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Anaplasmosis-induced hemophagocytic lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening inflammatory syndrome of severe immune system activation. It is a diagnostic challenge with high morbidity and mortality. We present a case of HLH due to anaplasmosis infection. A 54-year-old man with chronic obstructive pulmonary disease presented with fever, nausea, vomiting, dyspnea, and arthralgias for 6 days. He had a rapidly progressive clinical decline requiring intubation for acute respiratory failure and dialysis for acute renal failure. He tested positive for anaplasmosis. His workup met criteria for HLH. He was treated with doxycycline and a steroid taper with clinical improvement allowing for extubation and renal recovery. Patients with persistent fevers, hepatosplenomegaly, cytopenias, and hyperferritinemia should be worked up for HLH.

KEYWORDS *Anaplasma*; hemophagocytic; HLH; lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) encompasses a variety of nonmalignant, life-threatening disorders.[1] It is further classified as either primary (genetic) or secondary (acquired) based on the underlying etiology.[1,2] Secondary HLH is often associated with a trigger that results in severe inflammatory states.[1,3] We present a rare case of anaplasmosis-induced HLH.

CASE REPORT

A 54-year-old man with a history of chronic obstructive pulmonary disease presented with nausea, vomiting, and dyspnea for 6 days. Physical exam was significant for respiratory distress and bilateral lower extremity petechiae. Laboratory investigations showed a white blood cell count of 2.8 K/μL, hemoglobin of 8.4 g/dL, platelet count of 17 K/μL, creatinine of 8.7 mg/dL, triglyceride level of 521 mg/dL, and ferritin level >7500 ng/mL. A peripheral smear revealed pancytopenia with marked thrombocytopenia. Chest x-ray was unrevealing. Further workup showed an antinuclear antibody titer of 1:320 with a homogenous pattern, soluble interleukin-2 receptor (sCD25) level of 36,628 pg/mL, *Anaplasma phagocytophilum* detected by polymerase chain reaction (PCR) with an IgM titer of >1:320 and IgG titer of 1:64, Epstein-Barr virus (EBV) not detected by PCR with an IgM titer of 33.8 U/mL and IgG titer of 194 U/mL, Varicella zoster (VZV) IgM titer of 1.34 U and IgG titer of 2134 U, and Parvovirus B-19 IgM titer of 1.08 U. Bone marrow biopsy revealed hemophagocytic histocytes with varying numbers of erythroid precursors and platelets.

His hospital course was complicated by respiratory failure requiring intubation. He developed acute renal failure due to acute tubular necrosis as evidenced by diffuse granular, muddy brown casts on urine microscopy requiring renal replacement therapy. He completed a 10-day course of doxycycline and a 14-day course of dexamethasone 20 mg daily. He was extubated and no longer required renal replacement therapy. He was discharged on a steroid taper following the HLH-94 protocol. On outpatient follow-up 2 weeks after discharge, laboratory investigations revealed improvement in ferritin to 1470 ng/mL and sCD25 to 1013 pg/mL.

DISCUSSION

HLH is a rare, life-threatening syndrome that is a diagnostic challenge. HLH results from overstimulation of the

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immune system leading to systemic inflammation, cytokine storm, and multiorgan failure.[3,4] The pathogenesis for secondary HLH is not well defined.[2] The current understanding of the pathophysiology includes an overactivation of $CD8^+$ T lymphocytes and macrophages that attack the liver, bone marrow, and central nervous system.[5] Patients with HLH syndrome experience a cytokine storm resulting in elevations in interleukin-2, interleukin-6, tumor necrosis factor-alpha, interferon-gamma, and other inflammatory mediators such as prostaglandins.[2] This results in massive overactivation of antigen-presenting cells and $CD8^+$ T cells, leading to end-organ damage.[2]

Clinically, HLH is characterized by persistent fevers, hepatosplenomegaly, cytopenias, and hyperferritinemia.[1,2,6] The diagnosis of HLH can be made if either a molecular diagnosis consistent with HLH is obtained or at least five of eight criteria are met from the HLH-2004 guidelines *(Table 1)*.[7,8] The H-score is a new diagnostic test used to identify suspected reactive HLH in adults. This score may have been more appropriate to use in our patient; however, it would not have changed his management.

Known triggers for secondary HLH include infections, malignancies (primarily lymphoma), and autoimmune disorders, among others.[7] Reports from East Asia have found rickettsial diseases resulting in HLH.[9] Limited reports have identified anaplasmosis-induced HLH.[10–12] Although our patient had elevated antibody titers for other potential etiologies including EBV, VZV, and parvovirus, the titers of the antibodies against these viruses were very low. We suspect that the formation of these antibodies was secondary to the significant inflammatory response that results from HLH. Our patient had a negative EBV PCR test and a positive *A. phagocytophilum* PCR test confirming the diagnosis of human granulocytic anaplasmosis.

