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A Rare Case of Hemophagocytic Lymphohistiocytosis Triggered by Sepsis Due to Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Krishna Vedala, MD, MPH[1], Mitchell Keel, MD[1], Shoaib Khan, MD[1], Anthony Kunnumpurath, MBBS[1], and Krishna Kakkera, MD[1]

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that occurs due to unregulated immune system activation induced by various causes including infection and cancer. In this article, we report a case of a 67-year-old male with history of small cell lung cancer who developed HLH triggered by methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. The patient was initially admitted for septic shock and gastrointestinal bleed. Further workup showed that the patient met criteria for HLH diagnosis as he was positive for 5 of the 8 parameters. Unfortunately, the patient's condition worsened and he eventually expired. With this case, we wish to draw attention to the fact that sepsis due to MRSA bacteremia can be a trigger for HLH.

Keywords

hemophagocytic lymphohistiocytosis, MRSA bacteremia

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that results due to unregulated activation of the immune system.[1] It occurs with the failure of natural killer (NK) cells and cytotoxic lymphocytes' elimination of activated macrophage, which results in unchecked activation and production of inflammatory cytokines leading to excessive inflammation and hemodynamic instability in patients.[1] HLH can be further classified into primary familial HLH, secondary HLH, and malignancy-associated hemophagocytic syndrome (MAHS).[2] HLH can be diagnosed based using 2 different methods. The first method is by a molecular diagnosis consistent with HLH such as mutations found in PRF1, UNCI3d, STXII, or STXBP2 genes.[3] Second, as shown in Table 1, the HLH criteria where the patient can meet 5 of the following 8 parameters: (1) fever, (2) splenomegaly, (3) cytopenia, (4) hypertriglyceridemia, (5) hemophagocytosis, (6) low or absent NK cell activity, (7) ferritinemia, and (8) elevated soluble CD25 (or soluble interleukin [IL] 2 receptor-α).[3] There have been 2 proposed criteria, the 2004 HLH criteria and the 2009 modified criteria.[4] HLH can present with other symptoms including acute liver failure, bone marrow failure, skin manifestations, pulmonary dysfunction, and even neurological symptoms such as seizures and hypotonia.[5] Treatment is focused on addressing the potential triggers and suppression of hyperactive immune system.[6] Yet, the prognosis for HLH is very poor in the absence of early identification and initiation of prompt treatment of the unchecked inflammatory response.[2] HLH is often associated with malignancy, primarily with lymphomas or leukemias of T-cells or NK-cells.[5] Other causes for HLH also include immune activation through viral illnesses, specifically Epstein-Barr virus.[2] In addition, HLH is also known to be triggered by bacterial infections.[7] Here, we describe a unique case of HLH induced by methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.

Case Description

The patient is a 67-year-old male with history of small cell lung cancer, coronary artery disease, chronic obstructive pulmonary disease, and type 2 diabetes who was admitted to the intensive care unit after presenting with weakness, pancytopenia, and sepsis due to urinary tract infection. Before

[1]White River Health System, Batesville, AR, USA

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Corresponding Author:
Krishna Vedala, MD, MPH, Department of Internal Medicine, White River Health System, 1710 Harrison Street, Batesville, AR 72501, USA.
Email: kvedala@wrmc.com

Table 1. HLH Criteria for Molecular Diagnosis Requiring 5 of the 8 Listed.

- Fever, persistently daily
- Splenomegaly
- Pancytopenia
- Hygertriglyceridemia or hypofibrinogenemia
- Hemophagocytosis in bone marrow, spleen, lymph node, or cerebrospinal fluid
- Low or absent natural killer cell function
- Elevated ferritin >500
- Soluble CD25 (IL2Ra) above normal limits

