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Authors

Vo, Sydnie
Yeh, Savannah
Abdo, Nasser

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CLINICAL VIGNETTE

Post-COVID-19 Hemophagocytic Lymphohistiocytosis as the Initial Presentation of Systemic Lupus Erythematosus

Sydnie Vo, MD[1], Savannah Yeh, MS[2] and Nasser Abdo, MD[3]

[1]UCLA Department of Family Medicine, Los Angeles, California
[2]UCLA David Geffen School of Medicine, Los Angeles, California
[3]Olive View-UCLA Department of Internal Medicine, Sylmar, California

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disorder characterized by a systemic life-threatening hyperinflammatory response secondary to uncontrolled proliferation of macrophages and impaired natural killer (NK) cell activity.[1] Primary HLH is the most common form in the pediatric population and is an autosomal recessive disease.[1] In adults, it may develop as sequelae of infection, rheumatoid disorders, malignancy, or drugs, in which case it is referred to as secondary HLH.[1] The most common cause is hematologic malignancies, followed by infectious diseases, and autoimmune disorders.[2] Since the start of the COVID-19 pandemic, several have reported the relationship between HLH and SARS-CoV-2 infection.[3-5] Regarding the association of HLH with rheumatoid disorders, the prevalence of HLH with systemic lupus erythematosus (SLE) is rare and has been reported as 0.9 - 4.6%.[6] Additionally, an association between SLE and COVID-19 has been found, with a few published case reports of SLE manifestation following COVID-19.[7-9] We describe a patient who developed HLH triggered by COVID-19 infection and underlying paucisymptomatic SLE.

Case Report

A 24-year-old female with a history of obesity and asthma presented with abdominal pain and distension for two weeks.

She developed fever, diffuse abdominal pain, nausea, vomiting, and melena two weeks prior to presentation at our hospital and tested positive for SARS-CoV-2. Her husband had presented with more typical COVID-19 symptoms and tested positive a few days prior. The patient presented to the emergency department of an outside hospital and was admitted to the intensive care unit for septic shock requiring pressor support. She was treated with broad spectrum antibiotics, but she did not require any treatment for COVID-19 as she was otherwise stable on room air. Computed tomography (CT) of the abdomen and pelvis revealed hepatosplenomegaly. Laboratory testing showed elevated ferritin, cytopenia, and elevated CD25. Antinuclear antibody (ANA) was negative at the outside hospital. The findings of fever, cytopenia, hepatosplenomegaly, hyperferritinemia, and elevated soluble CD25 fulfilled five of the eight diagnostic criteria for HLH. She was started on treatment for presumed HLH with methylprednisolone and a dose of tocilizumab with plans for a bone marrow biopsy.

The patient later left the outside hospital and re-presented at our hospital with abdominal pain and anasarca. She also reported bilateral leg pain in the joints and muscles, numbness, and weakness, as well as girdle weakness that started two weeks prior to presentation. She did not have a family history of autoimmune conditions. She tested negative for SARS-CoV-2. CT of the abdomen and pelvis showed soft tissue anasarca, bilateral pleural effusions, and ascites. Physical exam was notable for diffuse anasarca, the absence of oral ulcers and malar rash, decreased shoulder strength and active range of motion, and decreased lower extremity strength.

Laboratory results (Table 1) were significant for anemia, thrombocytopenia, hypofibrinogenemia, hypertriglyceridemia, hypocomplementemia, and an ANA titer of 1:1280 with an atypical speckled pattern. Given that she appeared to have responded well to the steroids at the outside hospital, she was continued on a dexamethasone taper as outlined in the HLH-94 protocol without the need for etoposide. During her admission, she developed oral ulcers and a faint malar rash and was started on hydroxychloroquine for presumed SLE upon discharge. At a follow-up appointment, she was found to be positive for beta-2 glycoprotein 1 antibody and cardiolipin antibody as well. At a one-month follow-up appointment, the patient was continued on the hydroxychloroquine for SLE and the dexamethasone taper for HLH and her symptoms had significantly improved.

