CASE REPORT

Rare Case of Refractory Hypoxia and Severe Multiorgan Failure from Secondary Lymphohistiocytosis Successfully Bridged to Treatment with Extracorporeal Membrane Oxygenation Support

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Abstract

Introduction: Acute respiratory distress syndrome (ARDS) is an uncommon complication of hemophagocytic lymphohistiocytosis (HLH). Non-specific findings that mimic other diseases make timely diagnosis and treatment challenging. We present a rare case of severe ARDS and multiorgan failure from secondary HLH due to peripheral T-cell lymphoma.

Case presentation: A middle-aged female presented with dry cough and fever for three days. On presentation, the patient was febrile to 105°F and hypoxic to 88% on room air. Chest X-ray showed bilateral interstitial infiltrates. Laboratory investigations showed lymphopenia and elevated inflammatory markers. The viral panel, including coronavirus disease-2019 (COVID-19), influenza, and respiratory syncytial virus (RSV), was negative. Her respiratory status progressively worsened, requiring invasive mechanical ventilation for ARDS. Despite lung-protective ventilation, prone positioning, and the use of paralytic agents, the patient continued to remain hypoxic, necessitating extracorporeal membrane oxygenation (ECMO) support. The patient was started on antibiotics and high-dose steroid. Thereafter, she developed a leukemoid reaction, and the ferritin level started rising; raising suspicion for lymphophagocytosis. During this time, she also developed acute liver and kidney failure and required multiple vasopressors and renal replacement therapy. Eventually, a diagnosis of mature peripheral T-cell lymphoma was established. Subsequently, her respiratory status and multiorgan failure significantly improved, and ECMO was explanted after 2 weeks. She was started on etoposide and steroid, and eventually discharged after 6 weeks.

Discussion: This is the first case describing a successful implementation of ECMO in an adult diagnosed with ARDS secondary to mature peripheral T-cell lymphoma; allowing for recovery of respiratory status, which was compromised during the initial cytokine storm and provided time to establish the diagnosis and initiate appropriate treatment of secondary HLH mature due to peripheral T-cell lymphoma, and in the end, prevented a fatality. We believe that ECMO may be appropriately instituted 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.

Keywords: Acute respiratory distress syndrome, Extracorporeal membrane oxygenation, Hemophagocytic lymphohistiocytosis, Multiorgan failure, T-cell lymphoma.

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Highlights

Hemophagocytic lymphohistiocytosis is a rare, fatal disorder resulting in multiorgan failure and ARDS is an uncommon complication. Successful implementation of extracorporeal membrane oxygenation in rapidly deteriorating patients with an unknown illness refractory to conventional therapy can allow for end-organ recovery, reach a diagnosis, and administer treatment.

Introduction

Acute respiratory distress syndrome is an uncommon complication of HLH. Non-specific findings that mimic other diseases make timely diagnosis and treatment challenging. We present a rare case of severe ARDS and multiorgan failure from secondary HLH due to peripheral T-cell lymphoma.

This is the first case describing a successful implementation of ECMO in an adult diagnosed with ARDS secondary to mature peripheral T-cell lymphoma, allowing for recovery of respiratory status, which was compromised during the initial cytokine storm and provided time to establish the diagnosis and initiate appropriate treatment of secondary HLH mature due to peripheral T-cell lymphoma, and in the end, prevented a fatality. We believe that ECMO may be appropriately instituted in rapidly deteriorating patients with an unknown illness refractory

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Statement of Ethics: This is a case report and does not contain any images or patient identifying information.

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Conflict of interest: None

Table 1: Infectious and rheumatological investigational studies

SARS-CoV-19	Negative	Histone antibody	Negative
Influenza virus A and B	Negative	Jo-1 antibody	Negative
Adenovirus antibody	Negative	La SSB antibody	Negative
Cytomegalovirus	Positive IgG	Ro SSA antibody	Negative
Mycoplasma	Negative	Scl-70 antibody	Negative
Herpes simplex virus 1 antibody	Positive	Myeloperoxidase antibody	Negative
Herpes simplex virus 2 antibody	Negative	Double-stranded DNA antibody	Negative
Viral culture HSV 1 and 2	Negative	Centromere antibody	Negative
Varicella culture	Negative	Cyclic citrullinated peptide antibody	Negative
HIV 1/2 Ag/Ab	Negative	Antinuclear antibody	Negative
HTLV I/II antibody screen	Negative	Smith antibody	Negative
Hepatitis B virus surface antibody	Negative	Proteinase 3 antibody	Negative

to conventional therapy to allow for end-organ recovery, reach a diagnosis, and administer appropriate treatment.

Hemophagocytic lymphohistiocytosis is a rare, fatal disorder characterized by extreme immune activation due to inadequate downregulation of lymphocytes and macrophages, resulting in multiorgan failure.[1] Despite this, ARDS is an uncommon complication of HLH. Herein, we describe a case of T-cell lymphoproliferative disorder in an adult presenting as severe ARDS and multiorgan failure from HLH, which was successfully bridged to treatment with venovenous extracorporeal membrane oxygenation support (VV-ECMO).

