

Introducing a real primary HLH patient case

Camden's journey

The diagnosis and management of primary hemophagocytic lymphohistiocytosis (HLH) in a newborn baby boy

The details presented in this case are true and have been shared with the permission of the patient and/or caregiver to help broaden the healthcare community's knowledge of this rare condition. This case represents one patient's experience and the clinical judgment of one treatment team. Individual results may vary.

Indication

Gamifant[®] (emapalumab-lzsg) is an interferon gamma (IFN γ)-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

Infections

Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFN γ release assay.

Please see Important Safety Information on page 8. [Click here](#) for full Prescribing Information for Gamifant, including Patient Information.

Overview



FEBRUARY 2016

While pregnant, Camden's mother suffered from unusual, persistent fevers. When no fetal movement was detected in utero, he was delivered via emergency C-section. At birth, Camden presented with "blueberry muffin spots" due to pancytopenia and severe ascites.

This case study details the factors that contributed to a confirmed diagnosis of primary HLH and the treatment plan that conditioned Camden for hematopoietic stem cell transplantation (HSCT).

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► Day 1: Initial presentation

February 24, 2016

Baby boy is delivered via emergency C-section in critical condition

- Pancytopenia
- Blueberry muffin spots
- Hepatosplenomegaly
- Severe ascites
- Multiorgan failure
- Hypotonicity
- Abdominal distension



Camden is initially diagnosed with a congenital infection, but when testing comes back negative, the treatment team begins to explore other possibilities.

Important Safety Information

Increased Risk of Infection With Use of Live Vaccines

Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

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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Differential diagnosis

▶ Day 1

February 24, 2016

On the day Camden is born, infectious disease (ID) specialists are called into the newborn intensive care unit (NICU) due to the presence of blueberry muffin spots, or purpura caused by extramedullary erythropoiesis. The team suspects that Camden has a congenital infection, and several tests are performed to confirm.

- Extensive testing is performed for TORCH syndrome, which is a group of infections that can affect a developing fetus or newborn



Though blueberry muffin spots have been documented in conjunction with HLH, the syndrome is not included in the differential diagnosis for a baby who presents with the spots. **Since hemophagocytosis is not typically encountered in skin specimens, HLH diagnosis should not rely on cutaneous biopsy and additional lab tests should be performed.¹**

▶ Days 2-10

February 25, 2016-March 4, 2016

Infectious disease tests come back negative and the NICU team performs additional laboratory tests, leading the hematologist/oncologist to suspect primary HLH.

- Biopsies of blueberry muffin spots and bone marrow are performed
- Bone marrow aspirate is performed
- Lumbar puncture is performed
- HLH-2004 criteria are used to evaluate Camden's symptoms
- Genetic testing is performed



Based on fulfillment of the HLH-2004 criteria, primary HLH is diagnosed and treatment is initiated.

▶ Day 11

March 5, 2016

Imaging tests are performed to rule out possible malignancies, which are considered unlikely in an infant.

- Abdominal ultrasound reveals no signs of malignancy

Important Safety Information

Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions ($\geq 10\%$) 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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Patient lab values

Infectious disease testing rules out congenital infection

Negative for: HIV, herpes, herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus, human herpesvirus 6, and toxoplasmosis

Tissue and fluid analyses suggest primary HLH

- Biopsies of blueberry muffin spots and bone marrow reveal dense histiocytic infiltration
- Bone marrow aspirate also shows dense histiocytic infiltration and hemophagocytosis
- Lumbar puncture reveals elevated protein and macrophages in spinal fluid

Camden exhibits most of the HLH-2004 diagnostic criteria

(5 out of 8 are required for diagnosis)

✓ Hypertriglyceridemia (fasting, ≥ 265 mg/dL) and hypofibrinogenemia (≤ 1.5 g/L)

✓ Hepatosplenomegaly

✓ Hemophagocytosis in bone marrow

✓ Pancytopenia: Hemoglobin < 100 g/L | Platelets $< 100 \times 10^9/L$ | Neutrophils $< 1.0 \times 10^9/L$

✓ Ferritin ≥ 500 $\mu\text{g/L}$

✓ Low or absent natural killer-cell activity

✓ Soluble CD25 levels elevated

✗ Fever was not present (this is considered atypical for patients with primary HLH)

Genetic testing and additional screening support for primary HLH diagnosis

- Genetic testing reveals a *PRF1* mutation
- Granzyme B is present
- CXCL9 levels are high

Magnetic resonance imaging (MRI)

- MRI revealed periventricular leukomalacia and hemorrhagic products in the occipital and posterior fossa, abnormalities that are commonly seen in HLH cases that affect the central nervous system (CNS)

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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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Treatment journey

Days 4-10

February 28-March 4, 2016

The NICU team performs lifesaving procedures to keep Camden alive during differential diagnosis.

