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emapalumab-lzsg

PRIMARY HLH PATIENT CASE STUDY

Primary hemophagocytic lymphohistiocytosis (HLH) is a rare genetic disease characterized by rapidly progressive, life-threatening inflammatory symptoms.

This hypothetical case study details the diagnostic delays and treatment challenges that are commonly seen in primary HLH.[1-3]

Patient Profile:

- **Name:** Tommy
- **Gender:** Male
- **Age:** 11 months
- **Presenting symptoms[1]:**
  Fever of 38.6°C (101.5°F) persisting over 3-4 days, skin rash

Due to a rise in fever, Tommy's parents take him to the pediatrician, who makes the following observations:

- **Notes:**
  Fever of 38.9°C (102°F), skin rash (generalized maculopapular erythematous rashes), elevated heart rate[1]
- **Instructions:**
  Come back if his fever progresses or persists for 24 hours

Indication and Usage

Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ)–blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

Important Safety Information

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1 Presentation

Worried by his rising fever, Tommy's parents bring him back to the pediatrician for a second visit.

PEDIATRICIAN

- Temperature[1]: 39.3°C (102.7°F)
- Heart rate: 120 bpm
- Appetite: Normal
- Skin[1]: Rash (generalized maculopapular erythematous rashes and petechiae)
- Disposition[1]: Unusual irritability
- Additional[4]:
  - Possible swelling of spleen
  - Normal neurological evaluation
  - Normal lymph nodes

Tommy is diagnosed with a fever of unknown origin (FUO), most likely due to infection, and is sent home with a prescription for amoxicillin.

AMOXICILLIN

Diagnostic delays

The diagnostic challenges of primary HLH can delay treatment and contribute to a median survival of < 2 months.[1] This is because the initial signs and symptoms can mimic other, more common conditions such as viral infections, bacterial sepsis, cancer, autoimmune disease, hepatitis, and encephalitis.[5-7] It's important to rule out other conditions that may cause symptoms, including potential malignancy, as early as possible.[1,5,6,8]

CLINICAL CLUE

A persistent fever of unknown origin above 38.9°C (102°F) is one of the key characteristics of primary HLH presentation.[1]

CLINICAL CLUE

Primary HLH presents as a heterogeneous syndrome of rapidly progressive, life-threatening inflammatory symptoms. **This heterogeneous presentation can lead to delayed diagnosis and treatment, contributing to a high mortality rate (50%-100%).[1,5]**

POSSIBLE DIAGNOSIS

- FUO likely due to infection[1]

Important Safety Information

During Gamifant treatment, patients should be monitored for TB, adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Patients should be administered prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to Gamifant administration.

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2 Progression

Tommy's fever continues for another day, and he appears sicker and weaker. Concerned, his parents take him to the emergency department (ED).

ED PHYSICIAN

- In the emergency department, the physician notes Tommy's signs and symptoms, including[1,4]:
  - Fever
  - Rash
  - Dry skin
  - Extreme weakness
  - Splenomegaly
  - Dehydration
- The ED physician is concerned by the degree and duration of signs and symptoms, and summons an infectious disease (ID) specialist

ID SPECIALIST

- The ID specialist worries Tommy may have sepsis.[7,8] Tommy is admitted and started on 2 antibiotics

AMPICILLIN and CEFOTAXIME

- The ID specialist also orders a full sepsis workup, including bloodwork and a ferritin test

MEASURE	RESULT	NORMAL
White blood cells (cells/mm^3)	1,500	5,000-15,000
Absolute neutrophil count (cells/mm^3)	400	> 1,500
Platelets (platelets/mm^3)	65,000	150,000-450,000
Hemoglobin (g/L)	73	90-200
Fibrinogen (mg/dL)	60	150-400
Triglycerides (mg/dL)	275	20-150
Lactate dehydrogenase (IU/L)	2,200	340-920
Aspartate aminotransferase (AST) (IU/L)	224	10-60
Alanine aminotransferase (ALT) (IU/L)	122	5-50
Ferritin (ng/mL)	13,420	20-236

CLINICAL CLUE

Because of the rarity and multisystemic nature of primary HLH, a patient may have to see many specialists before they are diagnosed.[1,9] The most common specialists involved include pediatricians, emergency department (ED) physicians, rheumatologists, infectious disease (ID) specialists, gastroenterologists/hepatologists, hematologists/oncologists, and intensive care physicians.

