

Case Report

A genetic storm in an adult: unmasking familial HLH – a rare presentation

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome, with familial (primary) HLH typically manifesting in infancy. Adult-onset familial HLH—particularly due to mutations in PRF1 (type 2)—is exceedingly rare. We report a 26-year-old veterinary student who presented with fever, jaundice, pancytopenia, hepatosplenomegaly, and shock. Investigations confirmed hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, hemophagocytosis on bone marrow, and EBV detection on PCR. Genetic testing revealed a pathogenic autosomal recessive PRF1 mutation, confirming familial HLH type 2. Despite initiation of high-dose steroids, IVIG, and supportive care, disease activity persisted, and the patient subsequently left against medical advice, before the proposed treatment could be initiated. This case underscores the importance of considering primary HLH even in adults, and the role of genetic testing to guide diagnosis and management.

Keywords: Hemophagocytic lymphohistiocytosis, Familial HLH type 2, Hyperinflammatory syndrome, Adult-onset HLH, PRF1 mutation, Hemophagocytosis

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory disorder characterized by uncontrolled activation of macrophages and cytotoxic lymphocytes, leading to fever, cytopenias, hepatosplenomegaly, coagulopathy, and multiorgan dysfunction.^{1,2}

While primary or familial HLH typically presents in infancy or early childhood, adult-onset familial HLH is rare but increasingly recognized, particularly in individuals harboring hypomorphic mutations that permit partial cytotoxic lymphocyte function.^{3,4}

Mutations in PRF1, which encodes perforin, account for familial HLH type 2.⁵ Although most PRF1-associated cases present in childhood, delayed presentations in adolescence and adulthood have been reported.^{3,6}

CASE REPORT

A 26-year-old male veterinary student, with no prior comorbidities, developed low grade fever (~100 °F) one month prior to presentation, accompanied by malaise but no chills. He was initially treated for typhoid fever with oral antibiotics for three days without improvement. Eleven days post onset, his condition worsened with high grade fever and jaundice, prompting hospital admission outside where CT scan chest and abdomen revealed hepatosplenomegaly. His clinical status rapidly deteriorated and he presented to us with features of shock, altered sensorium, and respiratory failure, requiring non-invasive ventilation and inotropic support. A history of recent travel to high altitude Spiti Valley was noted.

Examination revealed pallor, icterus, massive hepatosplenomegaly, and moderate ascites. Laboratory tests showed pancytopenia with severe neutropenia, direct

hyperbilirubinemia, markedly elevated transaminases, and raised inflammatory markers (Table 1). Microbiological workup was largely negative, except for detection of EBV

by PCR which was positive (Table 2). Blood cultures grew NDM positive *E. coli*, leading to tailored antibiotic therapy.

Table 1: Laboratory results with reference ranges.

Parameters	Patient value	Reference range
Hemoglobin (Hb) (g/dl)	6.5	13.5–17.5 (M)
Total leukocyte count (TLC) (/μl)	0.29×10^3	$4-11 \times 10^3$
Differential leukocyte count (DLC) (%)	N 7, L 78, M 15	N 40–80, L 20–40, M 2–10
Platelets (/μl)	17×10^3	$150-450 \times 10^3$
Mean corpuscular volume (MCV) (fl)	88.2	80–100
Blood urea nitrogen (BUN) (mg/dl)	8.5	7–20
Creatinine (mg/dl)	0.55	0.6–1.3
Calcium (mg/dl)	7.02	8.5–10.5
Phosphorus (mg/dl)	3.06	2.5–4.5
Sodium (mEq/l)	129	135–145
Potassium (mEq/l)	4.24	3.5–5.0L
Uric acid (mg/dl)	2.98	3.4–7.0 (M)
Total bilirubin (mg/dl)	14.57	0.3–1.2
Direct bilirubin (mg/dl)	10.26	0.1–0.4
Total protein (g/dl)	3.47	6.0–8.3
Albumin (g/dl)	1.82	3.5–5.0
SGOT (AST) (IU/l)	1310	10–40
SGPT (ALT) (IU/l)	681	7–56
Alkaline phosphatase (ALP) (IU/l)	315	44–147
GGT (IU/l)	130	9–48
ESR (mm/hr)	≥30	0–15
CRP (mg/l)	29	<5
Procalcitonin (ng/ml)	6.39	<0.05
Serum cortisol (μg/dl)	≤1	5–25 (AM)
Iron (μg/dl)	133	60–170
UIBC (μg/dl)	13	150–375
Transferrin (mg/dl)	102	200–360
Transferrin saturation (%)	92	20–50
Zinc (μg/dl)	51.35	70–120
Folic acid (ng/ml)	5.29	2.7–17.0
Ferritin (ng/ml)	31212	30–400
Triglycerides (mg/dl)	478	<150
Fibrinogen (g/l)	1.18	2.0–4.0
Vitamin B12 (pg/ml)	2000	200–900
LDH (IU/l)	970	140–280

Table 2: Infective workup.

