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Rand Abou Shaar

Kyle D. Perry

Zaher K. Otrock

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# Hemophagocytosis on ascitic fluid cytology: Diagnosis of HLH

Rand Abou Shaar MD | Kyle D. Perry MD | Zaher K. Otrock MD

Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, Michigan, USA

**Correspondence**
Zaher K. Otrock, Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA;, Transfusion Medicine, Henry Ford Hospital, Department of Pathology - K6, 2799 West Grand Blvd, Detroit, MI 48202, USA.
Email: zotrock1@hfhs.org
zaherotrock@hotmail.com

## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of pathologic immune response characterized by excessive activation of macrophages. Hemophagocytosis is one of the diagnostic criteria for HLH, and it usually involves the bone marrow, spleen, lymph nodes, or any part of the reticuloendothelial system. Hemophagocytosis in the ascitic fluid has rarely been reported in HLH. Here, we report the case of a patient who presented with fever and abdominal distention and ascites. Ascitic fluid cytology showed hemophagocytosis which was the clue for HLH diagnosis. We also review the literature for this rare cytological occurrence.

**KEYWORDS**
ascitic fluid, cytology, hemophagocytosis

## 1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of pathologic immune response characterized by excessive activation of macrophages.[1] HLH is categorized into two forms: primary (familial) or secondary (acquired). Primary HLH mostly affects children and results from genetic defects in cytotoxic T cells and natural killer cells. Secondary HLH typically occurs in adults and is frequently triggered by infections, malignancies, or autoimmune diseases.[2,3] The available diagnostic criteria for HLH were originally established in pediatric patients in 1991,[4] and were revised in 2004.[5] The HLH-2004 criteria are used to diagnose adult HLH. Patients frequently present with fever, cytopenias, hyperferritinemia, and splenomegaly.

Hemophagocytosis is one of the diagnostic criteria for HLH, and it usually involves the bone marrow, spleen, lymph nodes, or any part of the reticuloendothelial system. Although the presence of hemophagocytosis is considered to be a characteristic of HLH, it is neither sensitive nor specific for HLH.[6] Hemophagocytosis may not be detected on initial bone marrow or tissue assessment, and it may occur late in the course of the disease. In addition, hemophagocytosis can be a physiologic finding following blood transfusion or surgery, or may be seen in infections, malignancies, and other acute illnesses.[7,8] Hemophagocytosis in the ascitic fluid has rarely been reported in HLH.[9,10] Here, we report the case of a patient who presented with fever and abdominal distention and ascites. Ascitic fluid cytology showed hemophagocytosis which was the clue for HLH diagnosis. We also review the literature for this rare cytological occurrence.

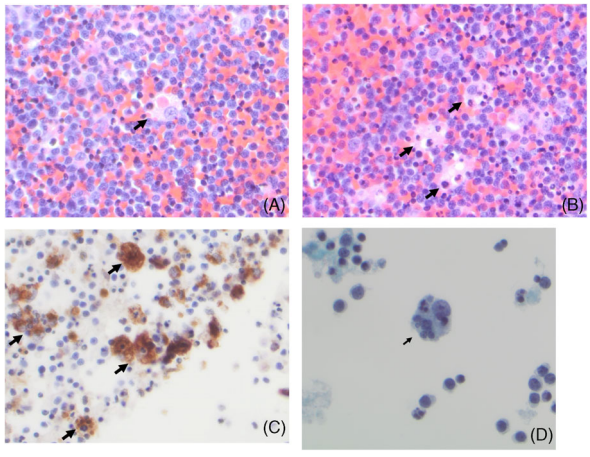


**FIGURE 1** Ascitic fluid cytology. (A), (B) Cell block preparation showing hemophagocytic histiocytes with engulfed erythrocytes and neutrophils (Hematoxylin & Eosin stain, ×60). (C) CD68 immunohistochemical stain highlighting abundant histiocytes with engulfed lymphocytes (×60). (D) Cytospin preparation showing histiocytes phagocytosing lymphocytes and a neutrophil (Papanicolaou stain, ×60) [Color figure can be viewed at wileyonlinelibrary.com]

  

## 2 | CASE PRESENTATION

A 53-year-old man with past medical history of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) on chronic steroids, obesity, and osteoporosis presented to the Emergency Department with fever and reported chills, myalgias, headache, abdominal distension and discomfort, and shortness of breath. The patient reported episodic fever responding to antipyretics 3 months earlier, for which an extensive workup for malignancy, autoimmune diseases, and infections was negative. Workup of fever of unknown origin included an evaluation for HLH which revealed only mild thrombocytopenia (platelet count $103 \times 10^3/\mu l$) and hyperferritinemia (ferritin 3340 ng/ml). Bone marrow biopsy evaluation performed 3 weeks prior to the current presentation was unremarkable.