POSSIBLE DIAGNOSIS[1,6,7]

- ~~FUO likely due to infection~~
- Sepsis

CLINICAL CLUE

Ferritin may be useful in distinguishing HLH from sepsis. Secreted by activated macrophages, ferritin can be extremely high in HLH.[1,10] **Patients with high ferritin values (ferritinemia) should be assessed for other HLH criteria.[1]**

Important Safety Information

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2 Progression
CONTINUED

Tommy has not responded sufficiently to the antibiotic treatment, or to subsequent treatment with antifungals.

- Tommy's lack of response leads the ID specialist to rule out sepsis. Meanwhile, Tommy's fever, irritability, and weakness persist
- The team looks at Tommy's latest bloodwork and soluble CD25 test
- In addition to Tommy's initial symptoms, the ID specialist notes[1,4]:
  - Shortness of breath
  - Signs of toxicity
  - Distended abdomen
  - Right convergent squint

CLINICAL CLUE

Because soluble CD25 levels correlate with HLH disease activity more than other indices, it is one of the most useful inflammatory markers.[1] Please note that soluble CD25 tests may need to be performed by specialty laboratories.[1] Because of this, it may take longer to obtain test results.[1]

Tommy's signs and symptoms lead physicians to worry about the possibility of cancer/leukemia and HLH.[7] They transport him to the pediatric intensive care unit (PICU).

POSSIBLE DIAGNOSIS[1,6,7]

- ~~FUO likely due to infection~~
- ~~Sepsis~~
- Cancer/leukemia
- HLH

PICU TEAM

- The PICU team includes subspecialists such as a hematologist/oncologist, hepatologist, and neurologist
- The neurologist orders a brain MRI, which reveals multiple ring-enhancing lesions in the supratentorial brain parenchyma, mainly at the gray/white matter junctions.[11] The MRI also shows calcification and generalized brain atrophy.[11] This CNS involvement explains the right eye squint observed earlier[1]
- The hematologist/oncologist is considering HLH. Based on Tommy's previous workup and symptom combination, the specialist orders a rapid immunologic workup and gene sequencing panel. A molecular diagnosis consistent with primary HLH will include a pathologic mutation of *PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4.*[1] ***Results of these genetic tests could take hours to weeks, so treatment for HLH should not be delayed while awaiting genetic test results***[12]
- The hematologist/oncologist also orders a bone marrow biopsy, which rules out cancer/leukemia, but does not conclusively show HLH[8]

CLINICAL CLUE

Because there are still some unidentified mutations underlying primary HLH, genetic tests are not always conclusive.[13] A patient may still have primary HLH even if the genetic test comes back negative or inconclusive.[13]

CLINICAL CLUE

Hemophagocytosis is neither necessary nor sufficient to diagnose HLH—it is only one part of the criteria.[8] Hemophagocytosis develops in a later stage of HLH, and may therefore be absent in some patients with HLH.[8]

Infusion-Related Reactions

Infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were reported with Gamifant treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.

