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J Case Rep Images Pediatr 2022;4(1):1–6.
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# Liver recovery in a child with hemophagocytic lymphohistiocytosis-induced acute liver failure

Charles Kreisel, Andrew Meshnick, Gregory Carlisle, Jeffrey Toretsky, Michael Terao, Alexandra Monde

## ABSTRACT

**Introduction:** Hemophagocytic lymphohistiocytosis is a rare condition with dysregulated multi-organ inflammation that may cause acute liver failure. It often presents with non-specific clinical features and can be difficult to diagnose.

**Case Report:** We present the case of a 2-year-old girl with lethargy, encephalopathy, poor oral intake, vomiting, and jaundice. Her labs indicated acute liver failure with additional findings of bicytopenia and elevated ferritin. Given high concern for hemophagocytic lymphohistiocytosis, we promptly consulted the hematology/oncology, transplant hepatology, and pharmacy services. Bone marrow biopsy initially showed no evidence of hemophagocytosis. Given our high clinical index of suspicion for hemophagocytic lymphohistiocytosis and its high mortality and morbidity, we initiated treatment with high dose dexamethasone, etoposide, and the recently approved biologic drug emapalumab, a monoclonal antibody against interferon gamma, despite not meeting full HLH-2004 diagnostic criteria. One day after treatment initiation, the final review of the bone marrow biopsy showed evidence of hemophagocytosis. Ultimately, with implementation of multidisciplinary rounds, close neurologic examinations, aggressive management of evolving hyperammonemia and cerebral edema, and early initiation of treatment, our patient achieved full liver recovery.

**Conclusion:** This patient's presentation emphasizes the importance of having a broad differential when a patient presents with liver failure and cytopenias. Our management of this patient showcases the importance of expedient, multidisciplinary management for a complex critically ill pediatric patient. The patient's survival and complete liver recovery with the treatment protocol given suggests emapalumab should be studied in future clinical trials as an important adjunctive treatment for patients with hemophagocytic lymphohistiocytosis with acute liver failure..

**Keywords:** Acute liver failure, Emapalumab, Hemophagocytic lymphohistiocytosis

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Received: 02 May 2022
Accepted: 15 June 2022
Published: 21 July 2022

How to cite this article

Kreisel C, Meshnick A, Carlisle G, Toretsky J, Terao M, Monde A. Liver recovery in a child with hemophagocytic lymphohistiocytosis-induced acute liver failure. J Case Rep Images Pediatr 2022;4(1):1–6.

Article ID: 100015Z19CK2022

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doi: 10.5348/100015Z19CK2022CR

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare condition characterized by dysregulated multi-organ inflammation that may cause acute liver failure (ALF). It affects fewer than one in every 100,000 children under one year of age and is even less prevalent in older children [1, 2]. It is divided into primary and secondary based upon etiology. Primary HLH has a known genetic association while secondary HLH is caused by an exogenous trigger such as infection, rheumatologic disease, or cancer [1].

While HLH-induced acute liver failure has been well characterized in the literature, a majority of patients described died of complications due to acute liver failure and HLH [3–5]. Further, though patients with HLH eventually require specialist consultation with hematology and oncology, often pediatric generalists and intensivists are the first physicians to encounter these patients at the inflection point in their disease course. To better equip the pediatric community to diagnose and manage this rare and potentially fatal, but treatable, disease, we comprehensively describe HLH-induced acute liver failure as well as our success in achieving full liver recovery with early disease recognition, initiation of treatment, and prompt coordination of care.

## CASE REPORT

A 2-year-old female with no significant past medical history presented to the Inova Children's Hospital's (ICH) Emergency Department with lethargy, encephalopathy, poor oral intake with vomiting, and jaundice. Three weeks prior, she presented to her primary care provider with a fever greater than 39°C and a diffuse maculopapular rash. At that time, she was diagnosed with an unspecified viral syndrome and supportive care was recommended. Given persistent symptoms and evolving jaundice, she presented to the ICH ED with the above complaints. She was found to be hypovolemic, hypoglycemic, and was noted to have severe electrolyte derangements, a marked leukocytosis ($28.5\times10^3/\mu L$), extremely elevated ferritin (>40,000 ng/mL), decreased fibrinogen (91 mg/dL), and other labs consistent with acute liver failure (Table 1). The patient was then admitted to the pediatric intensive care unit (PICU) for further care and evaluation. Due to diagnostic factors suggesting acute liver failure progression, she was transferred to MedStar Georgetown University Hospital (MGUH) for further management and liver transplant evaluation.

