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# Chicken Coop-Induced Hemophagocytic Lymphohistiocytosis

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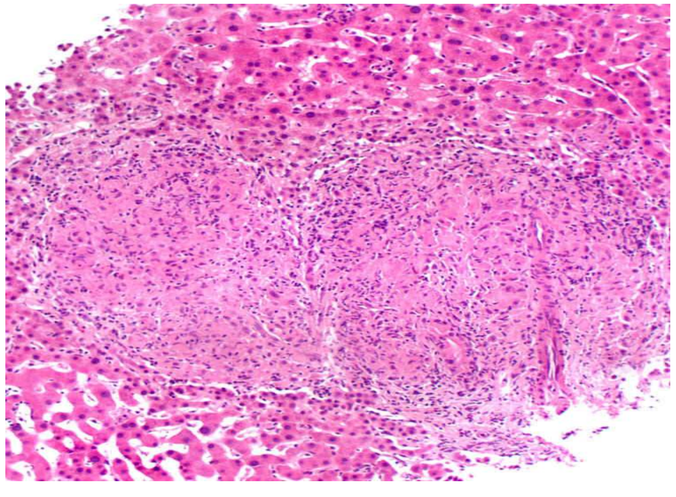
## Introduction

- Hemophagocytic Lymphohistiocystosis (HLH) is a rare and often fatal condition
- It is characterized by an overactive but ineffective response of the immune system
- There have been several documented causes of HLH, which include genetic predisposition, malignancy, infection, autoimmune disease and chronic immunosuppressive therapy
- Due to its non-specific presentation, HLH is often under-recognized, severely aggressive, and associated with high mortality rates

## Case Presentation

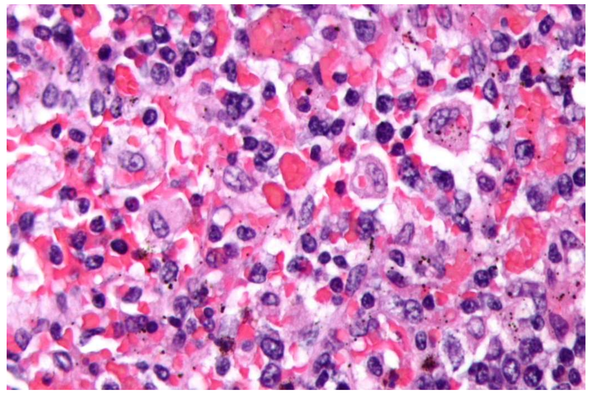
- A 42-year-old woman with a two-year history of ankylosing spondylitis, who was recently initiated on Infliximab, presented with abdominal pain, fevers, and jaundice.
- She was found to have a temperature of 104F and was noted to have leukocytosis.
- She was suspected to have acute cholangitis and was initially treated with antibiotics, however, several imaging studies, including ultrasound, HIDA, and MRCP did not appreciate intra or extra hepatic duct dilatation, bile duct wall thickening, or cholelithiasis/choledocholithiasis.
- Her clinical condition worsened, progressing to renal failure, cerebral edema and new onset seizures. She remained febrile and had persistent elevation of her liver enzymes and bilirubin.
- Liver biopsy was obtained and demonstrated acute granulomatous hepatitis secondary to fungal organisms, morphologically consistent with histoplasmosis (figure 1).
- Interestingly, further history from the patient revealed that she had been maintaining a chicken coop in her back yard for the past several years and may have been the source of *Histoplasma capsulatum.*



- Figure 1. Example of liver biopsy in patient with disseminated histoplasmosis. Portrayed is an example of the granulomas that may form that consist of focal accumulations of macrophages. (retrieved from https://basicmedicalkey.com/histoplasmosis-6/)

## Case Presentation (continued)

- Due to persistent fevers, cytopenia and a ferritin level of greater than 20,000, the suspicion for HLH continued to grow
- Bone marrow biopsy was performed which noted hemophagocytic cells (figure 3), as well as fungal yeast forms, seen with use of GMS stain.
- This patient ultimately was found to have met six of the eight diagnostic criteria for HLH as documented in Table 1 [fever, bi-cytopenia, hypertriglyceridemia, elevated ferritin, elevated soluble IL-2 receptor, and hemophagocytosis on bone marrow biopsy]
- She was started on Amphotericin B for treatment of disseminated histoplasmosis, as well as Etoposide (total two doses) and Dexamethasone for treatment of HLH.
- Her clinical condition improved, and within three weeks of initial diagnosis of HLH, she was ultimately discharged home with continued anti-fungal treatment with Itraconazole, as well as a four-week taper of Dexamethasone.



- Figure 2. Micrograph depicting hematopoetic cells within macrophages as described in cases of HLH. (retrieved from https://en.wikipedia.org/wiki/Hemophagocytic_lymphohistiocytosis)

## Diagnostic Criteria of HLH

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| Molecular diagnosis consistent with HLH; mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 |
| **OR** |
| (B) 5 of the 8 criteria listed below to be fulfilled: |
| 1. Fever > 38.5C |
| 2. Splenomegaly |
| 3. Cytopenias (affecting 2 of 3 lineages in peripheral blood) |
| 4. Hypertriglyceridemia (>265 mg/dL) or Hypofibrinogenemia (<150 mg/dL) |
| 5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver |
| 6. Low or absent NK-cell activity |
| 7. Ferritin >500 ng/mL |
| 8. Elevated sCD25 (IL-2 receptor) |

Table 1. Histiocyte Society HLH-2004 criteria for diagnosing HLH

## Discussion

- HLH is a rare but potentially fatal disease, characterized by persistent immune activation and cytokine release, stimulating bone marrow macrophages to engulf hematopoietic cells
- This case illustrates a patient, who after initiation of treatment with an anti-TNF agent for ankylosing spondylitis, developed HLH due to disseminated infection with *Histoplasma capsulatum*
- Due to its aggressive nature, it is crucial to identify the underlying insult for triggering HLH, as it will determine which therapeutics to seek.
- Diagnosis of the disease is outlined in table 1
- Recommended within the Histiocyte Society HLH-2004 guidelines, the current standard treatment for HLH entails initiating cytotoxic chemotherapy and prospective bone marrow transplant. However, as described in our case, prompt diagnosis and directed treatment to the underlying cause of HLH, may improve outcomes in patients with this fatal condition.
- Interestingly, case reports have shown that patient's receiving anti-tumor necrosis factor-alpha therapy, with drugs including Infliximab, have an increased risk of developing disseminated infections with *Histoplasma capsulatum.*
- Our case presents the importance of having prompt recognition of HLH in patients with non-specific constitutional symptoms such as fever and fatigue and in patients whose origin of fever remains unknown. Especially in patients who are immunocompromised, assessment of serum ferritin level may aid in the diagnosis of HLH.

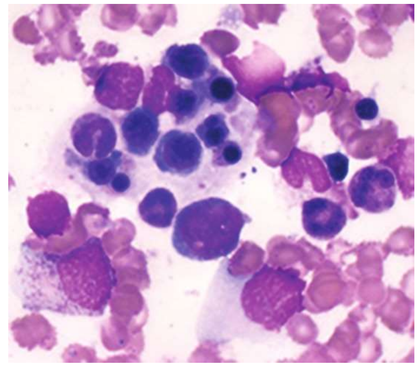

Figure 3. Example of a bone marrow biopsy showing significant hemophagocystosis. (retrieved from http://www.haematologica.org/content/103/10/1635)

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