Table 1. HLH-2004 diagnostic criteria

Criteria	Patient meeting criterion
Fever (≥38.5°C)	No
Splenomegaly	No
Cytopenias (≥2)	Yes: hemoglobin 8.4 g/dL, platelets 17 K/μL
Hypertriglyceridemia	Yes: 521 mg/dL
Hemophagocytosis	Yes: in bone marrow
Low or absent NK cell activity	–
Ferritin >500 ng/mL	Yes: >7500
Elevated soluble CD25	Yes: 36,628 U/mL
Elevated CXCL9	–

The HLH-94 protocol is the gold standard of treatment for HLH in both adult and pediatric patients. The patient's clinical improvement and downtrend in his ferritin and sCD25 after treatment with doxycycline and steroids (*Figure 1*) per the HLH-94 protocol supports the diagnosis of anaplasmosis-induced HLH. The standard HLH-94 protocol includes treatment with etoposide in combination with dexamethasone.[12] The decision to not treat the patient with etoposide or anakinra was made after discussion with nephrology, given the patient's acute renal failure. HLH-2004 added cyclosporine A up front in addition to dexamethasone and etoposide; however, this was not explored due to the patient's impaired kidney function.[13] In prior cases of anaplasmosis-induced HLH, symptoms and laboratory markers improved with doxycycline alone.[10,11] It is unclear why our patient suffered such severe disease. It may be the anaplasmosis that predisposed him to such severity. Follow-up in the outpatient setting revealed further improvement in the inflammatory markers ferritin, lactate dehydrogenase, and sCD25.

Morbidity and mortality in patients with HLH continue to be very high. The incidence of shock ranges from 50% to 80%.[6] The incidence of acute respiratory failure requiring mechanical ventilation varies from 58% to 100%.[6] The incidence of acute renal failure requiring renal replacement therapy has been reported to be as high as 59%.[6] Anaplasmosis rarely causes renal failure and is unlikely to have caused the renal failure in our patient.[14] Therefore, physicians need to consider the diagnosis of HLH in hospitalized patients who worsen despite treatment for the purported diagnosis. This case report further supports *Anaplasmosis* as an etiology of secondary HLH. Anaplasmosis should be considered as a

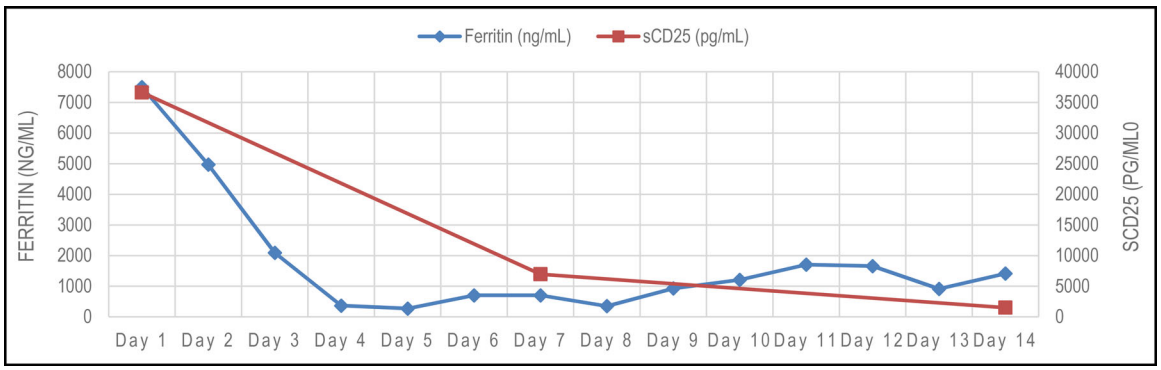

Figure 1. The trend of ferritin and sCD25 levels after initiation of dexamethasone and doxycycline treatment.

potential trigger in patients with HLH due to unknown etiology and in populations with a high incidence of tick-borne disease.

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In memoriam

Joseph W. Fay, MD

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Joseph Wayne Fay, MD, a pioneer of the marrow transplant service at Baylor University Medical Center, died on February 18, 2022, at the age of 75. Born on May 4, 1946, in Barberton, Ohio, he graduated from Barberton High School, where he met his wife, Joanne Marinich. He majored in chemistry at the College of Wooster and also played basketball and baseball there. He attended medical school at The Ohio State University, where he was a member of Alpha Omega Alpha. After training in hematology and oncology at Duke University Medical Center, he was commissioned as a lieutenant commander in the Navy for the National Cancer Institute. In 1976, he returned to Duke to develop a bone marrow transplant program. He was recruited to Baylor University Medical Center in 1982. During his 35-year career there, he established the Marrow Transplant Service, the first program of its kind in North Texas, and was among the first in the US to use unrelated hematopoietic stem cell donors. In the 2000s, he became director of the Baylor Institute for Immunology Research; his research focused on dendritic cell technology for the treatment of melanoma and other cancers. Funded with numerous NIH grants, he had over 150 abstracts and publications in peer-reviewed journals. He also mentored numerous physicians nationwide in bone marrow transplant. In addition to his wife of 53 years, Joanne, he is survived by his children, Nathan Wayne Fay and Lauren Fay Holmes, and five grandchildren.