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Case Report

Acute Respiratory Distress Syndrome from Hemophagocytic Lympho Histiocytosis: A Case Report

Kramer B[1]*, Heard C[2] and Al-Ibrahim O[1]

[1]Department of Pediatrics, Statue University of New York at Buffalo School of Medicine and Biomedical Sciences, USA

[2]Department of Anesthesiology, Statue University of New York at Buffalo School of Medicine and Biomedical Sciences, USA

***Corresponding author:** Kramer B, Department of Pediatrics, Statue University of New York at Buffalo School of Medicine and Biomedical Sciences, Women and Children's Hospital of Buffalo, 219 Bryant St., Buffalo, NY 14222, USA

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Abstract

Hemophagocytic Lympho Histiocytosis is a syndrome that is life-threatening. Initial symptoms mimic common infections making diagnosis a challenge. Many patients have clinical findings similar to acute respiratory distress syndrome.

A 13 y.o. female was brought with complaints of fatigue, fever, and cough. Her examination revealed a cachectic appearance, lower lob crackles, and cervical lymphadenopathy. Her labs revealed pancytopenia. A CXR showed pulmonary nodules. She was diagnosed with pancytopenia, hypoxia, and malnourishment. All labs were negative except for persistent pancytopenia, hypofibrinogenemia and suppressed NK-cell activity; she underwent a bone marrow biopsy and was diagnosed with HLH. On day 10, she experienced a decompensation in and was subsequently intubated for ARDS. Then, her course was further complicated by a pulmonary hemorrhage. On day 18 she became acutely hypoxic. The patient was cannulated for ECMO and started on Etoposide and steroids for treatment of HLH. She received chemotherapy while on ECMO and showed significant improvement. After 7 days of ECMO support, the patient was decannulated and eventually discharged home.

This case illustrates the potential for ARDS as a mode of death in HLH. Timely initiation of ECMO can improve the survival of these patients by buying more time for the treatment of the illness.

Keywords: Hemophagocytic lympho histiocytosis; Acute respiratory distress syndrome; Extracorporeal membrane oxygenation

Abbreviations

Hemophagocytic Lympho Histiocytosis (HLH); Human Immunodeficiency Virus (HIV); Acute Respiratory Distress Syndrome (ARDS); Natural Killer (NK); InterLeukin (IL); Extra Corporeal Membrane Oxygenation (ECMO); VenoArterial (VA); Prothrombin Time (PT); International Normalized Ratio (INR); Partial Thromboplastin Time (PTT); Erythrocyte Sedimentation Rate (ESR); Lactate DeHydrogenase (LDH); Computerized Tomography (CT); Purified Protein Derivative (PPD); Cluster of Differentiation (CD); Perinuclear Pattern AntiNeutrophil Cytoplasmic Antibodies (p-ANCA)

Case Presentation

Hemophagocytic Lympho Histiocytosis (HLH) is a familial or a viral-associated hemophagocytic syndrome that is aggressive and potentially life-threatening. The estimated incidence is 1 in 50,000-100,000 live births [1]. While most cases affect infants between birth and 18 months, there are patients with HLH occurring secondary to other condition such as viral, bacterial, or fungal illnesses, autoimmune disease, or lymphoma. The most common infections associated with HLH are Epstein-Barr virus, cytomegalovirus, parvovirus, varicella-zoster, HIV, gram negative bacteria, tuberculosis, and fungal infections [2,3,4]. Initial signs and symptoms of HLH mimic common infections, hepatitis, multiorgan failure syndrome, and/or encephalitis. In one study [5], prominent early clinical signs included: fever (91%), hepatomegaly (90%), splenomegaly (84%), neurologic symptoms (47%), rash (43%), and lymphadenopathy (42%). Many patients have clinical and radiologic findings similar to Acute Respiratory Distress Syndrome (ARDS) [6], with alveolar opacities and pleural effusions.

Diagnostic criteria for HLH is defined by a set of presenting major signs and symptom [7] that include fever, splenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia, hypofibrinogenemia, and tissue demonstration of hemophagocytosis. Additional criteria include low or absent NK-cell activity, elevated serum ferritin concentration, and elevated soluble IL-2 receptor levels.

