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Case Report

Hemophagocytic Lymphohistiocytosis Activation Syndrome with Multi-Organ Co-Infections: A Therapeutic Dilemma

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder caused by dysregulation of lymphocytes and histiocytes resulting in inflammation and multi-organ failure. Primary HLH is due to genetic mutations and typically presents in childhood. Secondary HLH is characterized by an inappropriately potent immune response to a triggering factor such as infection, malignancy, autoimmune disorders, macrophage activation syndrome, prolonged intravenous (IV) nutrition, and immunocompromised states.[1] Diagnosis of HLH requires five of the nine following criteria: fever; splenomegaly; cytopenia of two or more lineages; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen, lymph node, or liver; low or absent NK cell activity; elevated ferritin >500 ng/mL; elevated soluble CD25; and elevated CXCL9H.[2] In 2014, Fardet et al.,[3] developed the H-score through a multicenter retrospective study which estimates a risk of having HLH and is useful in distinguishing HLH from other proinflammatory states such as sepsis and malignancies when current guidelines are insufficient. HLH is a widely underrecognized phenomenon and its incidence is still undergoing investigation.

While HLH alone is a rare disease, HLH in combination with specific infections is rarer. During the COVID-19 pandemic, multiple case reports of post-infectious HLH were published and a retrospective study estimated that 20% of COVID-19 patients met criteria for secondary HLH.[4] Limited cases of HLH and TB have been published, with one study reporting only eight cases of combined HLH and TB out of 91 patients with infection-associated HLH.[5] All eight patients underwent antitubercular therapy and six of them were treated for both tuberculosis and HLH. A case report and literature review found 20 cases of HLH and Hepatitis A with various treatment strategies used.[6] After thorough literature review, we could not find any case reports of secondary HLH due to multiple simultaneous infections.

Current treatment guidelines for HLH include the use of etoposide, dexamethasone, and cyclosporine.[7] However, personalized management considering clinical presentation, laboratory findings, and presence of any infections is imperative for optimal patient care. Here we describe a young, previously healthy Sudanese patient who acquired HLH associated with tuberculosis, hepatitis A, and COVID-19 and who was successfully treated despite therapeutic challenges and multiple organ failure.

CASE REPORT

A previously healthy 34-year-old man was admitted to the intensive care unit with septic shock and multiple organ failure manifesting as poor oral intake, fever, altered mental status, anorexia, and dyspnea. He had alcohol use disorder but no other past medical history. He immigrated from Sudan eight years previously. He was employed at a meat processing plant.

Physical examination revealed a thin male who was awake and alert but disoriented. He had scleral icterus and dry mucosal membranes. Cardiac exam revealed tachycardia without murmurs. He had bilateral rales and rhonchi. His abdomen was soft and nontender but distended. His temperature was 35.8 degrees Celsius, heart rate 152 beats per minute with sinus rhythm, respiratory rate of 42 breaths per minute, blood pressure 114/75 mmHg on low dose norepinephrine, oxygen saturation 97% on heated high flow nasal cannula oxygen therapy at 30 liters with FiO2 of 70%.

He had leukopenia of WBC 2.6 x10^3/µL, elevated lactic acid at 4.3 mmol/L, hyperbilirubinemia of total bilirubin 4.3 mg/dL with direct bilirubin 3.48 mg/dL, elevated liver enzymes of aspartate transaminase (AST) 423 units/L, alanine transaminase (ALT) 495 units/L, alkaline phosphatase (ALP) 218 units/L, and normal ammonia level. Urine toxicology screen was positive only for benzodiazepines. His arterial blood gas and complete metabolic panel revealed acute respiratory acidosis and anion gap metabolic acidosis with hypoxic respiratory failure. COVID-19 PCR was positive. Microangiopathic hemolytic anemia was ruled out based on laboratory and peripheral blood smear findings. Computer tomography (CT) of the chest, abdomen, and pelvis without contrast revealed multifocal pneumonia, right-sided pleural effusion, cardiac enlargement, severe hepatosplenomegaly with steatosis, gallstones with pericholecystic fluid, enlarged kidneys, mesenteric edema, diffuse abdominal lymphadenopathy, and omental nodularity.

