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Hemophagocytic Lymphohistiocytosis Complicated by Acute Respiratory Distress Syndrome and Multiorgan Failure

Louisa Liu, MD[1], Hanad Bashir, MD[2], Hassan Awada, MD[2], Jafar Alzubi, MD[2], and Jason Lane, MD[2]

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition that is characterized by an overactive response of the immune system with excessive production of proinflammatory cytokines. Initial presentation of this condition often mimics and overlaps with many diseases including infections, sepsis, and multiorgan failure syndrome, which makes diagnosis the diagnosis of HLH challenging. Herein is described a case of a patient who developed acute respiratory distress syndrome and multiple organ failure related to HLH in a setting of probable viral pneumonia. The diagnosis was established based on laboratory and bone marrow biopsy findings. This patient was treated with the standard chemotherapy regimen of intravenous dexamethasone, etoposide in addition to intrathecal methotrexate for central nervous system involvement.

Keywords

hematology oncology, pulmonary critical care, hemophagocytic lymphohistiocytosis, acute respiratory distress syndrome, multiorgan failure

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition that is characterized by an overactive and abnormal response of the immune system with excessive production of proinflammatory cytokines.[1] The diagnosis of this condition is challenging because of its nonspecific signs and symptoms that often mimic other disease processes, for instance, infectious diseases.[2] Acute respiratory distress syndrome (ARDS) is a rare and life-threatening presentation of HLH and only a few cases have been reported in the literature to date. Herein is described a case of a patient who developed ARDS and multiple organ failure related to HLH in a setting of probable viral pneumonia. This patient was treated with the standard chemotherapy regimen.

Case Presentation

A 74-year-old female with a past medical history significant for ulcerative colitis s/p remote colectomy and ileostomy and hypertension presented to the emergency department (ED) with fatigue, myalgia, and confusion. On presentation, she had a temperature of 100°F, blood pressure of 108/60 mmHg, heart rate of 106 beats per minute (bpm), and respiratory rate of 20 breaths per minute. She was disoriented to the surrounding environment, but her neurologic examination was otherwise unremarkable. Upon cardiac auscultation, she had normal S1 and S2 without murmurs, gallops or rubs. Lung auscultation revealed decreased breath sounds on lung bases without crackles or rales. Initial lab analysis was significant for sodium of 128 (136-145 mEq/L), creatinine of 1.21 (0.51-0.95 mg/dL), and elevated lactate at 3.0 (0.4-2.0 mEq/L) with urinalysis suggestive of urinary tract infection (UTI). Complete blood count (CBC) showed a white blood cell count of 8.8 (3.98-10.04 k/cmm), hemoglobin of 15.1 (11.2-15.7g/dL), and platelet count of 131 (147-409 k/cmm). Computed tomography (CT) of the brain and initial chest X-ray were unremarkable for any acute abnormality. She was resuscitated with intravenous fluid and started on IV ceftriaxone for suspected UTI, and admitted for treatment of sepsis secondary to UTI and delirium. The patient was discharged after 3 days of hospitalization following improvement of mentation to baseline and resolution of her acute kidney injury (AKI), hyponatremia, and lactic acidosis.

[1]University of California, Riverside, USA
[2]Akron General Health System, OH, USA

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Corresponding Author:
Louisa Liu, MD, University of California, Riverside, Internal Medicine, 26520 Cactus Ave, Moreno Valley, CA 92555, USA.
Email: louisal@medsch.ucr.edu

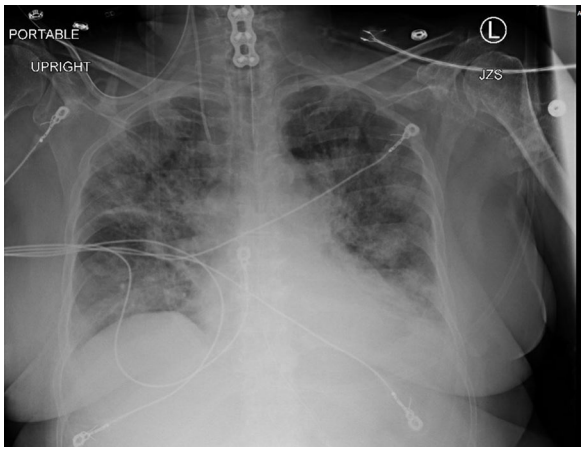

Figure 1. Patient's chest radiograph demonstrating bilateral diffuse infiltrates consistent with acute respiratory distress syndrome.