After querying the Extracorporeal Life Support Organization registry, we found that there are only 12 reported cases of HLH placed on ECMO, with only 3 of these patients surviving (Table 1). We report a case of a patient with HLH who was placed on ECMO and survived. Our patient is a 13 year old, 36 kg; previously healthy female was brought to Women and Children's Hospital of Buffalo with complaints of weight loss, anorexia, fatigue, fevers, and cough. She has no past medical or surgical history and was taking no medications at the time of admission other than over the counter antipyretics. Her immunizations were up to date at the time of admission. Her family history is remarkable for a twin sister who is healthy and a mother who had Human Immunodeficiency Virus (HIV), but died from a homicide. Socially she lives with her father, twin sister, father's fiancée, and the fiancée's two young children. She is currently in 9th grade and doing well in school. She denies drugs, alcohol, or tobacco as well as any sexual activity. Her physical exam at the time of admission

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Table 1: ELSO Registry of diagnosis of hemophagocytic syndromes.

Patient	Primary Diagnosis	Secondary Diagnosis	Mode	Support Type	Hours On	Reason for Discontinuation	ECLS Year
1	Hemophagocytic Syndrome		VA	Pulmonary	101	Lung Recovery	2007
2	Primary PHTN	Hemophagocytic Syndrome	VA+V	ECPR	124	Lung Recovery	2007
3	Hemophagocytic Syndrome		VA	ECPR	194	Died-Organ Failure	2007
4	Hemophagocytic Syndrome		VA	Pulmonary	141	Died-Organ Failure	2009
5	RSV Pneumonia	Hemophagocytic Syndrome	VVDL	Pulmonary	473	Lung Recovery	2009
6	Other Alveolar Pneumonopathy	Hemophagocytic Syndrome	VA	Pulmonary	70	Died-Organ Failure	2009
7	Hydropsfetalis	Hemophagocytic Syndrome	VA	Pulmonary	361	Lung Recovery	2009
8	Parvovirus B10	Hemophagocytic Syndrome	VVDL+V	Pulmonary	120	Died-Dx Incompatible w/ Life	2009
9	Osteoarthosis	Hemophagocytic Syndrome	VA	ECPR	44	Died-Organ Failure	2010
10	Adenovirus Pneumonia	Hemophagocytic Syndrome	VVDL	Pulmonary	323	Died-Organ Failure	2010
11	Myeloid Leukemia	Hemophagocytic Syndrome	VV	Pulmonary	166	Lung Recovery	2010
12	Hemophagocytic Syndrome		VA+V	Pulmonary	104	Died-Organ Failure	2010
13	ARDS	Hemophagocytic Syndrome	VA	Pulmonary	159	Lung Recovery	2011

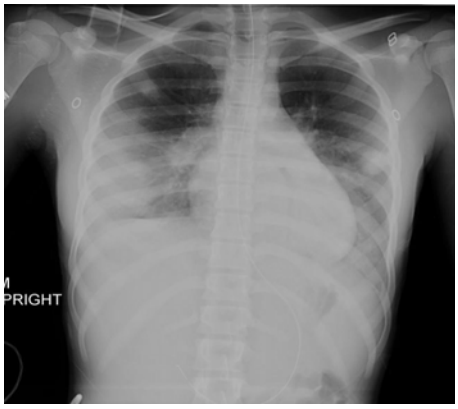

Figure 1: CXR.

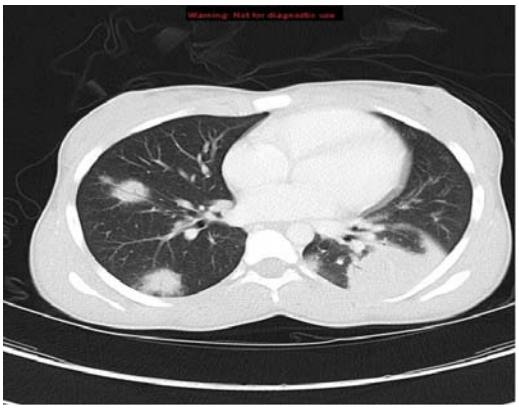

Figure 2: CT Chest.

was positive for a generalized cachectic appearance, crackles over her left lower lung fields, and bilateral cervical lymphadenopathy. She did have hepatosplenomegaly as well. She had no notable rashes or bruises and the remainder of her presenting physical exam was normal. Her initial labs revealed a white count of 2.2 (56% neutrophils, 22% bands, and 17% lymphocytes), hemoglobin of 10.5 g/dL, platelets of 136 x10^9/L, normal PT, PTT, INR, and an elevated ESR (55 mm/hr) and LDH (398 units/L). The remainder of her complete metabolic profile, Uric Acid, and urinalysis were normal. She had a chest radiograph (Figure 1) that demonstrated multiple bilateral pulmonary nodules and a CT chest (Figure 2) with similar findings.