At time of admission to MGUH, she was febrile with grade one encephalopathy and diffuse jaundice. Continued investigation for other etiologies of acute liver failure revealed no evidence of acetaminophen toxicity or acute viral hepatitis. Given the clinical and laboratory picture, a diagnosis of HLH was highly suspected. Within 30 hours of admission, the hematology/oncology and transplant gastroenterology services were consulted, a computed tomography (CT) scan of the patient's chest, abdomen, and pelvis was obtained, and a bone marrow biopsy was performed. The CT scan ruled out lymphoma and the initial review of the bone marrow biopsy showed no evidence of either leukemia or hemophagocytosis. Due to a high index of clinical suspicion, HLH remained the most likely etiology of the patient's acute liver failure and dexamethasone therapy was initiated on hospital day two. On hospital day 3, final pathology from the bone marrow biopsy confirmed the presence of hemophagocytosis. Shortly thereafter, etoposide and emapalumab were administered.

The patient's course was complicated by acute liver failure which led to worsening encephalopathy requiring mechanical ventilation. Her persistent hyperammonemia raised concern for the development of cerebral edema and necessitated initiation of continuous veno-venous hemodialysis (CVVHD) followed by plasmapheresis. In the 48 hours following initiation of renal replacement therapy and pharmacologic therapy with dexamethasone, etoposide, and emapalumab, the patient began to show clinical and laboratory evidence of liver recovery. On hospital day 6, a lumbar puncture was performed, and intrathecal methotrexate was administered. Soon after, the patient was extubated and transferred out of intensive care. Figure 1 shows the changes in key laboratory values

Table 1: Selected laboratory values on presentation to Inova Children's Hospital and MedStar Georgetown University Hospital

| | Inova Children's Hospital | MGUH initial presentation |
|---|---|---|
| WBC count ($\times10^3/\mu L$) | | 28.5 |
| Hemoglobin (g/dL) | 9.8 | 7.4 |
| Platelets ($\times10^3/\mu L$) | 54 | 56 |
| INR | 2.7 | 3.5 |
| Fibrinogen (mg/dL) | 91 | <60 |
| AST (units/L) | 2129 | 1297 |
| ALT (units/L) | 1553 | 905 |
| Total bilirubin (mg/dL) | 5.2 | 5 |
| Direct bilirubin (mg/dL) | 4.1 | 3.9 |
| Alkaline phosphatase (units/L) | 597 | 295 |
| Ferritin (ng/mL) | >40,000 | >16,500 |
| Tylenol (mcg/mL) | <7 | |
| Hepatitis A IgM | Not reactive | |
| Hepatitis B core IgM | Not reactive | |
| Hepatitis B surface antigen | Not reactive | |
| Hepatitis C antibody | Not reactive | |

*Abbreviations*: WBC: White blood cell, MGUH: MedStar Georgetown University Hospital, INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

as well as timing of important treatments throughout the MGUH PICU stay. After discharge from the MGUH PICU, she had full liver recovery and continued to receive HLH treatment. Her course was subsequently complicated by *Staphylococcus aureus* bacteremia. She was later found to have systemic onset juvenile idiopathic arthritis as the trigger for her HLH. Once she received treatment targeted toward her systemic onset juvenile idiopathic arthritis, her HLH went into remission. She received her last doses of HLH directed therapy approximately three months after her initial presentation. Our last follow-up with this patient was approximately eight months after her initial presentation at which time her HLH remained in remission, she continued to have intact liver function, and her systemic onset juvenile idiopathic arthritis also was well controlled.