admission, he was reportedly bed-bound for the previous 3 days at home. He had been undergoing both chemotherapy with etoposide and carboplatin and radiation therapy for the past 6 months. He also did have one dose of atezolizumab in the past but was unable to tolerate it due to gastrointestinal adverse effects. He was started on broad-spectrum antibiotics, neuopogen, and further supportive therapy. The next morning, the patient was found to have hematemesis and developed blood-loss anemia. Blood counts were stabilized posttransfusion. Peripheral smear did not show any schistocytes or abnormal platelet morphology, but did confirm pancytopenia and spherocytes. Both computed tomography and computed tomography angiography of abdomen/pelvis were unequivocal in identifying a source of bleeding and surprisingly did not show any splenomegaly. Pertinent laboratory tests include hypertriglyceridemia (at 385) and elevated ferritin (32 100). Both initial and repeat blood cultures (5/5) persistently grew MRSA raising suspicion for endocarditis, but a transthoracic echocardiogram did not show any evidence of vegetation. HLH was becoming likely diagnosis in lieu of fever, pancytopenia, hyperferritinemia, and hypertriglyceridemia. High-dose steroids were started. Initially, starting etoposide was discussed with the patient, but was then withheld due to worsening sepsis and exacerbating immunosuppression. He continued to decline and overnight required resuscitation and intubation. He was started on pressors, but failed to make any improvement at which point his family was contacted and after significant discussion, decision was made to make him comfort care only. He subsequently expired within the day. Postmortem, an elevated soluble IL2 receptor (sIL2-r) at 22268 U/mL was noted, thereby supporting a diagnosis of HLH.

Discussion

Here, we report a rare case of HLH in the setting of MRSA-related infective endocarditis complicated with secondary HLH. Although our patient was being treated with chemotherapy, his most recent cycle was 4 months ago and imaging from a month prior to admission showed no recurrence of disease. Therefore, HLH triggered by MRSA-septicemia is suspected to be more likely than MAHS.

MRSA-associated HLH is a rare clinical manifestation. One study shows incidence of MRSA-HLH to be as little as 3.23%.[4] Another study from India showed that out of 28 sepsis-associated HLH cases, there was only one case (3.6%) of sepsis-associated HLH due to MRSA.[7] The same study showed that approximately the etiology of 29% of secondary HLH can be attributed to bacterial causes, while 19% of secondary HLH remain unknown.[7]

Xu et al report an interesting case of secondary HLH due Methicillin-resistant *Staphylococcus epidermidis* endocarditis (MRSE) in a 40-year-Asian woman.[8] She was initially admitted for repeat fevers over previous 1 month. She was noted to also have liver failure, elevated ferritin, and pancytopenia. A soluble CD25 was ordered due to concern for HLH and was noted to be 15 386 U/mL.[8] Duke criteria were met as blood cultures were noted to be positive for MRSE with cardiac vegetation confirmed on imaging. Her condition kept deteriorating despite starting treatment with daptomycin, dexamethasone, and intravenous immunoglobulin.[8] Hematology was consulted and etoposide and cyclosporine were both started. She made significant improvement afterward and underwent successful aortic valve vegetation removal.[8]

Another key finding in our case is elevated IL2 receptor and ferritin. The HLH-2004 review emphasizes the low or absent NK-cell activity and sIL2-r as diagnostic markers for HLH.[2] In 2017, Hayden et al demonstrated that serum sIL2-r is an optimal rule-in marker for HLH in adults with 72.5% specificity when concentration is >10 000 U/mL.[6] A 2015 case report showed that hyperferritinemia (>10 000 ng/mL) is significantly associated HLH in a 50-year-old female patient who also presented with MRSA bacteremia. The investigators also showed an inverse trend between ferritin and clinical condition, as the patient's ferritin levels started falling as she improved.[9]

In conclusion, our case shows MRSA-induced bacteremia is also capable of triggering HLH. In addition, HLH can be very difficult to diagnose, but we recommend HLH always be kept as a differential diagnosis specifically in sepsis cases that are treatment-resistant. Both the traditional HLH 2004 or the modified 2009 HLH criteria are good tools to help direct treatment and prognosis. However, more research is needed in better understanding HLH pathophysiology and in developing faster diagnostic tools in order to improve outcomes in treating HLH.

Authors' Note

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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

Written informed consent was obtained from the patient for anonymized information to be published in this article.

ORCID iD

Krishna Vedala https://orcid.org/0000-0002-1524-6535

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