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## Case and Review

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# Hemophagocytic Lymphohistiocytosis Secondary to Unknown Underlying Hodgkin Lymphoma Presenting with a Cholestatic Pattern of Liver Injury

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## Keywords

Hemophagocytic lymphohistiocytosis · Hodgkin lymphoma · Cholestatic biliary injury · Fever of unknown origin · Autoimmune disease

## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon disease that often presents with nonspecific findings. A high index of suspicion is necessary to make a prompt diagnosis and prevent fatal disease. A 45-year-old man presented with fever, hypotension, abdominal pain, nausea, and vomiting. Imaging showed hepatosplenomegaly and laboratory tests revealed pancytopenia, increased ferritin, and a cholestatic pattern of injury with elevated alkaline phosphatase and total bilirubin. Due to a history of Crohn disease, systemic lupus erythematosus, and rheumatoid arthritis, the patient was on immunosuppressants, including infliximab. After multiple negative cultures, persistent fever, and days of empiric broad spectrum antibiotics, our differential shifted to fever of unknown origin. A liver wedge biopsy revealed areas of sinusoidal dilatation with enlarged, activated macrophages containing

erythrocytes and intracytoplasmic iron, consistent with hemophagocytosis due to HLH. The portal tracts showed mixed lymphoplasmacytic inflammation, a prominent bile ductular reaction, periportal fibrosis, and scattered large cells with occasional binucleation and prominent nucleoli. These cells stained positive for Epstein-Barr virus encoding region in situ hybridization, PAX5, CD15, and CD30, and hepatic involvement by classic Hodgkin lymphoma was diagnosed and determined to be the cause of the HLH and cholestatic pattern of injury. Simultaneously, a bone marrow biopsy showed diffuse involvement by Hodgkin lymphoma with a similar staining pattern. Aggressive treatment failed and the patient succumbed to multiorgan failure. HLH is a rare, potentially fatal disease, with nonspecific signs and symptoms, and should be considered in any patient presenting with fever and pancytopenia, especially if they are immune compromised.

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## Background

HLH is a rare disease that often has a nonspecific presentation and may be missed if there is not a high index of clinical suspicion [1]. Primary or familial HLH occurs most often in the pediatric age group, with roughly 20–50% of cases due to mutation of *PFR1* resulting in perforin defects. Less common mutations occur in other genes involved in the regulation and use of cytotoxic granules. Disruption of these cellular pathways leads to improper activation of natural killer cells, macrophages, and lymphocytes, resulting in overstimulation of the immune response, which can lead to multiorgan failure and death [1, 2]. The secondary form of HLH is the type most often observed in adults and it has a number of etiologies including all types of infections (i.e., viral, bacterial, parasitic, fungal, and mycobacterial), malignancies (e.g., T-cell/natural killer cell lymphomas, anaplastic large-cell lymphoma, acute lymphoblastic leukemia, Hodgkin lymphoma, multiple myeloma, acute erythroid leukemia), and acquired immunodeficiency (e.g., HIV/AIDS, transplantation, chemotherapy, immunosuppressive treatment) [3]. In fact, secondary HLH has been found to be present in approximately 1% of patients diagnosed with hematologic malignancies. HLH is associated with multiorgan failure and high rates of morbidity and mortality [4]. The currently accepted criteria are shown in Table 1, which includes clinical, laboratory, and histopathologic data. At least 5 of the 8 features must be present for diagnosis. Fardet et al. [5] developed a diagnostic score, the HScore, in an attempt to aid in the prompt diagnosis of secondary HLH. The score assigns points to variables most commonly associated with the diagnostic criteria for HLH, with the addition of underlying immunosuppression and an elevated aspartate transaminase. The summation of these points corresponds to the probability that patients have HLH. We present a unique case involving an immunocompromised man with fever and a cholestatic pattern of injury of unknown origin.

## Case Presentation

A 45-year-old Caucasian man presented with persistent fever that was associated with abdominal pain, nausea, and vomiting. He also reported 4 weeks of weakness, fatigue, and

unintentional subjective weight loss, which he attributed to his chronic autoimmune diseases. He had a clinical history of multiple autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and Crohn disease for which he previously underwent subtotal colectomy with ileocolic anastomosis. His surgical history included a previous right pneumonectomy for recurrent right-sided pneumothorax with nonhealing bronchopleural fistula. His only medication upon admission was infliximab.

