnostic Criteria for HLH[4]

Fulfillment of 5 of the 8 criteria listed below:
1. Fever
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood):
• Hemoglobin <9 g/100 mL (in infants <4 wk: hemoglobin <10 g/100 mL)
• Platelets $<100 \times 10^9$/L
• Neutrophils $<1 \times 10^9$/L
4. Hypertriglyceridemia (fasting, ≥265 mg/100 mL) and/or hypofibrinogenemia (≤150 mg/100 mL)
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent natural killer cell activity
7. Ferritin ≥500 ng/mL
8. Soluble CD25 (soluble interleukin-2 receptor) >2400 U/mL (or per local reference laboratory)

ECMO flow was initiated on a centrifugal pump with a diffusion membrane oxygenator (Quadrox-iD; Maquet Cardiovascular) at 500 mL/min and increased to a maximum rate of 3300 mL/min (120 mL/kg/min) over 15 minutes. His blood oxygen saturation quickly improved after ECMO cannulation. Initially, the patient was placed on rest ventilator settings of pressure-control ventilation with peak inspiratory pressure 25, positive end expiratory pressure 10, pressure support 10, rate 10, fraction of inspired oxygen 30%. On day 4 of ECMO, the patient developed several episodes of profound hematochezia, totaled >1 L in volume, and required packed red blood cells (PRBCs), fresh-frozen plasma (FFP), and platelet transfusion. Given the profound gastrointestinal (GI) bleed, the patient was switched to HFOV for lung recruitment as an effort to shorten the ECMO course in case it became necessary to discontinue ECMO emergently. HFOV was set to mean airway pressure 33, hertz 11, δ P 76, fraction of inspired oxygen 40%. These settings resulted in marked improvement in chest radiograph and allowed for a successful capping trial. On day 5, the patient had a flexible bronchoscopy to remove secretions occluding subsegmental bronchi.

Profound coagulopathy and GI bleeding, which began before cannulation, remained problematic during his ECMO course. He required transfusions with PRBCs, FFP, platelets, and activated recombinant factor VII (2 mg) to stabilize bleeding before cannulation. Additionally, the patient received a loading dose and continuous infusion of IV aminocaproic acid as well as IV phytonadione. Heparin infusion (10 U/kg/h) was titrated to maintain acceptable activated clotting time levels (average 159 seconds). Heparin assays (anti-Xa level) were maintained at the lower therapeutic range due to bleeding (average level 0.29 U/mL). Furthermore, GI bleeding on ECMO day 4 required heparin infusion to be held for 9 hours until bleeding status improved. Hematochezia was treated with PRBCs, platelets, and FFP transfusions.

He received doxycycline for treatment of ehrlichiosis, along with dexamethasone and etoposide for HLH during his ECMO course.

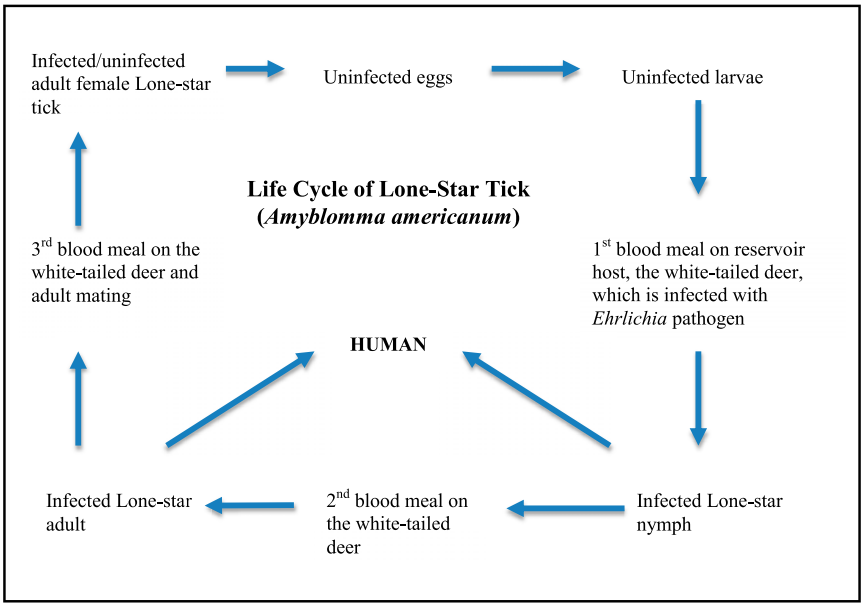

FIGURE 1
Life cycle of *E chaffeensis*.

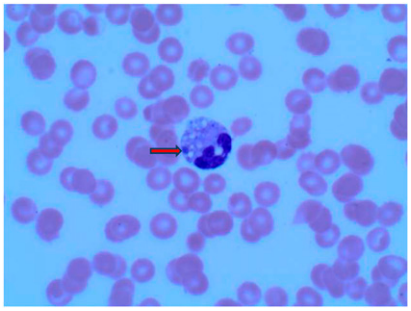

FIGURE 2
Patient's peripheral blood smear: note cytoplasmic inclusions consistent with *E chaffeensis* (Wright Giemsa Stain, 100x oil).

