Secondary HLH: Why Didn't I Think of That First?

Jessica Corder, MD[1]; Daniel Shields, DO[1]; Brett Sadowski, MD[2]

[1]Naval Medical Center Portsmouth, Department of Internal Medicine; [2]Naval Medical Center San Diego, Department of Gastroenterology

INTRODUCTION

• Hemophagocytic lymphohistiocytosis (HLH) is hallmarked by widespread immune activation and ultimately multi-organ failure.

• Two subsets: primary, typically with onset in childhood, and secondary that occurs in response to another disease process.

• Diagnosis of secondary HLH hinges heavily on excluding other more common diagnoses, a high index of suspicion, and interpretation of lab data.

THE CASE

• A 52-year-old previously healthy male presents to the emergency department with one month of bilateral lower extremity edema and abdominal pain.

• Initial lab work showed pancytopenia, conjugated hyperbilirubinemia, and mild transaminitis.

• CT abdomen/pelvis was consistent with hepatosplenomegaly, gallbladder wall thickening, and intrahepatic ductal dilation.

• Broad spectrum antibiotics were started and ERCP with stent placement performed however no stones, sludge, or purulent discharge were found during the procedure.

• Repeat imaging with MRCP noted splenomegaly and dilation of the main portal vein suspicious for cirrhosis.

• Given the confusing clinical picture and doubt that cirrhosis was the unifying diagnosis, a liver biopsy was performed which showed hemophagocytosis.

• A bone marrow biopsy to evaluate his profound pancytopenia also showed hemophagocytosis.

• Expanded lab work showed ferritin >35,000 and IL2 soluble receptor of 16,000; the diagnosis of secondary HLH was made.

FIGURES

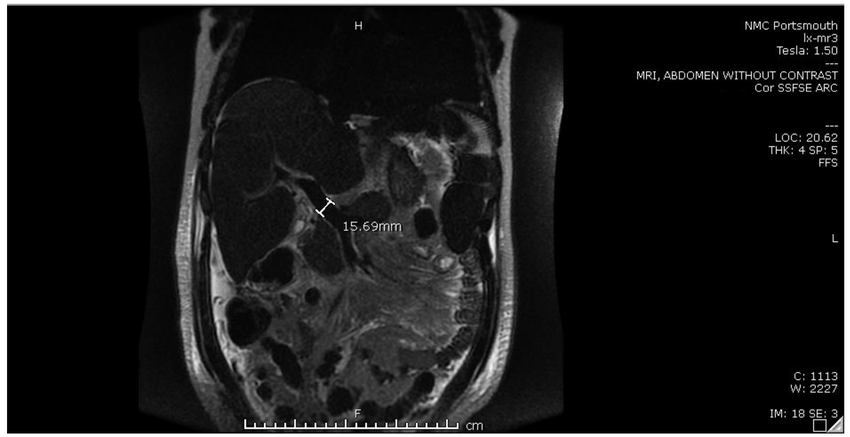
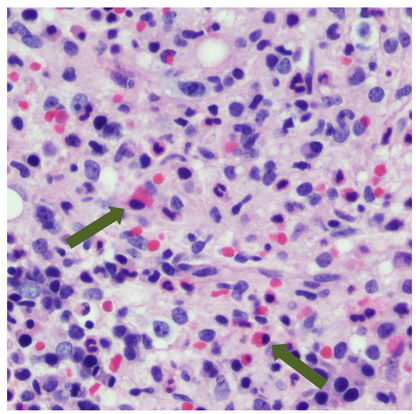


Figure 1: MRCP imaging demonstrating hepatomegaly and main portal vein dilation



The diagnostic of hemophagocytic lymphohistiocytosis can be established by fullfilling five of the eight following criteria.

Clinical criteria
Fever (> 7 days)
Spleen enlargment
Laboratory criteria
Bicytopenia without marrow hypoplasia, including
Hemoglobin<9g/L
Platelet count<$100x10^9$/mm^3
Neutrophil count<$1x10^8$/mm^3
Hypertriglyceridemia (>3,0mmol/L, fasting value) and/or hypofibrinemia (<1,5g/L)
Hyperferritinemia (>500µg/L)
Low/absent Natural Killer cell activity
Increased soluble CD-25 levels (>2400IU/mL)
Histological criteria
Hemophagocytosis

Figure 2: Bone marrow aspirate performed on patient; arrows indicate hemophagocytic cells (40x magnification), Figure 3: Diagnostic criteria for hemophagocytic lymphohistiocytosis per the HLH-2004 protocol of the Histiocyte Society. An HLH diagnosis can be established by fulfilling five of the eight proposed criteria.

THE CASE CONTINUED

• Infectious, autoimmune, and malignancy workups yielded no evidence of an underlying condition.

• Steroid treatment was deferred due to a possible undiagnosed smoldering infection vs hematologic malignancy.

• The patient succumbed to his profound illness shortly after diagnosis.

DISCUSSION

• This case demonstrates the importance of keeping secondary HLH on the differential in the setting of liver injury.

• Cholangitis, cirrhosis, and acute liver failure were all considered given the lab and imaging findings, however the inability of the patient to improve after interventions created the need to explore alternative diagnosis.

• It is important to start this workup early given the high mortality associated with HLH.

• The mainstay treatment of HLH involves treating the underlying causes, but also blocking the dysregulation of the immune system.

• As most protocols for HLH call for high dose steroids, caution was taken in this case given the concerns for an infection.

REFERENCES

1. Buyse S, Teixeira L, Galicier L, Mariotte E, Lemiale V, Seguin A, Bertheau P, Canet E, de Labarthe A, Darmon M, Rybojad M, Schlemmer B, Azoulay E. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med. 2010 Oct;36(10):1695-1702. doi: 10.1007/s00134-010-1936-z. Epub 2010 Jun 8. PMID: 20532477.
2. Li J, Wang Q, Zheng W, et al. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. Medicine (Baltimore) 2014;93:100–5
3. Lin S, Li Y, Long J, Liu Q, Yang F, He Y. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults: A case report and review of the literature. Medicine (Baltimore). 2016 Nov;95(47):e5431. doi: 10.1097/MD.0000000000005431. PMID: 27893685; PMCID: PMC5134878.
4. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol 2015;90:220–4.
5. Parikh SA, Kapoor P, Letendre L, et al. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. Mayo Clinic Proc 2014;89:484–92.