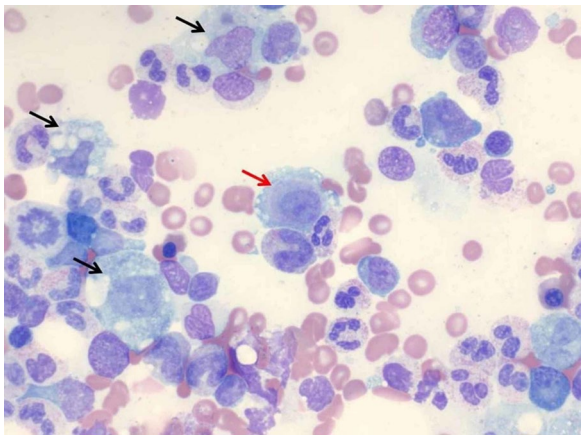

Figure 2. Wright stain aspirate smear of bone marrow
Histiocytes are noted to be increased (black arrows) demonstrating evidence of hemophagocytosis, with one histiocyte showing ingestion of an immature granulocyte (red arrow).

Two days later, the patient returned to the ED with complaint of significant weakness and inability to ambulate. Upon return to the ED, her vital signs were notable for an elevated temperature of 103°F, heart rate of 115 bpm, blood pressure of 90/65 mmHg, and respiratory rate of 24 breaths per minute with normal mental status. Lab analysis was significant for a white blood cell count of 3.31 (3.98-10.04 k/cmm), hemoglobin of 13.2 (11.2-15.7 g/dL), platelet count of 60 (147-409 k/cmm), and lactic acid of 5.4 (0.4-2.0 mEq/L). Other labs showed aspartate transaminase (AST) of 237 (15-37 U/L), alanine transaminase (ALT) of 189 (12-78 U/L), and alkaline phosphatase of 146 (45-117 U/L. Chest X-ray showed right middle lobe infiltrates; hence, she was started on vancomycin and piperacillin-tazobactam for possible hospital-acquired pneumonia and admitted to the medical floor. Four days after admission, she developed worsening respiratory status requiring noninvasive mechanical ventilation and was transferred to the medical intensive care unit. She was found to have bilateral pleural effusions on CT of the chest, and subsequently underwent a thoracentesis resulting in the removal of 750cc of exudative fluid. She became progressively hypoxemic with serial chest X-rays (Figure 1) showing bilateral interstitial infiltrates consistent with ARDS and ultimately required intubation. Despite empiric treatment with broad-spectrum antibiotics, the patient's fever persisted with a continuous decline in her state. Multiple blood, sputum, urine, and stool cultures were negative for bacterial, fungal, mycobacterial, and parasitic infections. Follow-up labs showed a white blood cell count of 1.4 (3.98-10.04 k/cmm), hemoglobin of 8.5 (11.2-15.7g/dL), platelet count of 45 (147-409 k/cmm) along with worsening kidney functions tests, with a creatinine of 2.1 (0.51-0.95mg/dL), and BUN of 65 (7-18mg/Dl). Moreover, liver transaminases had continued to rise to thousands and her jaundice worsened with remarkable coagulopathy and an elevated international normalized ratio (INR) at 8 (0.9-.1.3), consistent with acute liver injury (ALI). Moreover, Factor V and factor VIII activity assays were normal which ruled out disseminated intravascular coagulopathy (DIC). Abdominal ultrasound was unremarkable and magnetic resonance imaging (MRI) of the liver and pancreas showed no evidence of acute cholecystitis or biliary ductal dilation. Additional investigation showed significantly elevated LDH at 1367 (84-246U/L), elevated triglycerides at 808 (0-149mg/dL), fibrinogen of 240 (200-400mg/dL) and elevated ferritin at 40,000 (8-252 ng/mL). Secondary HLH was suspected with significantly elevated ferritin. Due to suspicion of HLH, a bone marrow biopsy was performed, which showed normocellular marrow with myeloid predominance, mild granulocyte atypia, and increased histiocytes (Figure 2). CD163 immunostaining of the core biopsy revealed markedly increased histiocytes with some cells showing ingested cellular material, which is consistent with HLH (Figure 3). Then, the patient was immediately started on an 8-week-regimen of dexamethasone and etoposide with subsequent improvement of her clinical status, cell counts and liver functions. To further investigate potential secondary causes of HLH, viral serologies were obtained, which were negative for human immunodeficiency virus (HIV), cytomegalovirus (CMV), Herpes simplex virus (HSV) type 1 and 2, Epstein-Barr virus (EBV), hepatitis B virus, and hepatitis C virus. Also, antinuclear antibody, double-stranded DNA antibody, rheumatoid factor, and autoimmune hepatitis workup were negative, ruling out the most common disorders associated with macrophage activation syndrome (MAS). Hereditary hemochromatosis was ruled out as the DNA assay for C282Y, H63D, and S65C loci of the gene HFE showed no mutations. Given these results, the