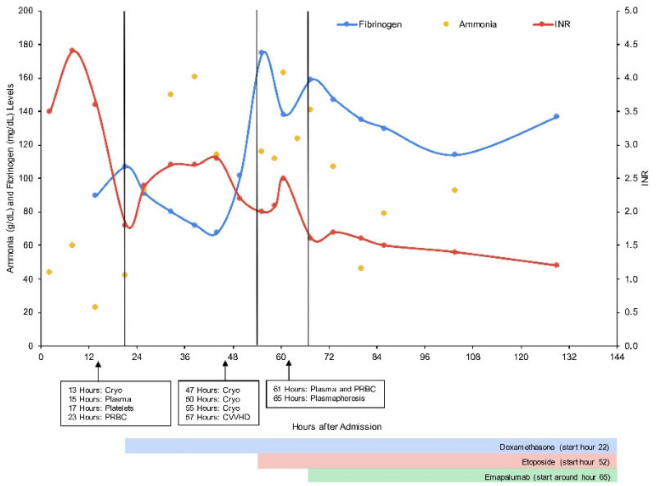


Figure 1: Key laboratory values and interventions during early hospitalization.

## DISCUSSION

Acute liver failure is a complex disease process characterized by synthetic liver dysfunction, hepatocellular damage causing the release of cellular contents, and impaired toxin clearance. Though no formal definition has been established, the inclusion criteria for the Pediatric Acute Liver Failure Registry includes evidence of hepatocellular damage characterized by elevated aminotransferases, synthetic liver dysfunction characterized by international normalized ratio (INR) greater than 1.5 not corrected by administration of vitamin K, and hepatic encephalopathy if the INR is = 2.0 [6]. These criteria encompass the most important features of acute liver failure and capture the physiologic changes clinicians should track in patients who have ALF. Notably, cytopenias are not a feature typically associated with acute liver failure. The presence of this laboratory finding shifted our suspicion toward HLH and prompted our quick evaluation.

To facilitate rapid diagnosis, the PICU team immediately consulted the hematology/oncology service who provided timely recommendations allowing prompt HLH investigation including: blood tests for soluble interleukin 2 receptor, C-X-C Motif Chemokine Ligand 9 (a cytokine induced by interferon gamma used to monitor efficacy of emapalumab), a bone marrow biopsy that ruled out leukemia, and a CT scan that excluded the diagnosis of lymphoma. However, because hemophagocytosis on biopsy may be only 58% sensitive in diagnosing HLH [7], we chose to initiate treatment without evidence of hemophagocytosis on the preliminary read of the bone marrow biopsy.

We practiced multidisciplinary and family-based rounds consisting of PICU, hematology/oncology, transplant hepatology teams, pharmacy, nursing, and the parents of the patient. Our rounds began with an assessment of nursing and parental concerns. Using a system-based approach to rounds, we invited our specialists to give their own assessments and recommendations when their system was being discussed. Finally, we reviewed medications with our pharmacy staff to ensure appropriate dosing of medications with particular attention paid toward renal and hepatic dosing. Multidisciplinary and family-based rounds may improve communication and understanding between the medical team and family as described by Rosen et al. in 2009 [8].

At time of presentation, the patient fulfilled four of the diagnostic criteria for HLH delineated in the HLH-2004 Study: fever, hyperferritinemia, cytopenias of at least two cell lineages, and hypofibrinogenemia [9] (Table 2). Lacking the etiology of the patient's acute liver failure, we prioritized the diagnostic workup while managing her evolving coagulopathy, encephalopathy, and electrolyte disturbances.

Coagulopathy in acute liver failure is complex given the depletion of both prothrombotic and antithrombotic plasma proteins. Because of this, we chose to reverse coagulability only prior to high-risk procedures. We did not target a specific INR goal given the risk of precipitating thrombosis. Additionally, we implemented fluid restriction to two-thirds maintenance and frequent neurologic examinations due to the fluid shifts that occur during acute liver failure. We chose to administer broad-spectrum antibiotic coverage to prevent opportunistic infection in the setting of immunosuppression both due to HLH as well as acute liver failure.

