Case Report

Hemophagocytic lymphohistiocytosis secondary to epstein-barr virus reactivation in a patient with COVID–19

Nurfixa Ladak1*, Kenneth Csehak2, Justin Chan3 and Farnoush Moen4

1Pathology Resident, NYU Langone Health Medical Center, NYU Grossman School of Medicine, USA
2Hematology & Medical Oncology Fellow, NYU Grossman School of Medicine, USA
3Assistant Professor, Department of Medicine, NYU Grossman School of Medicine Director, Infection Prevention and Control, Bellevue Hospital Center, USA
4Clinical Assistant Professor, Department of Pathology, NYU Grossman School of Medicine Director, Hematology and Hematopathology, Bellevue Hospital Center, USA

Abstract

Hemophagocytic Lymphohistiocytosis is a recognized complication of severe coronavirus disease 2019 (COVID-19). However, this phenomenon has been reported most often in the setting of acute infection. Here we present a case of a patient with a history of COVID-19 that subsequently developed HLH weeks after treatment and discharge from the hospital. Upon re-admission, subsequent work-up demonstrated the patient was experiencing Epstein-Barr virus (EBV) reactivation. As EBV infection is a known etiological trigger of HLH, this case provides an alternative mechanism for HLH seen in patients with a history of COVID-19 who present after the resolution of acute symptomatology.

Introduction

Infection with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is associated with a complex host immune response, with the loss of immune regulation to the point of exacerbation ultimately implicated in disease progression. Such a hyperinflammatory clinical picture in a subgroup of patients develops into hemophagocytic lymphohistiocytosis (HLH), a recognized complication in patients with coronavirus disease 2019 (COVID–19) [1,2]. In addition, reports of reactivation of opportunistic infections, such as Epstein–Barr Virus (EBV) in the setting of COVID–19 infection have also been described [3,4]. Here we present a unique case of EBV reactivation in a patient with COVID–19 infection and subsequent HLH.

Case report

An 84-year-old Hispanic male with a medical history of dementia, hypertension, cerebrovascular accident and recent COVID–19 infection presented to the emergency department with altered mental status, urinary incontinence, and decreased oral intake.

Of note, he was hospitalized one month prior with COVID–19 that was complicated by prolonged hypoxia and shortness of breath, requiring 3–4 liters of oxygen by nasal cannula. He received dexamethasone and remdesivir and was admitted to the medicine service for four days.

Upon improvement, he was discharged home on supplemental oxygen to be used on exertion. On subsequent...
follow-up in the geriatric clinic post-discharge, he was noted
to be tachycardic with a low-grade fever. He also had ongoing
confusion, fatigue, and dyspnea on exertion. He was therefore
sent to the emergency department for further workup. On
presentation at the emergency department, he was afebrile
at 98.4°F. Yet he remained tachycardic at 125bpm, with a
respiratory rate of 24, and a SpO₂ of 95% His CRP was elevated
at 227mg/L with a ferritin of 812.8 ng/mL. Hemoglobin was
10.3g/dL, white blood cell count 7.17×10³/mcL and platelets
255×10³/mcL. Given his history and persistent symptoms,
it was suspected that the patient could be having a post-
COVID inflammatory syndrome, or could have a superimposed
bacterial infection. He was admitted for further workup.

A full workup including lumbar puncture was unremarkable.
His chest Computed Tomography Angiography (CTA) was
negative for a pulmonary embolism and brain Magnetic
Resonance Imaging (MRI) displayed no acute changes, with
evidence of his prior lacunar infarct.

However, his inflammatory markers continued to climb
and his fever persisted despite the use of broad-spectrum
antibiotics. Peripheral blood flow cytometry revealed the
presence of a known Chronic Lymphocytic Lymphoma (CLL)
clone, with the extent of involvement stable at approximately
5%.

Infectious disease consult determined that the patient
had a high EBV viral load, reaching up to 25,200IU/mL over
the course of his admission. A finding that was suspicious
for EBV reactivation, offering a likely etiology for his fevers.
Furthermore, it was noted that his hemoglobin continued to
trend down, as did his platelets and white count. Given the
patient’s febrile illness associated with marked inflammation
with a CRP peaking at 279.19mg/L and ferritin peaking at
11,000ng/mL, in the setting of EBV viremia and concomitant
pancytopenia, the concern for HLH secondary to EBV was
raised and a bone marrow biopsy was obtained.