Case Presentation

A middle-aged female with Crohn's disease presented with a sudden onset of fever, nonproductive cough, and diffuse abdominal pain for three days. The patient was febrile to 105°F, blood pressure of 114/59 mm Hg, heart rate of 91 beats/minute, and oxygen saturation of 88% on room air. Laboratory investigations were significant for leukocyte count of 9900/µL, erythrocyte sedimentation rate of 56 mm/h, C-reactive protein of 20.49 mg/dL, lactic acid of 2.0 mmol/L, procalcitonin 0.74 ng/mL, and D-dimer of 1923 ng/mL. A viral respiratory panel including COVID-19 was negative. Chest X-ray was initially unrevealing. However, computed abdomen/pelvis tomography revealed diffuse bilateral ground-glass opacities.

On the night of admission, the patient developed worsening respiratory distress. Chest radiography was repeated, showing evidence of diffuse airspace disease consistent with ARDS. Given the ongoing COVID pandemic, steroids and Remdesivir were started. Due to persistent oxygen desaturations, she was intubated, and antibiotics were broadened. Despite maximum lung-protective ventilatory-support-prone positioning, the patient remained hypoxemic and demonstrated respiratory acidosis. In progressive respiratory insufficiency with a FiO_2 of 100% with shunting in her lungs and oxygen saturation of only 68% and increased vasopressor requirements, VV-ECMO was initiated on day three.

A bronchoscopy was performed to determine the underlying etiology of her ARDS. Inspection of her airways showed markedly abnormal airways with multiple areas of erythema, ecchymosis, and endobronchial mucosal sloughing. Additional workup for infectious and autoimmune etiologies was negative (Table 1). Following the initiation of VV-ECMO, she developed worsening kidney injury, and continuous venovenous hemofiltration (CVVH) was initiated.

The patient developed a leukemoid reaction with a leukocyte count of 73,400/µL, and ferritin level rose to 25,873 µg/L from an initial level of 12, raising suspicion for HLH (Fig. 1). Subsequently, she was started on Anakinra due to a suspected inflammatory condition. Further workup for HLH was conducted. Peripheral smear and flow cytometry revealed a normal T-cell clone with 54% circulating lymphocytes. Quantitative immunoglobulins and lymphocyte subsets were ordered to evaluate the underlying malignancy. Polymerase chain reaction (PCR) identified T-cell rearrangement (TCR) gamma gene rearrangement, demonstrating an aggressive T-cell mature lymphoproliferative neoplasm that was CD30/ALK(-).

The patient's clinical condition improved on Anakinra and steroids and was successfully decannulated from VV-ECMO 13 days after implantation and extubated to a high-flow nasal cannula (Fig. 1). For the remaining 3 weeks, she continued on high-dose steroids and etoposide. The patient was deemed stable for discharge 6 weeks following initial presentation, transitioning to oral steroid taper.

Discussion

The primary form of HLH is common in children and is sporadic or familial associated with autosomal-recessive gene mutation, whereas the secondary form occurs most commonly in adults and is associated with infections, hematological malignancies, autoimmune diseases, and drugs.[2,3] We present a secondary form of HLH caused by an aggressive peripheral T-cell lymphoma.

Our case highlights several unique and important features: first, to the best of our knowledge, this is a rare case of T-cell lymphoma presenting as ARDS, which turned out to be an HLH in an adult. A set of diagnostic criteria, HLH-2004 criteria, must be met to make the diagnosis. This is often challenging, as not all diagnostic criteria might be present and can be misdiagnosed as sepsis or multiorgan dysfunction syndrome.[3,4] This case illustrates the diagnostic difficulties that arise when determining the underlying etiology of a rapidly progressively deteriorating patient with an unknown illness and refractory to the conventional therapy; third, despite the overall reported very high mortality (up to 75%) of patients with HLH and poor prognostic features, including severe thrombocytopenia, clinical shock, and elevated ferritin levels, our patient did not benefit from ECMO but was successfully discharged from our hospital.[1,2]

The development of noninfectious adult respiratory distress syndrome by peripheral T-cell lymphoma caused by HLH is rare.[5–8] The underlying pathophysiology is not entirely understood, but