Upon admission, he was febrile (39.4°C), normotensive (111/60 mm Hg), tachycardic (140 beats/min), and tachypneic (22 breaths/min). Initial physical examination revealed a cachectic man with decreased breath sounds on the right lung field. His abdomen was soft, tender to palpation but without guarding or rigidity. Initial basic laboratory studies on admission were notable for anemia (hemoglobin 6.2 g/dL), thrombocytopenia (platelet count  $82 \times 10^3/\mu\text{L}$ ), hyponatremia (sodium 124 mmol/L), and elevated alkaline phosphatase (290 U/L). Computed tomography of the abdomen showed hepatosplenomegaly, a dilated small bowel, and prominent celiac, periaortic, and retroperitoneal lymph nodes. After blood cultures were taken, empiric antibiotic treatment was initiated for sepsis and possible underlying, undiagnosed infection. At this time the likely source of infection was thought to be small intestinal obstruction, given his history of Crohn disease and dilated bowel observed by imaging. On day 2 after admission, his diarrhea continued and a substantial electrolyte imbalance with absent flatus was noted. Bowel rest and intravenous hydration were recommended at this time, although there was discussion about possible exploratory laparotomy if his condition did not begin to improve. On hospital day 3 laboratory results showed a worsening pancytopenia (white cell count  $2.8 \times 10^3/\mu\text{L}$ , hemoglobin 7.1 g/dL, platelet count  $33 \times 10^3/\mu\text{L}$ ), hyperferritinemia, and a cholestatic liver injury profile (elevated total bilirubin and alkaline phosphatase) (Table 2).

The patient was unresponsive to empiric antibiotics and all blood cultures were negative. On day 5 after admission, his hepatic enzymes revealed a worsening cholestatic pattern of liver injury, with a total bilirubin of 5.3 mg/dL and an alkaline phosphatase of 146 U/L. On day 12, he was still not showing any signs of clinical improvement and, since his symptoms were suggestive of worsening bowel obstruction, an exploratory laparotomy was conducted in which multiple abdominal adhesions were lysed and a portion of the small bowel was resected, with no pathologic changes identified. Due to his worsening hepatic function and cholestatic liver injury profile (total bilirubin was now 12.6 mg/dL), a wedge biopsy of the liver was obtained during the surgery. After surgery, the patient was unable to be weaned from mechanical ventilation and required intravenous vasopressors to maintain hemodynamic stability. The following day, due to worsening pancytopenia, a bone marrow biopsy was performed. Unfortunately, despite aggressive supportive measures, the patient succumbed to multiorgan failure prior to obtaining the liver and bone marrow biopsy results.

The main histopathologic findings in the liver biopsy revealed areas of sinusoidal dilatation with enlarged, activated macrophages (highlighted best with the iron stain) that contain prominent intracytoplasmic iron, focal bile, and aggregates of intracytoplasmic red blood cells (Fig. 1). The portal tracts showed mixed lymphoplasmacytic inflammation, moderate periportal fibrosis, a prominent bile ductular reaction with focal cholangitis, and hepatocellular cholestasis, and scattered large cells with occasional binucleation and prominent nucleoli were identified, primarily within the portal tracts. These cells stained positive for CD15, CD30, and Epstein-Barr encoding region in situ hybridization, confirming them as

classic Reed-Sternberg cells. Immunohistochemical stains confirmed that the portal inflammation was composed primarily of CD3+ T lymphocytes, interspersed CD20+/*PAX-5*+ B cells, and focal histiocytes (Fig. 2). These features support the diagnosis of HLH due to liver involvement by classic, lymphocyte-rich Hodgkin lymphoma. The laboratory studies and biopsy findings both showed evidence of biliary injury; however, there was no evidence in the biopsy that the infiltrative process was causing chronic biliary obstruction (copper was negative for periportal staining, and cytokeratin 7 showed a moderate ductular reaction; Fig. 3). Concurrently, the bone marrow biopsy showed diffuse involvement by Hodgkin lymphoma, which had a similar phenotype to that described in the liver.