Tests	Result
Urine routine microscopy	Normal
Urine culture	Sterile
Blood culture	<i>E. Coli</i> NDM positive strain
Dengue NS1/IgM	Negative
Malarial antigen	Negative
Typhidot IgM	Negative
Scrub typhus IgM	Negative
Brucella SAT	Negative
Leptospira IgM	Negative
Histoplasma urinary antigen	Negative

Continued.

Tests	Result
Galactomannan antigen test	Negative
1,3 Beta-D glucan assay	Negative
Hepatitis B	Negative
Hepatitis C	Negative
Hepatitis A	Negative
Hepatitis E	Negative
HIV workup	Negative
EBV PCR	Detected
CMV PCR	Negative

Given the constellation of fever, cytopenias, hepatosplenomegaly, and inflammatory markers, HLH was suspected. Further workup confirmed hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia, meeting HLH 2004 criteria.

In order to rule out any malignancy or occult infection, a PET CT was done which showed FDG avid bone marrow, pleural effusions, and hepatosplenomegaly. Bone marrow aspirate demonstrated hemophagocytosis in a hypocellular marrow; biopsy showed increased T lymphoid cells, preserved hematopoietic lineages, and absence of granulomas or fungal elements; NGS fungifast was also negative.

Patient was treated as a case of HLH secondary to EBV. Constant monitoring of EBV viral load was done. However, despite reduction in the EBV copies, there was no improvement in the HLH markers. Primary HLH was then considered as a possibility. Genetic tests (PRF1 gene sequencing by NGS panel) for the same were sent.

Genetic analysis revealed a pathogenic autosomal recessive PRF1 mutation, confirming familial HLH type 2. The patient was referred to Clinical hematology/hematology and bone marrow transplant department for disease specific therapeutic options. High dose IV dexamethasone, IV immunoglobulin, transfusive support was administered. However, the patient subsequently left against medical advice due to some personal issues, before the proposed treatment could be initiated.

DISCUSSION

Familial HLH type 2 is caused by biallelic pathogenic variants in PRF1, resulting in impaired perforin-mediated cytotoxicity by natural killer cells and cytotoxic T lymphocytes.⁵ The consequent failure to terminate immune activation leads to persistent macrophage and T-cell activation, cytokine excess, and progressive tissue injury.^{1,5} Although familial HLH classically manifests in infancy, late-onset disease has been described in adolescents and adults, particularly in association with hypomorphic variants that allow residual cytotoxic function.^{3,4}

Adult-onset familial HLH is diagnostically challenging because secondary HLH related to infection, malignancy,

autoimmune disease, or sepsis is more common in adults.⁷ EBV is a well-recognized infectious trigger of HLH and may precipitate disease in genetically predisposed individuals.⁸ In the present case, EBV detection and NDM-positive *E. coli* bacteremia initially supported a diagnosis of infection-associated HLH. However, persistence of HLH activity despite reduction in EBV viral load raised suspicion for an underlying primary immune defect, which was subsequently confirmed by genetic testing.

Previous reports have documented adult-onset HLH associated with PRF1 mutations. Nagafuji et al. described perforin gene mutations in adult-onset HLH, supporting the concept that familial HLH may present beyond childhood.⁶ Zhang et al. further demonstrated that hypomorphic mutations in PRF1, UNC13D, and STXBP2 are associated with adult-onset familial HLH.³ More recently, Liu et al. reported a 27-year-old male with adult-onset familial HLH type 2 due to compound heterozygous PRF1 mutations who achieved remission with HLH-directed therapy. These reports reinforce the need to consider familial HLH in adults with severe or refractory hyperinflammation, even when an infectious trigger is identified.

Management of familial HLH requires rapid control of hyperinflammation using HLH-directed immunochemotherapy and supportive care, followed by consideration of allogeneic hematopoietic stem cell transplantation for curative intent where feasible.² Early genetic testing is therefore clinically relevant, as it can distinguish primary HLH from secondary HLH and guide counseling, donor evaluation, and definitive treatment planning.

CONCLUSION

This case emphasizes that familial HLH—specifically type 2 due to PRF1 mutations—can present in adulthood, albeit rarely. Maintaining a high index of suspicion in adult patients with persistent hyperinflammation, cytopenias, and organomegaly is critical. Genetic testing facilitates accurate diagnosis and enables tailored treatment, potentially including allogeneic haematopoietic stem-cell transplantation (HSCT) for curative intent. Early recognition is key to improving outcomes in this life-threatening disease.

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