- Paracentesis is performed 4 times to drain ascites
- Frequent blood transfusions are administered in response to cytopenia

Days 5-56

February 29-April 20, 2016

Intrathecal hydrocortisone is administered weekly to normalize proteins in spinal fluid.

Day 10 | March 4, 2016

Dexamethasone is initiated as the NICU team rules out infection and suspects primary HLH.

- Though some members of the treatment team remain uncertain of the diagnosis, Camden's blood counts stabilize
- Ascites and liver enzymes improve
- Though transfusion dependence decreases, transfusions are still required

Day 22 | March 17, 2016

Etoposide is initiated at a starting dose of 5 mg/m² twice weekly in an effort to achieve transfusion independence.

- Camden experiences several severe toxicities during treatment with dexamethasone and etoposide, including hyperglycemia, hypertension, neutropenia, and posterior reversible encephalopathy syndrome, which resulted in cortical blindness
- A granulocyte colony-stimulating factor (G-CSF) regimen is initiated to mitigate neutropenia
- Inflammatory markers remain elevated
- Transfusions are still required



While treatment with dexamethasone continues, insulin and antihypertension medications are administered to mitigate toxicities.

Days 44-47 | April 8-11, 2016

Alemtuzumab is initiated due to persistent HLH activity.



As treatment options are exhausted, a special approval process for Gamifant (not yet commercially available) is held, delaying the desired date of initiation.

Days 103-131 | June 6-July 4, 2016

Gamifant is initiated at a starting dose of 1 mg/kg and is eventually increased to 6 mg/kg.*

- Camden receives Gamifant every 3 to 4 days until July 4
- Camden's optic function improved and treatment with dexamethasone is discontinued
- Frequency of etoposide treatment decreases to once weekly
- G-CSF is discontinued

Day 146 | July 19, 2016



After months of conditioning, Camden successfully undergoes HSCT.

*The recommended starting dose for Gamifant is 1 mg/kg as an intravenous infusion over 1 hour, twice per week. Subsequent doses may be increased based on clinical and laboratory criteria. Please refer to full Prescribing Information for guidance on assessing patients for safety prior to Gamifant initiation and premedications.²

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Clinical response

► Day 131

July 4, 2016

After approximately 1 month of treatment with Gamifant, Camden's condition stabilizes.

- Primary HLH symptoms, including cytopenias and levels of ferritin and CXCL9, improve
- Transfusion independence is achieved
- Considering his positive response to Gamifant, the treatment team delays HSCT to give Camden additional time for improvement

► Days 147+

July 19, 2016-September 9, 2021

Camden still has follow-up appointments with his hematologist/oncologist and neurologist to monitor his progress.

- CNS involvement requires close follow-up
- Though some of his vision problems improved when conventional therapies were discontinued, Camden still has some impairment that may have been caused by primary HLH



Camden is a happy little boy who enjoys spending time with family and going to school.

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Thank you for reviewing Camden's case

Diagnosing primary HLH can be challenging.

Visit [Gamifant.com](https://www.gamifant.com) to learn more about primary HLH and Gamifant.

If you'd like to consult a primary HLH treatment expert, contact your local Sobi Health Systems Director.

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References: 1. Larson KN, Gaitan SR, Stahr BJ, Morrell DS. Hemophagocytic lymphohistiocytosis in a newborn presenting as "blueberry muffin baby." *Pediatr Dermatol.* 2017;34(3):e150-e151. doi:10.1111/pde.13128 2. Gamifant (emapalumab-lzsg) prescribing information. Stockholm, Sweden: Sobi, Inc. 2022.



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