## Discussion

The most common causes of secondary HLH in adults are infections (49%), neoplasms (27%), rheumatoid arthritis (7%), and immunodeficiencies (6%) [6]. Excessive cytokine secretion by T lymphocytes leads to overactivation of macrophages, causing multiorgan failure. Development of HLH is commonly associated with hematologic malignancies, often non-Hodgkin lymphoma [7]. The initial clinical suspicion regarding our patient was sepsis due to possible small bowel obstruction; however, the presence of a cholestatic liver injury profile in the setting of hepatosplenomegaly prompted a liver biopsy to be obtained, which led to the diagnosis of HLH due to underlying Hodgkin lymphoma. Due to the sepsis-like presentation and history of complicated Crohn disease, diagnosis was delayed. His cholestatic injury pattern was likely due to portal and biliary infiltration by lymphocytes and histiocytes [7]. Periportal copper deposition is identified in 50–94% of chronic cholestatic disease. Cholangiolar metaplasia leads to cytokeratin 7 positivity in hepatocytes in 70% of biopsies of chronic cholestatic disease [8]. The absence of associated findings suggests that although these infiltrates resulted in bile duct injury, they had not caused chronic biliary obstruction.

There is insufficient research to definitively explain the pathophysiology behind the cause of HLH secondary to hematologic malignancy. HLH extension to the liver by Hodgkin lymphoma is typically seen in advanced disease, which was not the case in our patient. Autoimmune disease is also associated with secondary HLH, with systemic juvenile idiopathic arthritis having been most described in the recent literature [9, 10]. Pediatric patients with inflammatory bowel disease have been reported to have a 100-times greater risk of developing HLH compared to the general population [11]. Although it has not been extensively studied in adults, there have been case reports suggesting a relationship between Crohn disease and HLH [12, 13]. It is presumed that immunosuppressant therapy in the treatment of inflammatory bowel disease plays a role in facilitating infection and thus predisposing to secondary HLH [13]. In particular, infliximab is independently associated with the development of Hodgkin lymphoma, as well as secondary HLH [14, 15]. Having both Crohn disease (an autoimmune process) and a hematologic malignancy may have put our patient at increased risk of developing secondary HLH.

One of the most difficult aspects of diagnosing this syndrome is the variable clinical presentation and nonspecific findings, creating a challenging situation for clinicians and delaying prompt treatment. In another documented case of HLH secondary to malignancy, a patient with metastatic renal cell carcinoma presented with flu-like symptoms, rapidly dete-

riorated requiring mechanical ventilation, and a clinical diagnosis of HLH was made after infectious causes were ruled out [16]. The patient recovered with high-dose steroid treatment. Underlying infection is another common trigger for secondary HLH. Anandh et al. [17] described a case of HLH confirmed by bone marrow biopsy after the patient presented with sepsis secondary to *Pseudomonas* bacteremia from a hemodialysis catheter. Cytomegalovirus pneumonia was also recently reported as an infectious association of HLH, where the patient presented with vague symptoms and developed acute hypoxic respiratory failure [18]. Because of the presence of high fevers in these cases, patients are often initially treated with broad-spectrum antibiotics while possible infectious causes are being ruled out. The patient with renal cell carcinoma was rapidly diagnosed with HLH, and the patient survived due to initiation of prompt treatment with high-dose steroids. The other 2 patients with infectious etiologies had bone marrow biopsies which demonstrated diffuse hemophagocytosis. However, the disease progressed and was still fatal, likely due to the additional insult of active infection on the immune system. Our patient had an unknown underlying malignancy with hepatic involvement and a cholestatic liver injury profile, which muddled diagnosis and clinical recognition of secondary HLH.

A heightened sense of awareness regarding the diagnostic criteria is critical – even if other unusual findings, such as a cholestatic liver injury pattern, are present. A review of multiple HLH cases determined that 100% of them presented with fever, 80–90% with hepatosplenomegaly by physical examination or imaging, and 80% with cytopenia [19]. In a patient presenting with high fever  $>37^{\circ}\text{C}$  unresponsive to broad-spectrum antibiotics, hepatosplenomegaly, pancytopenia, and/or elevated ferritin, HLH should be suspected, especially in immune-compromised patients. If any of these main criteria are present, even if other findings such as cholestatic biliary injury are complicating the clinical picture, HLH needs to be reasonably excluded. This uncommon disease can have a nonspecific presentation and requires a high index of clinical suspicion for diagnosis; delay may result in unnecessary procedures and improper management, and may be fatal.

### Statement of Ethics

The authors have adhered to the ethical guidelines of the journal and there is no identifying patient information in the manuscript.

