5-2021

Severe Colitis and Malnutrition in Association with Neonatal Hemophagocytic Lymphohistiocytosis

Laura Tarantino

Severe Colitis and Malnutrition in Association with Neonatal Hemophagocytic Lymphohistiocytosis (HLH)

Laura Tarantino, BSN, MS3[1]; Brianna K. Brei, MD[2]; Danita Velasco, MD[3]; Hana B. Niebur, MD[4]; Chittalsinh Raulji, MD[5]; Courtney McLean, MD[2]

[1]Creighton University School of Medicine, Omaha, NE
[2]Division of Neonatology, Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE
[3]Munroe-Meyer Institute for Genetics and Rehabilitation, University of Nebraska Medical Center, Omaha, NE
[4]Division of Allergy & Immunology, Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE
[5]Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE

Child Health Research Institute

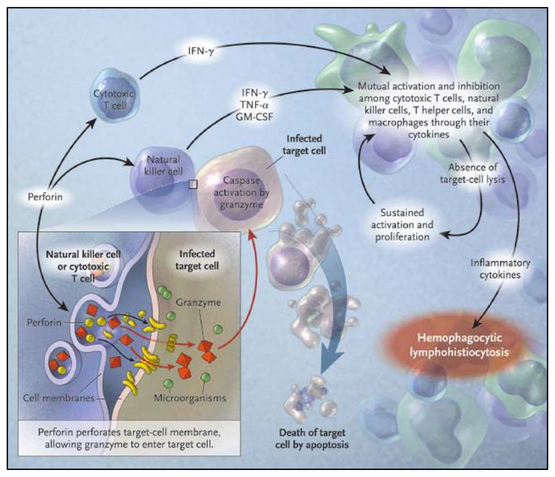
University of Nebraska Medical Center | Children's Hospital & Medical Center

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of overwhelming immune activation causing multiorgan dysfunction that may be genetic and/or acquired *(Figure 1).* Patients with familial HLH often present by one year of age, though most are asymptomatic in the first month of life. We present the case of a neonate with diarrhea and malnutrition who developed signs and symptoms consistent with a clinical diagnosis of HLH.

Figure 1: *Genetic abnormalities associated with HLH result in impaired cytotoxic function of NK and T cells, leading to sustained activation of macrophages.*

Woods et. al. Advances in Neonatal Care *(2009)*



CASE

- **HPI:** Neonate born at 35 5/7 weeks, transferred to a Level IV NICU at 39 4/7 weeks for failure to thrive
  - Feeding adequately, but had persistent diarrhea on multiple formulas, only gained small amounts of weight via total parental nutrition *(Figure 2)*
- **Family/social history:** first child of consanguineous parents of South Asian descent, otherwise noncontributory
- **Physical exam:** Appeared malnourished but non-dysmorphic
- **Gastrointestinal workup:** Inconsistent with milk soy protein intolerance and malabsorption syndromes.
  - Considered very-early-onset inflammatory bowel disease and congenital diarrheas/enteropathies
  - Endoscopy with intestinal biopsy concerning for an underlying primary immunodeficiency
- **Genetic and immunology workup**: Mild increase in T cells and low IgM
  - Chromosomal microarray with 7.8% genome wide regions of homozygosity, supporting increased risk of autosomal recessive conditions
  - Lymphocyte proliferation to mitogens and expression of FOXP3, XIAP, and SAP by flow cytometry all unremarkable
  - Perforin/granzyme B expression was increased
- **Clinical course:** At age 44 weeks, he acutely became lethargic, with fevers up to 40˚C and metabolic acidosis
  - Further developed anemia, thrombocytopenia, lymphocytosis, transaminitis, and hepatosplenomegaly *(Figure 3)*
  - Hypofibrinogenemia, hyperferritinemia (>10,000), and elevated Soluble IL-2R led to HLH diagnosis *(Table 1)*
- **Treatment**: Dexamethasone and etoposide per HLH 94 protocol; emapalumab also administered
- **Outcome**: Developed fulminant liver failure and uncontrollable DIC despite treatment
  - Life-sustaining treatments were withdrawn and he died at 46 3/7 weeks

Table 1: *Diagnostic criteria for HLH (need 5 of 8)*

1. Fever
2. Splenomegaly
3. Cytopenias (at least 2 lines affected)
4. Elevated TG or Hypofibrinogenemia
5. Hemophagocytosis
6. Low or absent NK Cell Activity
7. Ferritin >500
8. Soluble IL-2R >2400