TABLE 1. Laboratory Results During Admission

ESR: estimated sedimentation rate; CRP: C-reactive protein

Test	Result	References Values
Hemoglobin (g/dL)	11.0	12.0 - 14.6
White blood cells (K/cumm)	16.0	4.5 - 10.0
Platelets (K/cumm)	160	160 - 360
Absolute Neutrophil (K/cumm)	13.6	1.8 - 8.0
ESR (mm/hr)	3	
CRP (mg/L)	24.4	0.0 - 7.0
Fibrinogen (mg/dL)	147	215 - 450
Ferritin (ng/mL)	641	5 - 204
Triglycerides (mg/dL)	220	≤ 149

TABLE 2. Rheumatology Labs During Admission

ANA: anti-nuclear antibody; C3: complement 3; C4: complement 4; dsDNA: double stranded DNA; IgM: immunoglobulin M; IgA: immunoglobulin A; IgG: immunoglobulin G; dRVVT: Dilute Russell's viper venom time; SSA: anti-Sjogren's syndrome-related antigen A; SSB: anti-Sjogren's syndrome-related antigen B; Anti-SM: anti-Smith; anti-RNP: anti-ribonucleoprotein

Test	Result	References Values
ANA Screen	Positive	
ANA Titer	1:1280	
ANA pattern	atypical speckled	
C3 (mg/dL)	33	90 - 180
C4 (mg/dL)	< 2.0	10.0 - 40.0
Rheumatoid factor (IU/mL)	< 10	≤ 13
Anti-citrullinated protein IgG (U/mL)	< 8	≤ 16 U/mL
Anti dsDNA:	Negative	
Beta-2 Glycoprotein 1 IgA Ab (SAU)	16	≤ 20
Beta-2 Glycoprotein 1 IgG Ab (SGU)	< 9	≤ 20
Beta-2 Glycoprotein 1 IgM Ab (SMU)	40	≤ 20
Dnase B Ab (U/mL)	< 95	< 301
Cardiolipin IgA (APL)	< 11	
Cardiolipin IgG (GPL)	25	
Cardiolipin IgM (MPL)	28	
dRVVT screen (seconds)	35	≤ 45
Lupus anticoagulant	Not detected	
Anti-SSA Ab	< 1.0	< 1.0
Anti-SSB Ab	< 1.0	< 1.0
Anti-smooth muscle Ab	< 1.0	< 1.0
Anti-SM/RNP Ab	< 1.0	< 1.0
Direct Coombs	Negative	

TABLE 3. Infectious Disease Labs During Admission

EBV: Epstein-Barr virus; CMV: cytomegalovirus; PCR: polymerase chain reaction; HIV: human immunodeficiency virus; HSV: herpes simplex virus; RPR: rapid plasma reagin; TB: tuberculosis

Test	Result	References Values
SARS-CoV-2	Negative	
Coccidiodes IgM and IgG	Negative	
Cryptococcus Ag	Negative	
Hepatitis A IgM	Nonreactive	
Hepatitis B Core IgM	Nonreactive	
Hepatitis Bc IgM	Nonreactive	
Hepatitis Bs Ag	Nonreactive	
Hepatitis Bs Ab (mIU/mL)	202.14	≥ 12
Hepatitis C Ab	Nonreactive	
EBV DNA PCR	Detected	
EBV Ab IgM to capsid[1]	< 0.36	< 0.36
EBV Ab IgG to capsid[1]	> 600.0	< 18.0
EBNA-IgG[1]	> 600.0	< 18.0
CMV DNA PCR	Not detected	
Parvovirus B19 IgM and IgG	0.2	< 0.9
HIV Ab/Ag screening	Nonreactive	
HSV 1 DNA	Not detected	
HSV 2 DNA	Not detected	
RPR	Nonreactive	
QuantiFERON TB Gold Plus	Negative	