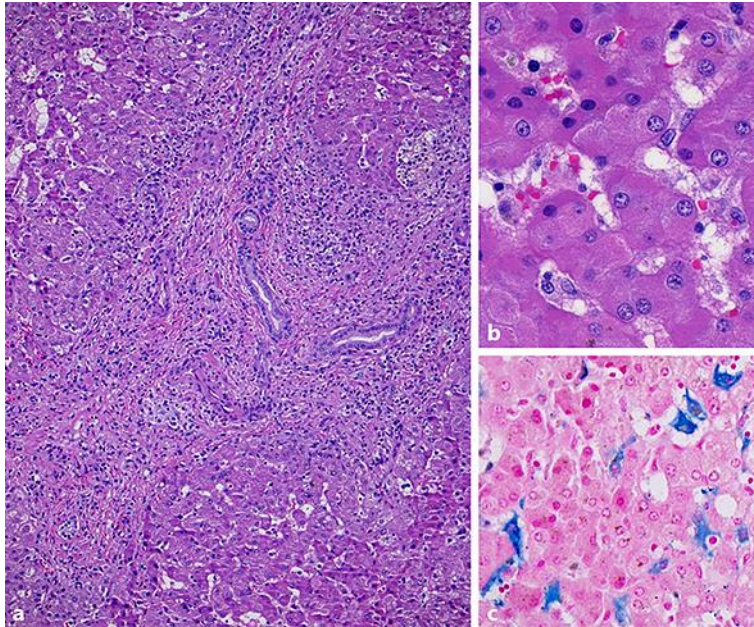
### Disclosure Statement

The authors have no conflicts of interest to declare.

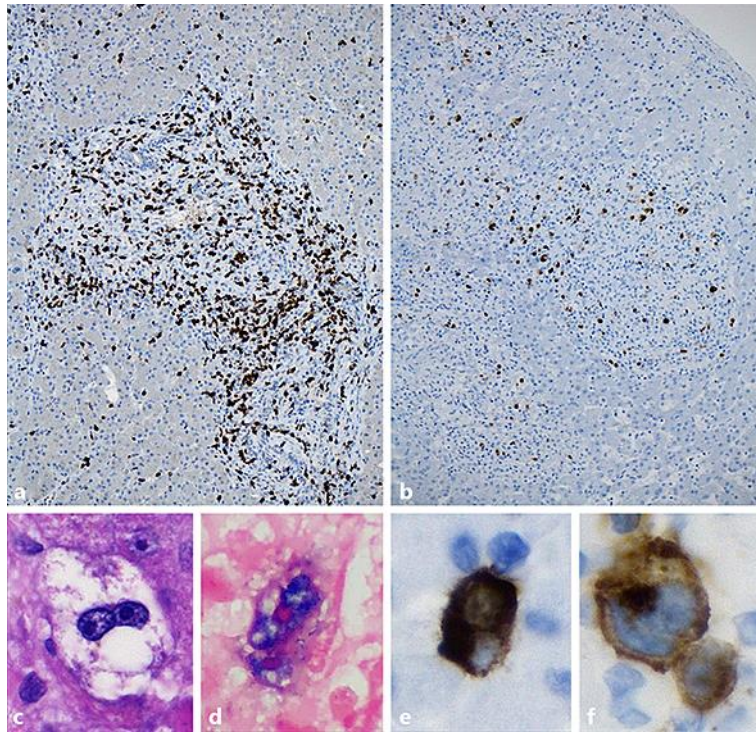
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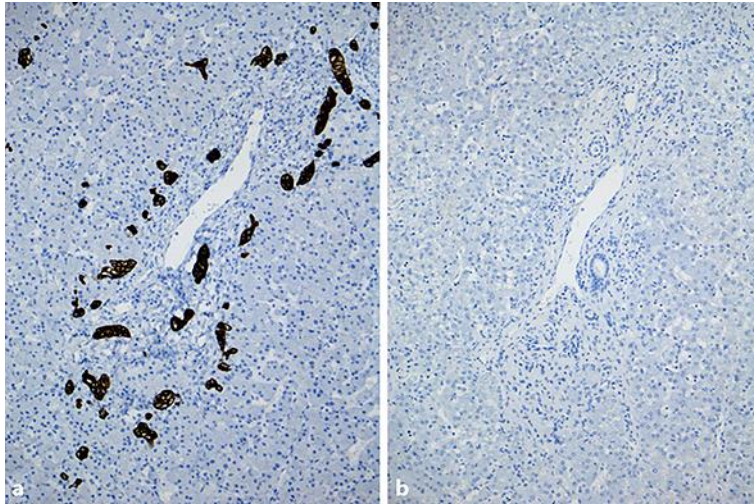