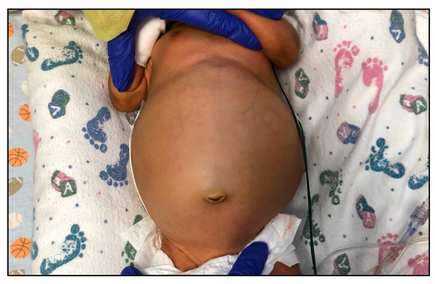
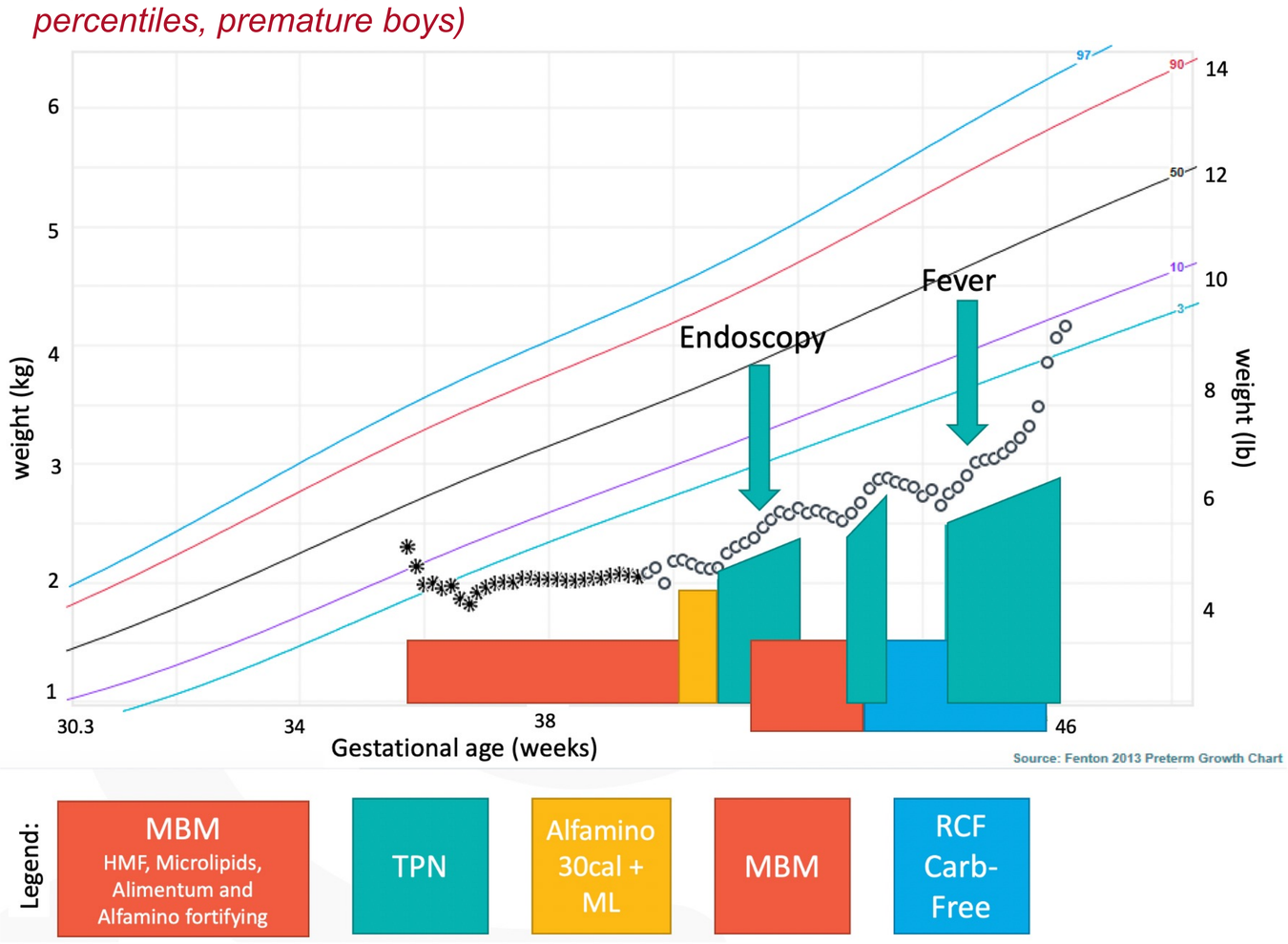