He was treated with six days of dexamethasone for COVID-19 pneumonia, but he could not receive remdesivir or tocilizumab due to acute hepatic injury. On hospital day two, acute decompensation required intubation and escalation of antibiotics. He developed worsening renal function requiring hemodialysis. Despite broad spectrum antibiotics and steroids, the patient continued to decline clinically, and his infectious work-up was expanded. Workup was negative for human immunodeficiency virus, hepatitis B, hepatitis C, syphilis, histoplasma, aspergillus, cryptococcus, candida, pneumocystis jirovecii, herpes simplex virus 1 and 2, cytomegalovirus, clostridium difficile, and malaria. His Epstein Barr virus serology was consistent with past exposure and immunity. A broad gastrointestinal stool polymerase chain reaction was negative. He had positive sputum cultures with pan-sensitive Klebsiella Pneumoniae, with antibiotics appropriately de-escalated. He had positive hepatitis A IgM serology. Additionally, interferon-gamma release assay (IGRA) was positive, raising concerns for latent versus active tuberculosis. Once acid-fast bacilli (AFB) cultures were reported positive a few days later, the patient was diagnosed with active tuberculosis.

Given initial concern for latent TB reactivation, his dexamethasone course for COVID-19 was discontinued prior to ABF cultures. Four-drug TB therapy was initiated, but it was discontinued after two days due to an immediate increase in bilirubin. Upon bilirubin improvement, treatment was restarted with rifampin, ethambutol, and pyrazinamide.

These drugs were started sequentially one drug at a time. Isoniazid was held due to concerns of persistently elevated liver enzymes. Levofloxacin was started in place of isoniazid after receipt of drug susceptibility report.

Concern for secondary hemophagocytic lymphohistiocytosis was raised as patient continued to experience worsening transaminitis, persistent fever, hepatomegaly, erythropenia, leukopenia, elevated ferritin of 77,455.2 ng/ml, elevated triglycerides of 252 mg/dl, and hypofibrinogenemia of 120 mg/dl. CXCL9 and soluble IL-1 receptor alpha were elevated at 232,385 pg/mL and 5867 units/mL, respectively. A bone marrow biopsy was planned; however, due to the patient's critical condition, it was deferred. Due to the uncertain diagnosis of HLH without bone marrow biopsy and pending inflammatory markers, H-score was calculated at 233 points, providing an approximate 97% probability of HLH in this patient. Empiric methylprednisolone was initiated. Etoposide was not initiated given his various infections, concurrent hepatic and renal impairment, and clinical improvement on steroids. He had required tracheostomy and percutaneous endoscopic gastrostomy which were removed before discharge. With recovery of renal function, the hemodialysis line was removed. He was discharged to a long-term care facility, continuing a steroid taper and a total of six months of anti-tuberculosis therapy with rifampin, ethambutol, pyrazinamide, and levofloxacin.

DISCUSSION

HLH is a life-threatening syndrome with an overactivation of lymphocytes and macrophages. In 1991, the Histiocyte Society was established and coined the term hemophagocytic lymphohistiocytosis (HLH). They later created the currently used HLH diagnostic and therapeutic guidelines, the HLH-2004 guidelines.[2] In 1994, the first international study dedicated to comparing the combination of chemotherapy and immunotherapy agents in children with familial HLH was initiated.[8] Patients received several weeks of etoposide and dexamethasone induction and tapering. If no remission was obtained after eight weeks, continuation therapy used pulsed dexamethasone and bi-weekly etoposide with the addition of cyclosporine. Results estimated a three-year survival rate of 55%, a significant improvement from a 1996 study that estimated a five-year survival rate of 21%.[9,10] Despite this study being exclusively conducted in pediatric patients with familial HLH, the HLH-2004 guidelines used this protocol as its foundation.[7] A 2017 study evaluated the long-term effects of therapy using the HLH-2004 protocol from 2004 to 2011 and reinforced the efficacy of using etoposide and dexamethasone, but showed limited benefit of initial cyclosporine use.[11]