Upon admission, she was diagnosed with an infectious process, likely pneumonia of either bacterial or fungal etiology, pancytopenia, hypoxia, hypotension, dehydration, and malnourishment with the intent to rule out a malignancy or autoimmune process. She was admitted to the pediatric ward and started on intravenous antibiotics and antifungals. She continued her work-up for malignancy, immunodeficiency, and/or rheumatologic diseases. All lab tests, including multiple bacterial and fungal cultures, PPD testing and HIV testing, were negative except for her persistent pancytopenia, suppressed serum CD3, CD4, and CD8 levels, positive pANCA, hypertriglyceridemia, hypofibrinogenemia, suppressed NK-cell activity, elevated serum ferritin concentration, and elevated soluble IL-2 receptor levels. She also underwent a bone marrow biopsy demonstrated macrophages containing phagocytosed red blood cells and was eventually diagnosed with HLH.

On day 10 of her hospital stay, she experienced an acute decompensation in her respiratory status manifested as shortness of breath, hypoxia, and increased work of breathing and was subsequently transferred to the pediatric Intensive Care Unit. Despite aggressive respiratory support, the patient required intubation for acute respiratory failure &ARDS, 48 hours later. A trial of plasma pheresis was attempted with unclear change in clinical symptoms. Her course was further complicated by a pulmonary hemorrhage and worsening hypoxia. On hospital day 18 she became acutely more hypoxic and developed pulmonary edema which necessitated a dramatic increase in her ventilator settings resulting in an oxygen index of 59. Her chest radiograph showed diffuse alveolar infiltrates consistent with progression of her ARDS and underlying disease process, suspected at the time to be either macrophage activation syndrome or hemophagocytic lympho histiocytosis. The patient was placed on VA ECMO and immediately started on chemotherapy with Etoposide and high dose steroids for treatment of HLH. She received 3 doses of chemotherapy while on ECMO and showed significant

improvement over one week. After 159 hours of VA ECMO support, the patient was successfully decannulated off ECMO support. She remained intubated for another week and then was successfully extubated. She was eventually discharged to home after completing 8 weeks of chemotherapy. She completed monthly outpatient chemotherapy for a subsequent 8 months. Her repeat bone marrow biopsy showed complete remission of her hemophagocytosis.

This patient had a complex presentation that mimicked other disease processes, as commonly seen in HLH. Our patient presented with clinical signs and symptoms consistent with either an infectious problem of bacterial, fungal, or viral nature or an immune compromised state. This was concerning given her family history of a parent with HIV. In the differential was also the possibility of an underlying rheumatologic disorder. All these diagnoses are in the differential for hemophagocytic lympho histiocytosis. The patient presented with pancytopenia and an elevated LDH. This was suspicious for HLH and led to further laboratory tests that aided in the diagnosis. It was ultimately her multiple lab tests that convinced the team to treat the patient for HLH once she was placed onto ECMO. Shortly after being placed on ECMO, her bone marrow biopsy confirmed the diagnosis. As reported in the literature [1], most diagnosis of HLH is made post-mortem and requires a high level of suspicion to make the diagnosis.

This case illustrates the potential for ARDS as a secondary result of hemophagocytic lympho histiocytosis and the value of ECMO as part of the management. Without the benefit that extracorporeal life support provided to this patient, she would have died. With acute respiratory failure, ECMO has been shown to improve survival by 50-70% [8] because it is a novel therapy that helps support failing organ systems. In addition to supporting failing organs, the allowance of more time is another important benefit of extracorporeal support. By placing this patient on ECMO, the team was given more time to treat her underlying condition and reverse her respiratory compromise from ARDS. Although HLH is rare, the respiratory complications *are* predictable. Recognition of these reversible complications, and timely placement onto ECMO, can facilitate the survival of these patients by allowing more time for the treatment of the primary illness.

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