Figure 3: *Patient after acute development of hepato-splenomegaly and ascites*

DISCUSSION

- Though colitis is not classically a feature of most primary HLH syndromes, it has been described in one subset of familial HLH (familial HLH 5 syndrome) along with hypogammaglobulinemia. However, sequencing of the associated gene (*STXBP2*) was normal in our patient.
- Similarly, among EBV-driven HLH, X-linked lymphoproliferative disease and XIAP deficiency are associated with hypogammaglobulinemia and colitis respectively, however expression of these was normal in our patient with no evidence of EBV viremia.
- Whole exome sequencing received after patient's death was ultimately nondiagnostic. Variants of unknown significance included:
  - *BCOR* (c.4927T>C; p.Ser1643Pro – maternally inherited)
  - *GUCY2C* (c.1092C>A; p.Asp364Glu – paternally inherited)
  - *STEAP3* (c.703G>A; p.Val235Ile – maternally inherited)
  - None of the associated conditions and molecular characteristics of these specific variants have adequate established phenotypic overlap with our patient's presentation to make them clinically actionable.
- Neonatal patients are more likely to have genetic causes for HLH; parental consanguinity increase the risk for expression of these autosomal recessive conditions.
  - Around 40% of neonatal presentations do not have an established genetic diagnosis after whole exome sequencing.
  - Additional genes associated with early HLH presentation are likely yet to be discovered.

Figure 2: Patient's growth chart with nutritional support *(Weight-for-age percentiles, premature boys)*



CONCLUSION

Timely recognition of HLH maximizes the potential for effective treatment like hematopoietic stem cell transplantation. Recognition of colitis as a presenting symptom may facilitate this challenging diagnosis. Rapid and inclusive genetic evaluation, including WES, may help identify the underlying etiology and guide treatment for neonatal HLH.

ACKNOWLEDGEMENTS

We express gratitude to the patient's family and to the many specialists and staff involved in his care.

REFERENCES

1. McLean, J, et al. Neonatal Hemophagocytic Lymphohistiocytosis. *NeoReviews*. 2019;20;e316.
2. McClain KL. Treatment and Prognosis of hemophagocytic lymphohistiocytosis. In: J.S. Tirnauer ed. *UpToDate*. Waltham, Mass.: UpToDate; 2020. www.uptodate.com. Accessed Jan. 25, 2021.
3. McClain KL. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. In: J.S. Tirnauer ed. *UpToDate*. Waltham, Mass.: UpToDate; 2020. www.uptodate.com. Accessed Jan 25., 2021.
4. Imashuku S, Ueda I, Teramura T, Mori K, Morimoto A, Sako M, Ishii E. Occurrence of haemophagocytic lymphohistiocytosis at less than 1 year of age: analysis of 96 patients. *Eur J Pediatr* 2005;164:315-319
5. Gassas A, Ashraf K, Zaidman I, Ali M, Krueger J, Doyle J, Schecter T, Leucht S. Hematopoietic Stem Cell Transplantation in Infants. *Pediatr Blood Cancer* 2015;62:517-521.
6. Isaacs H. Fetal and Neonatal Histiocytosis. *Pediatr Blood Cancer*. 2006;47:123-129.
7. Ouachee-Chardin M, Elie, C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, Neven B, Casanova JL, Tardieu M, Cavazzana-Calvo M, Blanche S, Fischer A. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: A single report of 48 patients. *Pediatrics*. 2006;117(4)e743-e750.
8. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052
9. Mehta RS, Smith RE. Hemophagocytic lymphohistiocytosis (HLH): a review of literature. *Med Oncol* 2013;30:740.
10. Chandrakasan S, Filpovich AH. Hemophagocytic lymphohistiocytiosis: Advances in pathophysiology, diagnosis, and treatment. *J of Pediatr*. 2013;163(5):1253-1259.
11. Woods CW, Bradshaw WT, Woods AG. Hemophagocytic lymphohistiocytosis in the premature neonate. *Advances in Neonatal Care*. 2009; 9(6):265-273.
12. Pagel J, Beutel K, Lehmberg K, et al. Distinct mutations in STXBP2 are associated with variable clinical presentations in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL5). *Blood*. 2012;119(25):6016-24. doi: 10.1182/blood-2011-12-398958.
13. Chinn IK, Eckstein OS, Peckham-Gregory EC, et al. Genetic and mechanistic diversity in pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2018;132(1):89-100. doi:10.1182/blood2017-11-814244.
14. Canna SW, Marsh RA Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332-1343. doi: 10.1182/ blood.2019000936.