**Fig. 1.** Histopathology revealed features of hemophagocytic lymphohistiocytosis syndrome due to hepatic involvement by Hodgkin lymphoma. **a** A portal tract with primarily lymphoplasmacytic inflammation and moderate periportal fibrosis. H&E.  $\times 100$ . **b** High-power magnification shows dilated sinusoids packed with enlarged, activated macrophages containing intracytoplasmic red blood cells.  $\times 600$ . **c** A Prussian blue stain for iron highlights the enlarged macrophages and hemophagocytosis.  $\times 100$ .



**Fig. 2.** There were also abundant CD3+ T cells (**a**;  $\times 200$ ) and scattered PAX8+ B cells (**b**;  $\times 100$ ) within the portal tracts. H&E shows Reed-Sternberg cells (**c**;  $\times 600$ ) throughout the portal and periportal areas positive for EBV (by Epstein-Barr encoding region in situ hybridization) (**d**;  $\times 600$ ), CD15 (**e**;  $\times 600$ ), and CD30 (**f**;  $\times 600$ ).





**Fig. 3.** Cytokeratin 7 immunostaining (**a**;  $\times 100$ ) of the liver wedge biopsy highlighted a moderate ductular reaction with no evidence of hepatocyte cholangiolar metaplasia and did not demonstrate periportal copper staining (**b**;  $\times 100$ ).

**Table 1.** Criteria for hemophagocytic lymphohistiocytosis (HLH) diagnosis

At least 5 of the 8 features must be present for diagnosis

- Fever
- Splenomegaly
- Cytopenia of  $>2$  blood cell lines
- Hypertriglyceridemia ( $>265$  mg/dL) or hypofibrinogenemia ( $<1.5$  g/L)
- Hemophagocytosis demonstrated in bone marrow, spleen, or lymph nodes
- Serum ferritin ( $>500$  ug/L)
- Soluble CD25 (soluble interleukin-2 receptor)  $>2,400$  U/mL

International Histiocyte Society HLH-2004. Adapted from Henter et al. [20].

**Table 2.** Laboratory tests obtained from blood and urine samples on hospital day 3.

Test name	Result	Reference range
White blood cell count	2.8×10 <sup>3</sup> /mm <sup>3</sup>	4.0–10.8
Red blood cell count	2.24×10 <sup>3</sup> /mm <sup>3</sup>	4.20–5.60
Hemoglobin	7.1 g/dL	14.0–18.0
Hematocrit	20.0%	42–52
Platelet count	33×10 <sup>3</sup> /mm <sup>3</sup>	130–400
Neutrophils relative	79.5%	37–80
Lymphocytes relative	7.4%	18–42
Monocytes relative	12.4%	0.0–12
Eosinophils relative	0.3%	0.0–4.6
Basophils relative	0.4%	0.0–2.5
Neutrophils absolute	2.2×10 <sup>3</sup> /mm <sup>3</sup>	1.5–8.6
Lymphocytes absolute	0.2×10 <sup>3</sup> /mm <sup>3</sup>	0.7–3.5
Monocytes absolute	0.3×10 <sup>3</sup> /mm <sup>3</sup>	0.0–1.3
Eosinophils absolute	0.0×10 <sup>3</sup> /mm <sup>3</sup>	0.0–0.8
Basophils absolute	0.0×10 <sup>3</sup> /mm <sup>3</sup>	0.0–0.3
Reticulocyte relative	0.6%	0.8–2.1
Bilirubin, total	3.1 mg/dL	0.3–1.2
Ferritin	6,148.9 ng/mL	22–322
Alkaline phosphatase	242 IU/L	56–119
Albumin	2.3 g/dL	3.5–5.0
Aspartate transaminase	48 U/L	13–40
Alanine transaminase	30 U/L	9–51
Prothrombin time	20.6 s	11.6–14
INR	1.73	0.88–1.10
Partial thromboplastin time	54.9 s	22.1–37.4
TB screen	negative	
HIV ½ antibody direct	negative	
HIV p24 antigen direct	negative	
Legionella pneumonia Ag, urine	negative	
Histoplasma antigen, urine	negative	
Blood cultures (bacteria, fungi)	negative	

INR, international normalized ratio; TB, tuberculosis; HIV, human immunodeficiency virus; Ag, antigen.