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A case of portal hypertension due to a superior mesenteric arteriovenous fistula

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A Case of Hemophagocytic Lymphohistiocytosis Secondary to Disseminated Histoplasmosis

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare clinical syndrome characterized by fever, hepatosplenomegaly, cytopenias, presence of activated macrophages in hematopoietic organs and progressive multiple-organ failure.¹ The secondary form of HLH is often triggered by infections, malignancies, and autoimmune diseases.² Disseminated histoplasmosis (DH) has been described as a potential trigger, most commonly in immunocompromised hosts. The pathogenetic mechanisms behind HLH are not well understood but involve cytotoxic lymphocyte dysfunction leading to an exaggerated inflammatory response, which ultimately causes tissue damage and progressive multiple organ failure.³ The liver, spleen, and lungs are the most frequently affected organs, but HLH can potentially affect all tissues in the human body. Patients with HLH are often severely ill making the establishment of the diagnosis challenging.

Case Presentation

A 42-year-old female presented to the emergency department with a 2-week history of jaundice, intermittent right upper quadrant abdominal pain and fevers. Her past medical history was significant for ankylosing spondylitis for which she was on chronic immunosuppression with prednisone, methotrexate and infliximab. On admission she had abnormal liver biochemistries (AST 538 unit/L, ALT 132 unit/L, alkaline phosphatase 623 unit/L, total bilirubin 6.9 mg/dL, direct bilirubin 6.2 mg/dL, INR 2.1). Other laboratory values included ferritin (20,308 ng/dL) and triglycerides (1409 mg/dL) as well as low levels of fibrinogen (105 mg/dL). Blood cultures, viral hepatitis panel, autoimmune panel, ceruloplasmin and cytomegalovirus DNA were negative. A right upper quadrant ultrasonography revealed cholelithiasis, gallbladder wall thickening and splenomegaly. She was initially started on broad-spectrum antibiotics to treat for suspected acute cholangitis. A subsequent MRCP showed no evidence of intra- or extrahepatic biliary dilatation.

The patient clinically deteriorated with worsening mentation, persistent fever, need of vasopressor support and mechanical ventilation. The hospital course was further complicated by a tonic-clonic seizure and anuric acute kidney failure requiring renal replacement therapy. Given the clinical decline and uncertainty of the source of sepsis, antimicrobial coverage was broadened to include amphotericin B and acyclovir; a liver biopsy was performed revealing marked granulomatous inflammation with numerous intracellular organisms that were morphologically compatible with *Histoplasma* (Figure 1 & 2). Serum histoplasma antigen was also positive. A bone marrow biopsy was obtained revealing hemophagocytic cells (Figure 3).

Since the patient met diagnostic criteria for HLH, she was started on dexamethasone and etoposide. The patient received a total of 14 days of amphotericin B and then was transitioned to oral itraconazole. She steadily recovered, resolving the renal failure, allowing for discharge home.

Pathology

Figure 1. Hematoxylin and Eosin stain. Liver biopsy showing non-caseating granulomas and intracellular fungal organisms.