During the current presentation, patient was febrile at 102.1°F and tachycardic at 129 beats/min. Laboratory results during the current presentation revealed WBC of $2.6 \times 10^3/\mu l$, hemoglobin of 12.2 g/dl, platelet count of $114 \times 10^3/\mu l$, sodium of 127 mmol/L, alanine aminotransferase of 57 IU/L, aspartate aminotransferase of 133 IU/L, ferritin of 18,356 ng/ml, fibrinogen of 95 mg/dl, and triglycerides of 376 mg/dl. Chest X-ray was unremarkable. Computed tomography (CT) scan of chest, abdomen, and pelvis showed ascites and was negative for hepatosplenomegaly. Soluble interleukin-2 receptor (CD25) was not elevated. Repeated Covid-19 testing was negative. Broad infectious work remained unremarkable. Extensive brain imaging due to CLIPPERS and concern for venous thrombosis was negative for acute changes.

The leading differential diagnosis was HLH in the setting of fever of unknown origin and elevated ferritin; however, previous evaluation for HLH including bone marrow biopsy was negative, and during the current presentation the patient did not fulfill five of the eight HLH-2004 diagnostic criteria yet. Patient underwent ultrasound guided paracentesis draining 4.5 L of clear yellow fluid consistent with transudate, the culture of which was negative. Ascitic fluid cytology comprised predominantly of an atypical lymphoid proliferation with several apoptotic cells. Frequent histiocytic cells showed evidence of hemophagocytosis (Figure 1). Although the patient did not fulfill the HLH criteria, the presence of hemophagocytosis in the ascitic fluid heightened the medical team concern for HLH possibly secondary to malignancy. A repeat bone marrow biopsy was negative for neoplasia but now showed evidence of hemophagocytosis. Patient had worsening cytopenias with WBC of $1.3 \times 10^3/\mu l$, hemoglobin of 8.9 g/dl, and platelet count of $59 \times 10^3/\mu l$. The diagnosis of HLH was established. Patient was treated with HLH-94 protocol (etoposide, dexamethasone, and intrathecal methotrexate) followed by allogeneic hematopoietic stem cell transplantation with good response. On 1-year follow up after transplant, patient is doing well without evidence of HLH recurrence.

## 3 | DISCUSSION

We described the case of a young patient with history of CLIPPERS who presented with fever of unknown origin, the workup of which was repeatedly non-revealing. Although HLH was on the differential, the patient did not fulfill the criteria and his initial bone marrow biopsy was negative for hemophagocytosis. However, ascitic fluid cytology showed hemophagocytic activity which increased the suspicion for HLH diagnosis. This triggered a repeat bone marrow biopsy now showing hemophagocytosis, which along with worsening cytopenias confirmed the diagnosis of HLH. This finding of hemophagocytosis on ascitic fluid has rarely been reported.[9,10] In addition to being a rare occurrence, this case illustrates the challenges in diagnosing HLH. Hemophagocytosis which is one of the diagnostic criteria for HLH, was not detected on the patient's initial bone marrow biopsy, thus delaying diagnosis. Ascitic fluid hemophagocytosis was the clue for HLH diagnosis which was later confirmed by repeat bone marrow biopsy. Ascitic fluid hemophagocytosis was one of the systemic manifestations of HLH.

### AUTHOR CONTRIBUTIONS

Rand Abou Shaar, Zaher K. Otrock: Study design, drafting the paper and revising it critically; Kyle D. Perry: pathology review.

### FUNDING INFORMATION

None.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ORCID

*Rand Abou Shaar* https://orcid.org/0000-0002-2947-1127
*Zaher K. Otrock* https://orcid.org/0000-0002-5823-2694

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