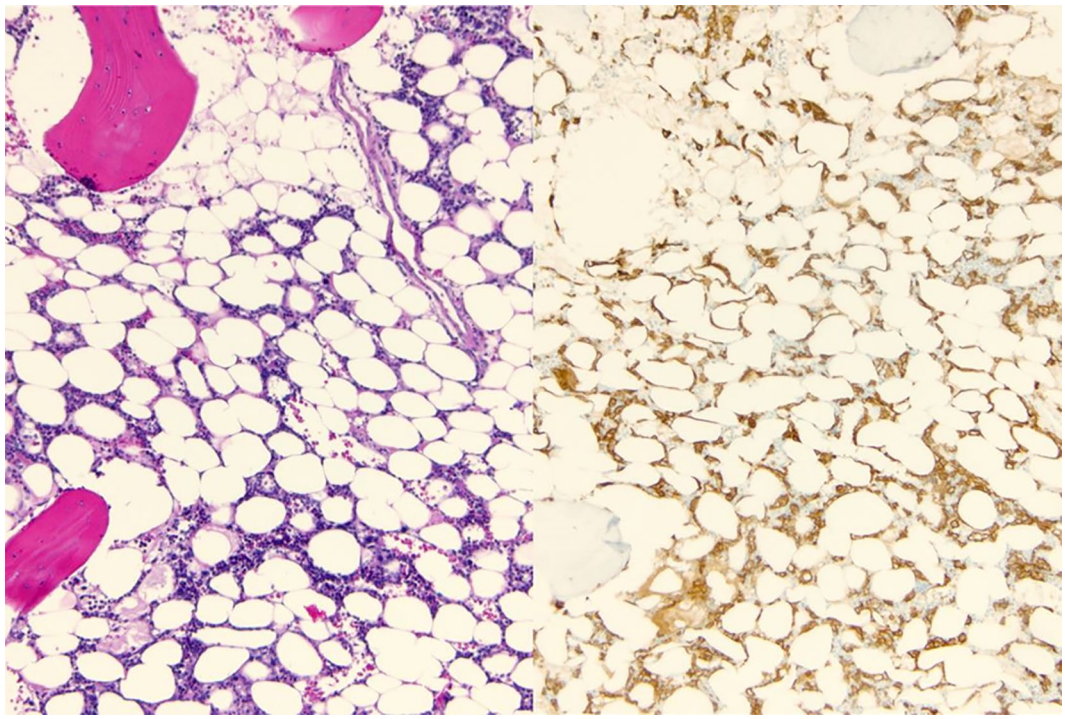

Figure 3. H&E and CD163 immunohistochemical stain of core bone marrow biopsy.
H&E stain showing normocellular marrow for age (approximately 30-35% cellularity). CD163 stain highlighting numerous histiocytes throughout the marrow space.