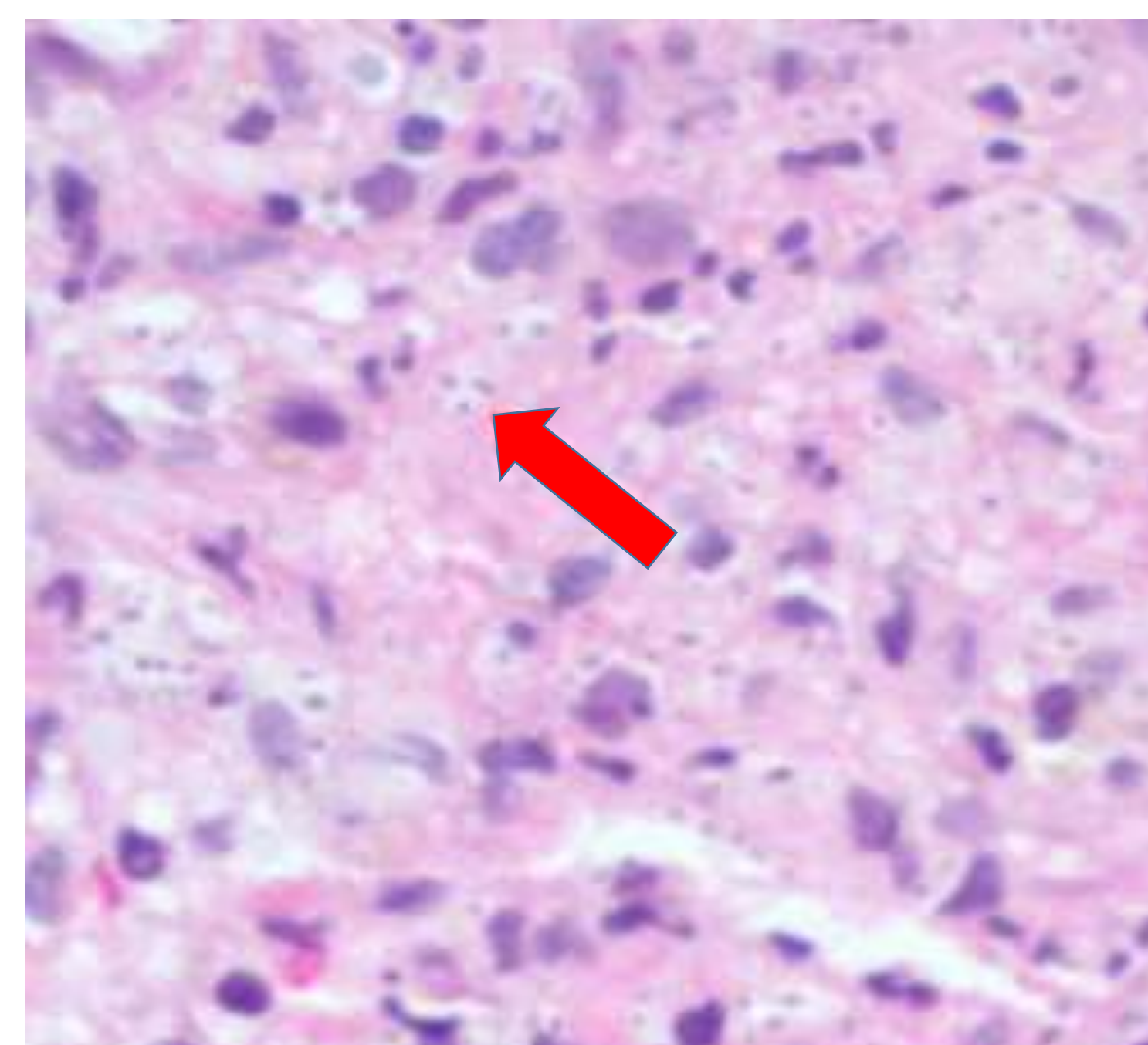
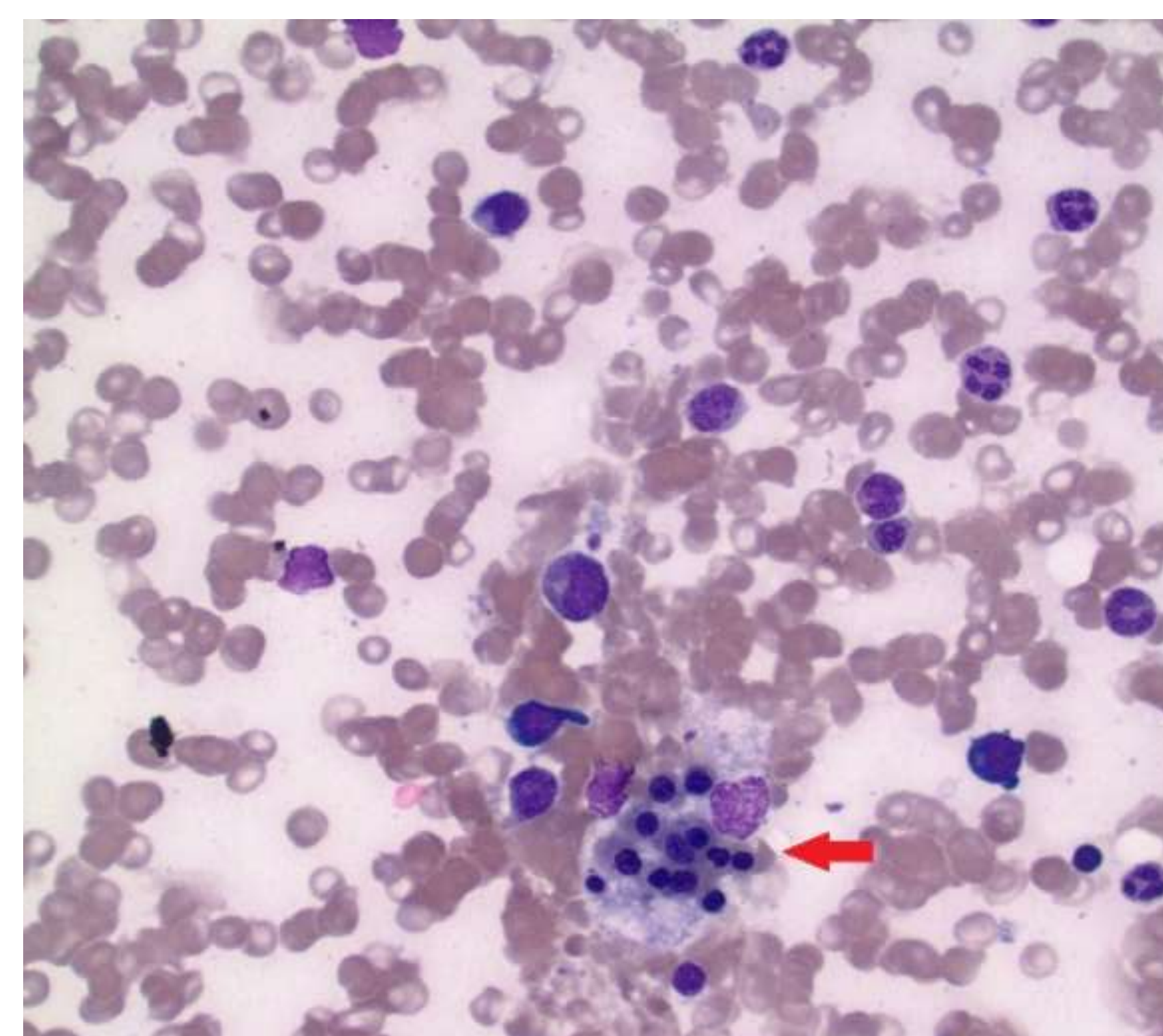