Most studies on HLH have focused on diagnostic challenges with few considering therapeutic challenges, particularly in patients with complex presentations or multiple infections. Some cases of HLH-associated infections have been published, but given the rarity of these presentations, no guidelines have resulted from these studies.[4-6] However, as secondary HLH can be triggered by infection, treatment guidelines for any present infections should be considered during HLH management. Our patient had co-infection of TB, COVID-19, and hepatitis A. The gold standard therapy for active TB is a six-month course of isoniazid, rifampin, pyrazinamide, and ethambutol. According to the NIH guidelines, clinical management in hospitalized COVID patients requiring supplemental oxygen includes dexamethasone, remdesivir, and potentially tocilizumab or baricitinib with clinical deterioration.[12] Hepatitis A typically is self-limited and treatment is focused primarily on supportive care and avoiding hepatotoxic medications.[13] Our patient's HLH treatment and management of co-infections was complicated by multiple factors, including liver dysfunction, renal failure, risk for tuberculosis reactivation, and multi-drug interactions.

Our patient had multiple etiologies of acute liver injury, including hepatitis A, sepsis, COVID-19 infection, and HLH. All these factors complicated management decisions. Hepatotoxic effects of TB treatment occur most commonly with isoniazid, but also with rifampin and pyrazinamide.[14] Additionally, rifampin is associated with acute biliary events.[15] In our patient, tuberculosis treatment was held due to transaminitis and hyperbilirubinemia. Patients are at greater risk for TB-therapy-associated hepatotoxicity if they have poor nutritional status, alcohol intake, or presence of concomitant infection; all of these factors present in this patient.[16] There are no set guidelines to recommend dosage adjustments to lower the risk of hepatotoxicity; therefore, risk stratification and frequent monitoring are needed to guide management. Etoposide is partially metabolized by the liver and excreted by the kidneys and biliary tract leading to obstructive jaundice.[17] Our patient's acute liver injury affected the decision to not initiate etoposide. In the setting of COVID-19 infection, remdesivir was not used as part of treatment as it can increase liver enzymes.

Our patient's renal failure further limited treatment options for HLH, tuberculosis, and COVID-19. The immunosuppressant cyclosporine, used as induction therapy for HLH, reduces renal blood flow by afferent arteriole vasoconstriction and can lead to dose-dependent nephrotoxicity.[18] Although an uncommon adverse effect, rifampin is the most frequent anti-tuberculous medication associated with acute interstitial nephritis.[19] Remdesivir and baricitinib are contraindicated in severe renal dysfunction.[20,21] These considerations affected risk management decisions regarding these drugs.

Given our patient's recent immigration from an endemic population with a high prevalence of drug-resistant TB, concerns for reactivation of latent TB arose and dexamethasone treatment of COVID-19 was stopped after his initial quantiferon test was positive.[22] For patients who are being treated with corticosteroids, the risk of TB reactivation increases 2.8- to 7.7-fold.[23] Additionally, novel immunomodulatory treatments for COVID also risk reactivating latent TB.[12,24] Methylprednisolone was initiated after diagnosis of HLH, as the risk of TB reactivation was deemed less than the risk of death from untreated HLH.

Multiple drug interactions complicated treatment strategies for this patient. Cyclosporine and etoposide are mainly metabolized by CYP3A4. Therefore, rifampin, a strong inducer of CYP3A4, can stimulate metabolism of these drugs, reducing their efficacy and requiring an increase in dose for therapeutic benefit.[24] Additionally, dexamethasone

enhances etoposide clearance.[25] While we did not use cyclosporine and etoposide, these dosage adjustment recommendations could be considered in other patients.

As secondary HLH is thought to be an immune reaction after a triggering factor, it may be postulated that treatment should be directed toward the inciting disease rather than HLH alone. In our patient, his inciting disease could have been COVID-19, TB, hepatitis A, or any combination thereof. Therefore, his HLH treatment included treatment of these diseases. Due to our patient's multiple co-infections and the adverse effects of the medications used to treat these co-infections, treatment of his HLH required complex decision making and risk-benefit analysis. He was successfully treated with methylprednisolone and anti-TB therapy, holding etoposide and cyclosporine due to the adverse effects associated with acute liver injury, renal failure, and drug interactions with anti-TB drugs. This case illustrates that although the HLH-2004 guidelines are a useful guide to management, clinical utility requires personalization, particularly in patients with complex presentations.

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