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3 Diagnosis

After ruling out malignancy, the team diagnoses Tommy with primary HLH and immediately starts treatment.[1]

- The diagnosis is based on Tommy's satisfactory fulfillment of HLH clinical diagnostic criteria, as well as other clinical observations (ie, elevated AST and ALT)[1,4]

HLH CLINICAL DIAGNOSTIC CRITERIA[1,4,*]
✓ Fever ≥ 38.5°C (101.3°F)
✓ Splenomegaly
✓ Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood) ✓ Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L) ✓ Platelets < 100 x 10^9/L ✓ Neutrophils < 1.0 x 10^9/L
✓ Hypertriglyceridemia (fasting triglycerides, ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L)
☐ Hemophagocytosis in bone marrow, spleen, or lymph nodes
☐ Low or absent natural killer (NK)-cell activity
✓ Ferritin > 500 µg/L
✓ Soluble CD25 (interleukin [IL]-2 receptor) ≥ 2400 U/mL (or per local reference laboratory)

✓ = criterion fulfilled in Tommy's case

*These criteria come from the HLH-2004 diagnostic protocol

HLH Clinical Diagnostic Criteria[3,10,14]

Although scientific consensus of the appropriate diagnostic criteria continues to evolve, 2 recognized options for confirming a diagnosis of primary HLH exist:

The fulfillment of 5 of the 8 HLH-2004 criteria in the absence of an underlying cause such as malignancy

OR

A positive genetic test for mutations associated with primary HLH or a family history consistent with HLH

CLINICAL CLUE

Even though the hem/onc has already ordered the genetic testing that could confirm primary HLH, it typically takes 3-8 weeks for results to come in. However, **without timely diagnosis and effective treatment, the median survival for patients with primary HLH is under 2 months.**[1] For this reason, Tommy's team does not wait for the genetic testing results, and looks to clinical diagnostic criteria.

Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions (≥10%) for Gamifant included infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%).

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4 Initial Treatment

The PICU team initiates treatment based on HLH-1994 treatment protocol, which differs from the HLH-2004 protocol used to diagnose Tommy.[4]

ETOPOSIDE, DEXAMETHASONE, INTRATHECAL METHOTREXATE (due to CNS involvement)

- Under HLH-1994 protocol, cyclosporine will be added in the maintenance phase[15]
- During treatment, Tommy also requires additional supportive care, including[1]:
  - Fever and infection management to prevent infection opportunities and reactivation
  - Close monitoring for internal bleeding due to low platelet counts; administration of platelets and fresh frozen plasma (FFP) as needed
  - Monitoring for worsening cardiac or respiratory function; use of respiratory support as needed
  - Ongoing CNS monitoring
- Tommy's team runs a workup that shows no perforin expression, but does reveal a decrease in CD107, which supports the diagnosis of primary HLH[1]
- The team must decide whether Tommy's response to initial treatment is adequate. If it is not, they will need to consider a different treatment option[1]
- The team looks at Tommy's bloodwork, which reveals:
  - Low platelets and white blood cells
  - Low fibrinogen
  - Elevated ALT
  - Elevated serum ferritin
  - Elevated sCD25 (soluble IL-2 receptor)

CLINICAL CLUE

The main goal of initial therapy is to suppress the life-threatening inflammatory process that underlies HLH.[1,12,16] Once their condition is stabilized, patients are either weaned off of therapy or transitioned to continuation therapy, which is intended as a bridge to hematopoietic stem cell transplantation (HSCT)—the only curative treatment for primary HLH.[1,5]

CLINICAL CLUE

Uncontrolled disease is a major cause of death prior to HSCT, and is associated with higher transplant-related mortality.[1,3,17]

Based on his bloodwork, the team feels that Tommy is not improving or responding adequately. Considering the rapidly progressive nature of the disease, they determine that his HLH is refractory and urgently consider a different treatment.

Deciding initial treatment isn't enough

A study found that roughly **half** of HLH patients are possible candidates for other treatment options.[1,*]

Of these possible candidates noted in the study

30% had a partial resolution of symptoms with initial treatment

20% died before they could undergo HSCT

*The other 50% achieved a full resolution of symptoms with initial treatment.

Adverse Reactions

Additional selected adverse reactions (all grades) that were reported in less than 10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

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5 Initiation of Gamifant® (emapalumab-lzsg)

Tommy's physicians start treatment with Gamifant.