Figure 2. Grocott-Gomori Methenamine Silver stain. Intracellular budding yeast forms.



Figure 3. Hemophagocytosis in bone marrow aspirate smear. The photomicrograph depicts a macrophage in the center of the smear ingesting nucleated red cell precursors.



Discussion

- Histoplasmosis is the most common endemic mycosis in the United States is usually transmitted after inhalation of the organism, which is present in soils contaminated by bird or bat droppings⁵.
- The disseminated form is more common in the immunocompromised host and extreme of ages. Liver involvement presents with abnormal liver biochemistries.
- Diagnostic tests include blood cultures, antigen detection, polymerase chain reaction assays and direct microscopic examination.
- DH is treated with amphotericin B for severe infections and itraconazole for mild to moderate disease.
- HLH presents as a febrile illness with multiorgan involvement including splenomegaly, cytopenias, coagulation abnormalities, extreme hyperferritinemia, hypertriglyceridemia, hemophagocytosis, and elevation of the soluble IL 2 receptor.
- Infection-related HLH cases should be treated aggressively with standard HLH protocols that include dexamethasone, etoposide and cyclosporine.

Conclusion

- This case portrays the challenges of diagnosing DH given the diverse clinical manifestations
- The presence of persistent fever and a cholestatic biochemical profile should raise the index of suspicion in the right clinical setting.
- Awareness of HLH avoids missing a life-threatening condition, but also prevents overdiagnosis that can lead to administration of corticosteroids and cytotoxic agents in critically ill individuals.
- Early recognition is crucial for a reasonable attempt at curative therapy, as treating the triggering event alone is usually not sufficient.

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