His subsequent extended hospital course was complicated by
worsening pancytopenia, with his hemoglobin reaching a nadir
of 6.3g/dL requiring pRBC transfusions, his platelets decreasing
to 20,000/mcL, and white blood cell count with an absolute
neutrophil count as low as 780/mcL. He also experienced
metabolic derangement in the form of hyponatremia and the
development of a small bowel obstruction. He was evaluated by
surgery who recommended no surgical intervention given the
severity of his illness. The medical team, family, and palliative
care discussed the patient and ultimately the family decided to
proceed with comfort care.

Unfortunately, the patient continued to deteriorate and
death was pronounced with family at the bedside, approximately
6 weeks post-admission.

Histopathological findings

Bone marrow biopsy revealed trabecular bone and marrow
elements. The marrow was hypercellular for age, with
cellularity estimated between 30–70%. There was an increase
in erythroid lineage noted, displaying full maturation, as well
as an increase in megakaryocytes with occasional dyspoiesis
including small hypo-lobated forms. Myeloid maturation was
present and complete (Figure 1). Iron stores were markedly
increased and reticulin fibrosis was increased at 3/3.

Most notably, a patchy infiltration of histiocytes containing
iron granules and erythroid elements was also present. Hemophagocytosis was also appreciated on the aspirate smear
and the iron stain of the aspirate smear (Figure 2).

Discussion

Here we present a case of HLH secondary to EBV
reactivation in the setting of a recent COVID-19 infection. HLH
is an aggressive and life-threatening syndrome of excessive
immune activation. HLH may be inherited (primary) or may
be secondary to malignancy, systemic autoimmunity, or viral
infection. The clinical distinction between the two may be
ambiguous in cases as in many patients with an underlying
genetic defect an infectious trigger is still also present [5]. Viral
infections are the most common cause of secondary HLH, with
viruses of the herpes family, especially EBV being the most
frequent. EBV-associated HLH is associated with EBV infection
of T or NK cells rather than B cells [6].

Our understanding of HLH has evolved and the current
consensus is that HLH is a syndrome of a dysregulated
inflammatory response, resulting in tissue destruction and
continued abnormal activation of the immune system [7,8].

Histopathological findings

Bone marrow biopsy revealed trabecular bone and marrow
elements. The marrow was hypercellular for age, with
cellularity estimated between 30–70%. There was an increase
in erythroid lineage noted, displaying full maturation, as well
This hyperinflammatory state is thought to be a result of the absence of normal feedback deactivation of macrophages. Natural Killer (NK) cells and cytotoxic T-lymphocytes, which typically act to eliminate activated macrophages, fail to do so in HLH. This results in a loss of feedback regulation that typically dampens the immune response. Persistent activation of macrophages and cytotoxic T-lymphocytes leads to excessive cytokine production [8]. These cytokines are thought to be responsible for the multiorgan failure and the high mortality of this syndrome (“cytokine storm”). In addition to the antigen presentation and cytokine production by macrophages described above, hemophagocytosis is also seen [7,9]. This occurs when host red blood cells, platelets, or white blood cells are taken up by histiocytes or macrophages and are seen in the cytoplasm. This phenomenon can be observed in tissue or bone marrow biopsies and is supportive of a diagnosis of HLH.

Clinically, a diagnosis of HLH can be made if 5 of the following 8 diagnostic criteria are met: fever (peak temperature >38.5°C for >7 days), splenomegaly (spleen palpable >3cm below costal margin), cytopenia involving >2 cell lines, hypertriglyceridemia or hyperfibrinogenemia, hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes), low or absent NK cell activity, serum ferritin >500ng/mL and elevated soluble interleukin-2 (CD25) levels [10]. It is recommended that treatment is commenced as soon as a diagnosis of HLH is considered, as delays in therapy pertain to a worse prognosis [11]. The goal of therapy is to suppress the uncontrolled inflammatory cascade that occurs in HLH. This is most often accomplished through induction therapy that consists of weekly dexamethasone and etoposide [11]. If a patient fails to improve, they are continued on therapy with the ultimate goal of allogenic stem cell transplant. What is unique in this case is the patient’s recent history of COVID-19 with the ultimate goal of allogenic stem cell transplant.

Conclusion

COVID-19 infection results in a complex interplay of immune responses which we are only just beginning to understand. Although HLH has been documented and is an accepted complication of immune over-activation in COVID-19 [1,2], an alternative etiology of EBV reactivation in the setting of COVID-19 and subsequent HLH also exists. This mechanism may underlie HLH that presents in the setting of sub-acute infection or “long COVID”/post-acute sequelae, seen in our case.

References