GAMIFANT® (emapalumab-lzsg) and DEXAMETHASONE

Timely Treatment[1,12]

To start treatment with Gamifant, **a genetic confirmation is not required when there is a clinical diagnosis** of primary HLH with refractory, recurrent, or progressive disease or intolerance to conventional therapy.

- After initiation of treatment with Gamifant, the physicians receive Tommy's genetic test results confirming his diagnosis of primary HLH. The test shows a mutation in the *UNC13D* gene, which is associated with Type 3, one of 5 known HLH subtypes[18]

Tommy shows improvement following the initiation of treatment with Gamifant. With his disease now under control, the treatment team begins preparing for the HSCT process, and conditioning for transplant.

Why did Tommy's doctors choose Gamifant?

- Gamifant is the only treatment **specifically designed to target interferon gamma (IFNγ),** the source of hyperinflammatory symptoms in primary HLH[10,19]
- Gamifant has **demonstrated safety and efficacy** for primary HLH in patients with refractory, recurrent, or progressive disease or intolerance to conventional therapy[10]

63% overall response rate (ORR)[10,*]

70% of patients proceeded to HSCT[10]

See how Gamifant neutralizes IFNγ to subdue hyperinflammation in patients like Tommy at Gamifant.com[10]

*ORR is defined as achievement of either complete or partial response or HLH improvement[10]

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REFERENCES

1. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011;118(15):4041-4052. **2.** Lehmberg K, Nichols KE, Henter J-I, et al; Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematol.* 2015:100(8):997-1004. **3.** Marsh RA, Haddad E. How I treat primary haemophagocytic lymphohistiocytosis. *Br J Haematol.* 2018;182(2):185-199. **4.** Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124-131. **5.** Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: a fulminant syndrome associated with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. *S Afr Med J.* 2014;104(6):401-406. **6.** Kim MM, Yum MS, Choi HW, Ko TS, Im HJ, Seo JJ, Koh KN. Central nervous system (CNS) involvement is a critical prognostic factor for hemophagocytic lymphohistiocytosis. *Korean J Hematol.* 2012;47(4):273-280. **7.** D'Souza E, Cheriathu JJ, Shamseldeen M. Rare case of hemophagocytic lymphohistiocytosis: a case report. *GMJ, ASM.* 2012;1(S1):S194-S197. **8.** Machowicz R, Janka G, Wiktor-Jedrzejczak W. Your critical care patient may have HLH (hemophagocytic lymphohistiocytosis). *Crit Care.* 2016;20:215. **9.** Imashuku S. Hemophagocytic lymphohistiocytosis: recent progress in the pathogenesis, diagnosis and treatment. *World J Hematol.* 2014;3(3):71-84. **10.** Gamifant [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2020. **11.** Sadek S, Al Terkait N. Case report: difficulties in the diagnosis of familial hemophagocytic lymphohistiocytosis. *Kuwait Med J.* 2008;40(3):241-243. **12.** Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int.* 2016;58(9):817-825. **13.** Ericson K, Fadeel B, Nilsson-Ardnor S, et al. Spectrum of perforin gene mutations in familial hemophagocytic lymphohistiocytosis. *Am J Hum Genet.* 2001;68:590-597. **14.** Sepulveda F, de Saint Basile G. Hemophagocytic syndrome: primary forms and predisposing conditions. *Curr Opin Immunol.* 2017;49:20-26. **15.** Henter J, Samuelsson-Horne A, Aricò M, et al; Histocyte Society. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002;100(7):2367-2373. **16.** George M. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med.* 2014;5:69-86. **17.** Mahlaoui N, Ouachée-Chardin M, de Saint Basile G, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. *Pediatrics.* 2007;120:e622-e628. **18.** Contino A, Trombatore G, Timeus F. Hemophagocytic lymphohistiocytosis in pediatric patients: a review. *J Blood Disord Symptoms Treat.* 2018;2(1):1-5. **19.** FDA approves first treatment specifically for patients with rare and life-threatening type of immune disease [news release]. Silver Spring, MD: US Food and Drug Administration; November 20, 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm626263.htm. Accessed July 21, 2020.

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