patient was diagnosed with HLH as she met 5 out of the 8 criteria (HLH-2004): fever, cytopenia of 2 cell lines, elevated ferritin>500 ng/mL, elevated fasting triglyceride >265 mg/dL and hemophagocytosis in bone marrow. Ultimately, patient's respiratory status improved and was weaned off mechanical ventilation. At discharge, her blood counts improved dramatically with normalization of liver enzymes. One month later, the patient was readmitted to the hospital with persistent confusion and was eventually diagnosed with HLH with central nervous system involvement based on worsening cognitive impairment and increased protein level and pleocytosis on cerebrospinal fluid. She was started on intrathecal methotrexate with not much improvement in her symptoms. The patient's family changed her goals of care to comfort care. The patient passed away 2 weeks later.

Discussion

Our patient initially presented with clinical signs and symptoms suggestive of infection. Despite treatment for severe sepsis with underlying possible pneumonia and urinary tract infection, the patient's clinical status deteriorated rapidly and she developed ARDS and ALI. She was later diagnosed with HLH, with no obvious infectious etiology, based on laboratory and bone marrow biopsy findings.

The true incidence and prevalence of HLH is unknown and remains difficult to establish accurately.[3] The diagnosis of HLH is challenging and often delayed because of its inconsistent presentation and the many nonspecific clinical features it shares with other disease processes. Currently, HLH is well described in the pediatric population, but less is known about the incidence and prevalence, appropriate workup and treatment, and pathophysiological mechanisms of the disease in adults. Most reported cases of HLH in adults have been described in association with viral infections, hematological malignancy; most commonly lymphoma, and autoimmune disease, with few reports documenting bacterial infection as the etiology.[4]

HLH is classified into primary and secondary forms. Primary HLH, or familial HLH, present in childhood, and is associated with certain gene mutations.[2] Secondary HLH or acquired HLH usually presents in adulthood and is acquired as a complication due to underlying conditions.[2] Left untreated, both forms of HLH may eventually progress to multi-organ failure and death. Without any treatment, the median survival for primary HLH is less than 2 months following diagnosis, while the prognosis for secondary HLH varies depending on the etiology.[3] The pathophysiology of HLH, whether primary or secondary, includes the defective function of natural killer (NK) cells

Table 1. HLH-2004 Diagnostic Criteria.

The diagnosis of HLH is established based on fulfilling one of the following criteria
A molecular diagnosis consistent with HLH
Five out of the following 8 criteria are fulfilled:
1. Fever .38.3c
2. Splenomegaly
3. Cyopenias (affecting at least 2 of 3 lineages in the peripheral blood)
4. Hypertriglyceridemia (fasting ?.265 mg/dL) or hypofibrinogenemia (5150 mg/dL)
5. Low or absent natural killer cell activity
6. Ferritin 500 ng/mL
7. Soluble CD252400 U/mL
8. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver

Abbreviation: HLH, Hemophagocytic lymphohistiocytosis.

and cytotoxic lymphocytes in eliminating activated macrophages.[5] This ultimately leads to the overactivity of macrophages with resulting excessive secretion of cytokines and interferon-gamma, which manifests with nonspecific signs, and symptoms of inflammation and even multiorgan failure, like our patient.[6] However, the immune system activation, in both primary and secondary forms, is intact with impaired the regulatory mechanisms responsible for the termination of the activated immune system. In our case, the patient initially had signs and symptoms suggestive of pneumonia, which triggered HLH and resulted in progression to severe systemic inflammatory response syndrome and multiorgan failure.