Management of HLH with emapalumab in the setting of severe hyperammonemia with plasmapheresis was challenging. Upon presentation, the patient's ammonia level was not significantly elevated. However, subtle changes in her neurologic exam and evolving hyperammonemia prompted aggressive management with CVVHD and plasmapheresis. Ammonia levels, at times, poorly correlated with changes in mental status and were difficult to accurately measure due to hemolysis and time lag between blood draw and analysis. Both acute liver failure and HLH contributed to the patient's

Table 2: HLH-2004 diagnostic criteria versus time

| Hospital day | 15 Days prior to admission | 1 Day prior to admission (admitted to ICH PICU) | Day 1 of admission (transferred to MGUH PICU) | Day 2 of admission | Discharge day 10 of admission |
|---|---|---|---|---|---|
| Fever | Present | Present | Present | Present | Present |
| Splenomegaly | No exam available | Absent | Absent on exam and US | Absent on US | Present |
| Cytopenias (2/3 lines)* | | | Present | Present | Present |
| Hypertriglyceridemia (≥ 265 mg/dL) or hypofibrinogenemia (≤150 mg/dL) | | | Present | Present | Present |
| Hemophagocytosis on bone marrow biopsy | | | | Present | Present |
| Low or absent natural killer cell activity (<10 lytic units) | | | | | Present |
| Elevated ferritin (≥500 ng/mL) | | | Present | Present | Present |
| Elevated soluble IL2R (≥2400 U/mL) | | | | | Present |
| 5/8 criteria needed for diagnosis | | | | Criteria met | |

*Hemoglobin <9.0 g/dL in children ≥4 weeks of age and <10.0 g/dL in children <4 weeks of age, platelets $<100\times10^9$/L, and neutrophils $<1.0\times10^9$/L.
*Abbreviations*: ICH: Inova Children's Hospital, PICU: Pediatric Intensive Care Unit, MGUH: MedStar Georgetown University Hospital, US: Ultrasound, IL2R: Interleukin-2 receptor.

progressive encephalopathy. These overlapping drivers complicated the decision to aggressively manage her hyperammonemia. We followed changes in deep tendon and Babinski reflexes as well as subtle changes in heart rate and blood pressure to monitor for evolving intracranial hypertension and impending cerebral edema.

Hemophagocytic lymphohistiocytosis management has progressed in recent decades; most current literature supports treatment with a combination of dexamethasone, etoposide, cyclosporine, and intrathecal methotrexate [10, 11]. In 2018, the monoclonal antibody emapalumab was approved for the treatment of primary HLH in adults; a recent study in New England Journal of Medicine demonstrated its safety and efficacy in children with primary HLH [12, 13]. The hyper-inflammatory response of HLH is mediated by natural killer cells, lymphocytes, and a special type of macrophage called histiocytes. Overactivation of immune cells causes a release of cytokines, including interferon gamma, which in turn activates histiocytes. Emapalumab treats HLH through blocking interferon gamma and thus downregulating histiocytes [2]. We were uncertain if our patient had primary or secondary HLH; however, there was no family history to suggest a primary HLH diagnosis. As a protein-based agent, emapalumab is susceptible to unintended filtration during plasmapheresis. Thus, we sequenced the delivery of emapalumab after plasmapheresis. Additionally, because of the patient's poor liver function, we administered 25% of the typical etoposide dosage and then increased the dosage as liver function recovered.

## CONCLUSION

Management of HLH-induced acute liver failure is a complex process that is best treated with a multidisciplinary treatment team including intensive care, hematology/oncology, hepatology, pharmacy, and nursing. While most patients who present in acute liver failure secondary to HLH die of their disease, our patient not only survived, but achieved full liver recovery. Our case highlights the importance of early initiation of treatment of HLH in the setting of acute liver failure, even in the absence of meeting full diagnostic criteria. Given the high mortality of acute liver failure due to HLH seen in previous reports, we suggest that a ferritin level should be drawn when there is evidence of acute liver failure, as outlined above, as well as cytopenias of multiple cell lineages. We also suggest consideration for administering emapalumab early in the course of HLH in the setting of acute liver failure, although further studies should be performed to delineate its use in this context. Finally, given our success, we suggest that identification of HLH should prompt early initiation of treatment, often in the absence of meeting full HLH-2004 diagnostic criteria.

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## Author Contributions

Charles Kreisel – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Andrew Meshnick – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Gregory Carlisle – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Alexandra Monde – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

## Guarantor of Submission

The corresponding author is the guarantor of submission.

## Source of Support

None.

## Consent Statement

Written informed consent was obtained from the patient for publication of this article.

## Conflict of Interest

Authors declare no conflict of interest.

## Data Availability

All relevant data are within the paper and its Supporting Information files.