In addition, he received plasma exchange therapy (centrifugation technique, Spectra Optia; CardianBCT, Lakewood, CO) for 5 days after meeting criteria for thrombocytopenia-associated MOF (ADAMTS 13 activity was decreased at 47%). Plasma exchange was performed with all FFP at 1.5 plasma volume on the first day and 1.0 plasma volume on the subsequent days. Continuous VV hemofiltration was initiated via the ECMO circuit due to AKI and generalized anasarca.

The patient had a successful decannulation after 140 hours of ECMO support. Continuous VV hemofiltration was stopped after ECMO decannulation. His serum ferritin and soluble interleukin-2 receptor levels continue to trend downward. His cardiac, hepatic dysfunction, and AKI completely resolved. The patient was successfully extubated on day 33 of hospital admission and transferred to the general care floor on day 38. He was discharged to the inpatient rehabilitation center on day 52. The patient is neurologically intact, and he continues to show clinical improvement at subsequent follow-up visits.

To ascertain previous experience with use of ECMO in patients with tickborne diseases, *E chaffeensis* infection, and HLH, we queried the database of the Extracorporeal Life Support Organization by using *International Classification of Diseases, Ninth Revision* codes. The Extracorporeal Life Support Organization registry is the world's largest database for pediatric and adult patients receiving extracorporeal support.[5] Six patients were identified in the database with tickborne disease as the primary diagnosis requiring extracorporeal support. None of the patients had ehrlichiosis or coexistent HLH. Cases were reported from 1998 to 2012. Median patient age was 3.5 years. Veno-arterial ECMO was used in all the children, and 50% survived to discharge. Median duration of the ECMO run was 73 hours (range 14–148 hours).

DISCUSSION

HLH is a clinical syndrome caused by uncontrolled activation of the cellular immune system. This disease mainly involves macrophages and T-lymphocytes, resulting in upregulation of inflammatory cytokines. Although Epstein-Barr virus is the most common trigger for secondary HLH,[6,7] other infectious agents, such as bacteria, fungi, *Mycobacterium*, protozoa, and rickettsial infections, have been documented in the literature.[8,9] There are only a few documented pediatric cases of HLH secondary to ehrlichiosis.

E chaffeensis is an obligate intracellular pathogen transmitted to humans through the bite of an infected lone star tick (*Amblyomma americanum*), often found in the southeastern and south-central part of the United States. The tick becomes infective after feeding on its primary reservoir host, the white-tailed deer (*Odocoileus virginianus*) (Fig 1). *E chaffeensis* follows a lytic life cycle, and preferentially infects leukocytes once it enters a human's bloodstream (Fig 2). Typical incubation period is 1 to 2 weeks before symptom onset of fever, headache, fatigue, and muscle aches.

Ehrlichiosis should be considered in any pediatric patient with fevers after known or possible tick exposure. Severe disease due to ehrlichiosis is seen in children with underlying immunosuppressive conditions (chemotherapy, organ transplantation).[10] Delay in early

recognition and initiation of treatment have been associated with worse outcomes.[11] Treatment should be considered as soon as possible without waiting for advanced laboratory testing, as case fatality rate is 1% to 2%.[3,12]

The severity of our patient's presentation did not fit the typical paradigm for ehrlichiosis, particularly the degree of his acute respiratory failure and our inability to adequately provide oxygenation despite using maximum oscillator settings and inhaled nitric oxide. The development of secondary HLH was also unusual, with no previous report of these patients requiring ECMO support. From the onset, we provided aggressive interventions for the treatment of his multiorgan dysfunction. Initiation of VV ECMO stabilized the patient's respiratory status while allowing time for other therapeutic agents (corticosteroids, chemotherapy, and IV doxycycline) to treat HLH and ehrlichiosis. Various strategies were used to carefully balance coagulation while he was on ECMO support. Given the patient's severe GI bleeding, he was presumed to have excessive fibrinolysis. Aminocaproic acid was used to inhibit fibrinolysis, as it has been shown to decrease surgical bleeding in ECMO patients.[13] Although activated factor VII has been noted to be associated with thrombosis in a few case series, more recent literature did not find an increased rate of thromboembolic complications in patients under ECMO support.[14] Plasma exchange likely reversed MOF by decreasing circulating inflammatory cytokines and was useful in improving coagulopathy.

The aim of etoposide and dexamethasone is to suppress the inflammatory response and control cell proliferation. Although this patient had a positive outcome on this treatment regimen, previous study has shown that less immunosuppressive and cytotoxic therapies, such as methylprednisone and IV immunoglobulin may have less toxic effects and better survival rates.[15] Because there are currently no randomized controlled trials, more studies are warranted.

CONCLUSIONS

We report the first successful use of VV ECMO to support a child with severe MOF due to HLH secondary to ehrlichiosis. In our patient, ECMO allowed a platform for stabilization and time for additional therapeutic interventions.

ABBREVIATIONS

AKI: acute kidney injury
ECMO: extracorporeal membrane oxygenation
FFP: fresh-frozen plasma
GI: gastrointestinal
HFOV: high-frequency oscillatory ventilation
HLH: hemophagocytic lymphohistiocytosis
IV: intravenous
MOF: multiple organ failure
PRBCs: packed red blood cells
VV: veno-venous

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