[1]*Labs obtained from outside hospital.*

Discussion

Based on outside hospital records, the patient had documented fever, hepatosplenomegaly, cytopenias, hyperferritinemia, and elevated soluble CD25, which fulfilled five of the eight diagnostic criteria needed for the diagnosis of HLH as defined by the HLH-2004 trial.[1] On further follow up at our hospital, bone marrow biopsy revealed marked hypocellularity and few hemophagocytic histiocytes. During her initial admission at the outside hospital, the patient did not originally meet criteria for SLE. However, during her admission at our hospital, the patient met clinical criteria for SLE: oral ulcers, acute cutaneous lupus, and pericardial and pleural effusion. Laboratory criteria included: antiphospholipid antibodies and low complement proteins. Though the anti-dsDNA was negative, a negative result can be seen in 38-43% of individuals with SLE.[10] Given the above findings and the positive ANA titer, she met the diagnosis of SLE as defined by the EULAR criteria.[11] Regarding her infection with COVID-19, the patient initially presented with fever as well as musculoskeletal and gastrointestinal symptoms. She developed septic shock requiring pressors but otherwise did not require ventilatory support or treatment with the hospital's standard COVID-19 protocol at the time. CT of the chest showed the typical bilateral ground-glass opacities seen in those infected with SARS-CoV-2.

HLH is a hyperinflammatory syndrome associated with the inappropriate activation of macrophages and lymphocytes and can result in extensive tissue destruction and life-threatening multi-organ failure. Primary (familial) HLH, the inherited form of HLH, accounts for about 25% of cases and primarily presents in infants and children.[12] In these cases, a hereditary genetic mutation affecting cytotoxic lymphocyte function can be identified. The remainder of cases are considered secondary (acquired) HLH which is generally seen in adults with underlying conditions including infection, malignancy, and rheumatologic conditions. However, both primary and secondary HLH can be triggered by conditions that activate the immune response, including infection or malignancy.

Secondary HLH associated with autoimmune diseases, such as SLE and systemic juvenile idiopathic arthritis, is also called macrophage activation syndrome (MAS). HLH/MAS is a rather rare complication in SLE with a prevalence between 0.9% to 4.6%.[13] With the emergence of COVID-19 and its reported link to hyperinflammatory conditions and autoimmune disease, it is important to explore the relationship of this novel coronavirus and HLH.

There have been recent case reports of HLH believed to be secondary to severe COVID-19 infection. COVID-19-related cytokine storm has also been found to have similar clinical and laboratory features as HLH, which has guided the development of novel COVID-19 therapies.[3,5] Furthermore, COVID-19 has

been implicated in the development of post-infection autoimmune conditions, such as Guillain-Barré syndrome.[5,14]

This case illustrates SLE initially presenting as HLH, which is rare. However, the presence of infection by SARS-CoV-2 may predispose patients with even mild SLE to develop HLH. Of note, the patient's serum EBV DNA PCR was incidentally detected, and given that she also had a positive EBV IgG and negative IgM, suggests a past infection. EBV is a known secondary cause of HLH though the proportion of EBV infection in HLH decreases significantly after the age of 2.[2]

The mortality rate in adult HLH cases ranges from 20% to 88% and is often due to refractory HLH, subsequent infections, and progression of the triggering disease.[15] Thus, it is important to have an increased clinical suspicion of HLH in patients who present with subclinical SLE in the setting of recent infection by SARS-CoV-2 as a late diagnosis of HLH may be fatal.

Conclusion

HLH as a primary presentation of SLE is extremely rare. However, infection by SARS-CoV-2 may increase the risk for developing HLH in those with mild SLE. The mortality rate of HLH is high, thus an increased clinical suspicion of HLH in cases of mild SLE and prompt treatment is important.

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