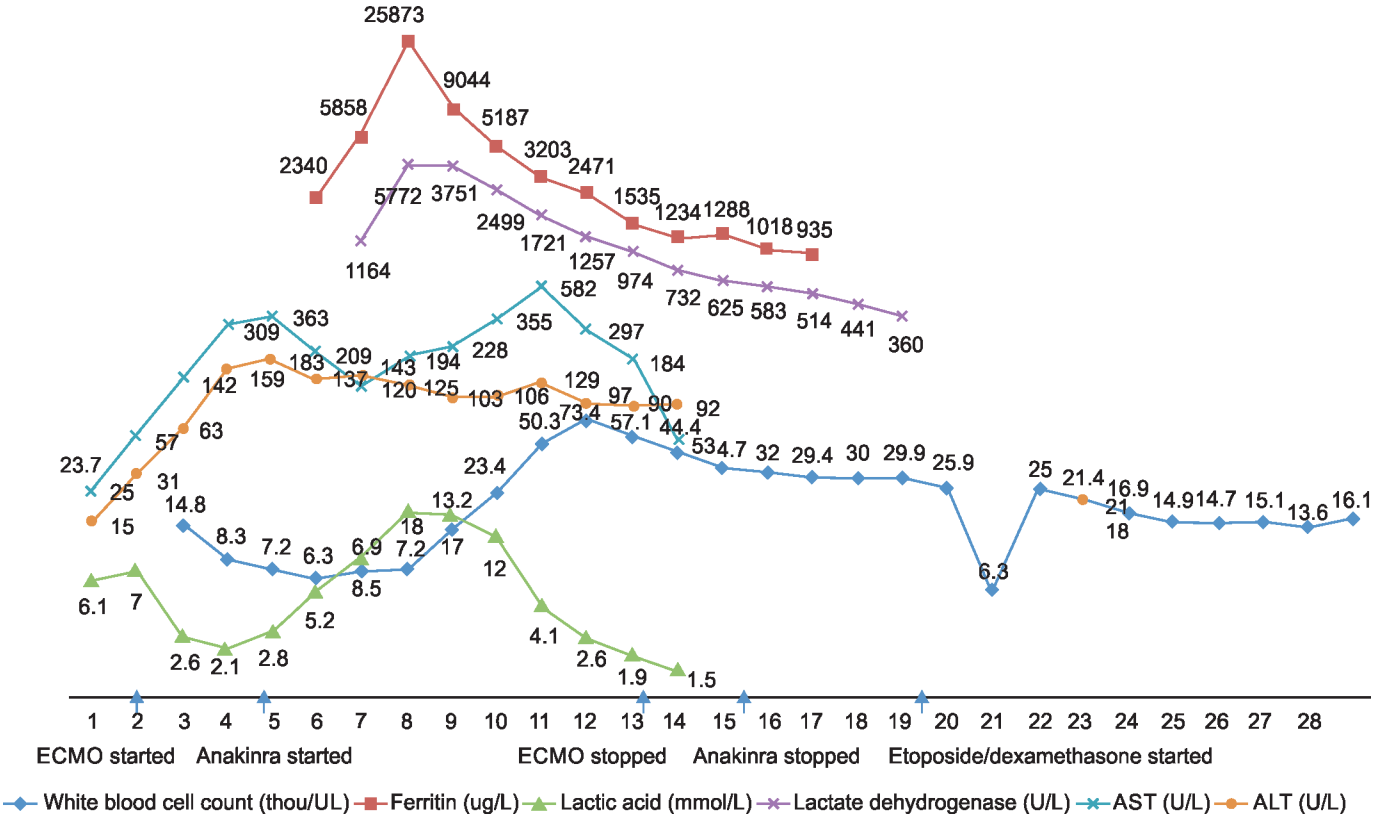

Fig. 1: Timeline of investigations and interventions

immune dysregulation is a major component.[8] The function of cytotoxic T cells and natural killer cells is impaired, leading to the activation of macrophages and the proliferation of cytokines.[8,9] While in ARDS, the permeability of the alveolar endothelial cells is altered by the cytokines, neutrophils, and macrophages, leading to alveolar hemorrhage.[8] Both ARDS and HLH are associated with high mortality rates and poor outcomes. A retrospective study from an intensive care unit in North India reported a 70% ICU mortality in patients diagnosed with HLH.[3]

Treatment includes supportive care and therapy to control the cytokine storm. Combination therapy with recombinant interleukin-one receptor antagonist, anakinra, methylprednisolone, and intravenous immunoglobulin is utilized as the first treatment option.[10] After stabilization, maintenance therapy can be continued, targeting the underlying etiology. Etoposide is preferred in malignancy-related HLH.[1] In severe and refractory cases, hematopoietic stem-cell transplant can be considered.[1]

Extracorporeal membrane oxygenation should be considered in rapidly deteriorating patients and developing refractory respiratory, and/or circulatory failure. It allows for end-organ recovery and provides additional time for diagnostic testing and therapeutic intervention. Extracorporeal membrane oxygenation improves survival by 50–70% in patients with acute respiratory failure.[6,7] It is difficult to assess the improvement in survival with ECMO implementation because HLH is a rapidly progressive disease, leading to irreversible organ damage. Any delay in treatment can lead to poor outcomes even with ECMO.

Conclusion

This is the first case describing a successful implementation of ECMO in an adult diagnosed with ARDS secondary to mature peripheral T-cell lymphoma. Our patient had several signs of poor prognosis at the time of presentation; however, an early heightened suspicion for HLH along with prompt initiation of immunosuppressive therapy due to a multidisciplinary approach led to a positive outcome.

Author Contributions

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