HLH often presents with nonspecific manifestations that mimic infections; however, our patient developed multiorgan failure with ARDS, ALI, and AKI, which is considered a rare presentation of HLH. HLH is often left out of the differential due to its nonspecific clinical presentation. As in our patient, the recognition of the disease can be challenging since its manifestation is often akin to septicemia. As such, it is important to include HLH in the differential diagnosis for patients with fever of unknown origin, ARDS, acute hepatitis or acute liver failure. Furthermore, a suspected case of HLH is difficult to confirm because there are currently no gold standard confirmatory tests. Therefore, it is important for systematic evaluation for both infectious and noninfectious agents in these patients.

Once other potential causes are ruled out, the diagnosis of HLH can be made utilizing the HLH-2004 criteria (Table 1).[7] In our case, the patient fulfilled 5 out of the 8-point diagnostic criteria for HLH including a fever of $>38.3°C$, 2 cell-line-cytopenia, hypertriglyceridemia, hyperferritinemia, and hemophagocytosis on bone marrow biopsy. It should be noted that HLH is an evolving diagnosis and that not all of the HLH diagnostic criteria may be met initially. Therefore, it is important to revisit the diagnosis frequently and to follow clinical signs and laboratory markers of pathologic inflammation, such as sCD25 and ferritin, repeatedly to diagnose potential HLH. It is also worth noting that the absence of hemophagocytosis in bone marrow does not rule out HLH in the presence of other signs, symptoms and laboratory findings suggestive of this condition.[8]

There was no suspicion for genetic predisposition in our patient. Therefore, we classified the patient as a case of secondary HLH. While she had a history of ulcerative colitis, she had a prophylactic colectomy and had not complained of any related symptoms before or during her hospital course. In addition, rheumatoid factor and autoimmune hepatitis workup had been negative, which ruled out autoimmune-associated HLH. All patients with suspected HLH should have a bone marrow biopsy, both to determine the cause of cytopenia as well as to detect hemophagocytosis. Our patient's bone marrow biopsy simultaneously demonstrated hemophagocytosis and ruled out malignancy. Lastly, we considered an infectious etiology. Among the infectious agents that trigger HLH, EBV is the most frequently reported virus that is associated with HLH.[9] Other infectious etiologies for secondary HLH described in the literature include CMV, HIV, human herpes virus, varicella-zoster, parainfluenza, and measles virus. Bacterial etiologies have been noted less commonly, but include mycobacteria, Brucella, Rickettsia, Serratia, and Haemophilus influenza, which were ruled out in our patient as well.[9] Although the viral serology in this patient was negative, serologic studies for viral infection in patients with the picture of a hemophagocytic syndrome may not be reliable because the impaired immune function may preclude a detectable antibody response.[10]

Once the cause is determined, therapy should be initiated promptly due to the high mortality rate associated with this condition if left untreated. Due to the life-threatening nature of the condition, timely diagnosis and treatment of HLH are paramount. While important, identifying and targeting the inciting infectious organism in infection-associated HLH is not adequate; these cases require aggressive management via standardized HLH protocols. Treatment according to HLH protocol involves targeting the excessive inflammation and immune dysregulation seen in the condition. Currently, the mainstay of treatment for HLH is immunosuppression with an 8-week-induction regimen, which includes etoposide and dexamethasone, which we initiated in our patient.[11] After eight weeks, many patients require treatment with pulses of dexamethasone. In many cases, hematopoietic stem cell

transplantation is needed if an adequate response is not achieved with the above regimen.[12] As it was true in our case, patients with central nervous system involvement require treatment with intrathecal methotrexate.[13]

Conclusions

In conclusion, this case illustrates various and rare presentations of HLH including ARDS and multiorgan failure. The true incidence of ARDS in adults diagnosed with HLH is still unknown. Hence, it is important to keep HLH in the differential diagnosis in patients presenting with acute respiratory failure and not responding adequately to appropriate antibiotic therapy. Early diagnosis and prompt treatment of this condition are crucial to prevent life-threatening organ failure. This patient was treated with a standard regimen of immunosuppressive therapy with resulting initial and dramatic improvement in her clinical condition and resolution of respiratory insufficiency.

Authors' Note

This case was previously published in abstract form and presented at the CHEST medical student and resident case report virtual conference October 18 to 21, 2020.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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