Autopsy Case Reports

Article- Autopsy Case Report

Fatal familial hemophagocytic lymphohistiocytosis with perforin gene (*PRF1*) mutation and EBV-associated T-cell lymphoproliferative disorder of the thyroid

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ABSTRACT

Familial hemophagocytic lymphohistiocytosis (FHL) is a rare fatal autosomal recessive disorder of immune dysregulation. The disease presents most commonly in the first year of life; however, symptomatic presentation throughout childhood and adulthood has also been identified. Biallelic mutation in the *perforin* gene is present in 20%–50% of all cases of FHL. Secondary hemophagocytic lymphohistiocytosis (HLH) in association with hematological malignancies is known; however, whether mutations in HLH-associated genes can be associated with FHL and hematolymphoid neoplasms is not well documented. Also, Epstein–Barr-virus- (EBV) positive systemic T-cell lymphoproliferative disease (SE-LPD) in the setting of FHL is not clearly understood. Here, we present the case of a young boy who presented with typical features of childhood FHL harboring the perforin gene (*PRF1*) mutation, and had SE-LPD diagnosed on autopsy, along with evidence of recent EBV infection. The patient expired due to progressive disease. Five siblings died in the second or third decade of life with undiagnosed disease. Genetic counseling was provided to the two surviving siblings and parents, but they could not afford genetic testing. One surviving sibling has intermittent fever and is on close follow-up for possible bone marrow transplantation.

Keywords
Epstein–Barr Virus Nuclear Antigens; Familial Hemophagocytic Lymphohistiocytosis, Lymphoma, *Perforin Gene* Mutation.

INTRODUCTION

Familial hemophagocytic lymphohistiocytosis (FHL) is a rare fatal autosomal recessive disorder of immune dysregulation characterized by genetic defects in cytotoxic cell function, resulting in uncontrolled T-cell and macrophage infiltration in multiple organs causing irreversible damage.[1] The disease usually presents in the first year of life; however, symptomatic presentation in childhood and even adulthood has also been identified.[2,3] Siblings have onset of disease at approximately the same age, with similar presentation

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and outcome.[3] Childhood FHL typically presents with liver dysfunction, neurological involvement, and bone marrow hemophagocytosis. Rash and lymphadenopathy are less common.[4] No specific clinical or histological findings distinguish secondary hemophagocytic lymphohistiocytosis (HLH) from FHL; however, genetic work-up often aids in the distinction between both. Diagnosis is based on clinical criteria, and is confirmed by molecular genetic testing.[4] Secondary HLH associated with hematological malignancies is well known.[5] However, it is not well studied whether mutations in HLH-associated genes can result in both malignancy (i.e. systemic T-cell lymphoproliferative disorders [SE-LPDs]) and FHL.[6] Four genetic loci have been identified in FHL, with biallelic mutations in the perforin gene (*PRF1*) being present in 20%–40% of all FHL cases worldwide.[4] All are part of the *PRF1*-dependent cytotoxic pathway leading to the abnormal function of NK-cells and cytotoxic T-lymphocytes.[7,8] Studies have shown that perforin and other mutations present in FHL are also present in a proportion of patients diagnosed with lymphomas who share clinical characteristics of HLH.[9,10] Here, we present the case of young boy with typical features of childhood FHL and systemic T-cell lymphoproliferative disorder along with evidence of recent Epstein–Barr virus (EBV) infection confirmed on autopsy. He had a significant family history of the death of five siblings in the second to third decades of life with undiagnosed disease. He had a prior difficult clinical course and presented a diagnostic challenge to both clinicians and pathologists.

CASE REPORT

A 15-year-old boy from Nepal presented to the medicine out-patient department with a history of high-grade fever associated with anorexia and weight loss (10 kg) for 5 months. There were no specific localizing symptoms, history of travel, exposure to ill-contacts or high-risk behavior. He had been treated with oral anti-tuberculosis therapy (3 weeks) by a local physician due to non-relenting fever. His past medical history was non-contributory except for fever and jaundice 3 years ago, which responded to conservative management. The patient was the youngest of eight siblings, born of a non-consanguineous marriage. The family history was significant for the death of five siblings due to undiagnosed illnesses with prolonged fever, two of whom also had jaundice (Figure 1).

All deceased siblings succumbed between the first and third decades of life. Anti-tuberculosis therapy had been initiated in three of these siblings in the absence of conclusive evidence of tuberculosis. The two surviving elder siblings also had a history of undiagnosed fever with jaundice, with spontaneous recovery in a few weeks. The details of treatment regimens and investigations of the deceased siblings were unavailable. On admission, our patient was conscious and oriented, had fever (38.3°C), tachycardia (pulse rate 110/min) and hypotension (blood pressure 95/60 mmHg). His respiratory rate was 20/min with 96% oxygen saturation on room air. Pallor and icterus were present. There was no rash, clubbing, cyanosis, or edema. The abdominal examination revealed hepatosplenomegaly. Initial investigations revealed severe pancytopenia with deranged liver function tests (Table 1).

In view of the possibility of drug-induced liver injury, anti-tuberculosis therapy was modified, and empirical antibiotics were given according to the febrile neutropenia regimen. The blood work-up revealed hyperferritinemia (3,346 ng/mL [reference range (RR): 20–250 ng/ml]), hypertriglyceridemia (33,658.1 mg/dL [RR: <150 mg/dL]) with raised LDH (1,748 U/L [RR: 60–170 Units/L]). These findings raised the suspicion of HLH syndrome and investigations to identify the underlying trigger were carried out. A high titer of EBV viral-capsid antigen (EBV-VCA) immunoglobulin M (IgM) antibody was suggestive of an acute EBV infection. Other tests for infection

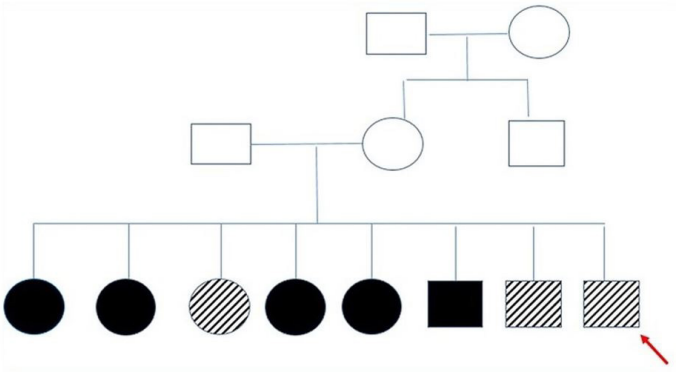

Figure 1. Pedigree analysis showing the death of five siblings (four sisters and one brother) due to unexplained fever and jaundice. The two elder surviving siblings also have history of self-resolving fever and jaundice. (Solid color: deceased; stripes: diseased; red arrow: index patient.).

Table 1. Laboratory parameters during hospital stay

Parameter	On Admission	Day 10*
Hemoglobin (g/dL)	6.1	5.0
Total leucocyte count (/mm3)	3,400	2,800
polymorphonuclear	38%	35%,
Neutrophils (cells/mm3)	1,340	980
MCV (fl)	75.2	60
MCH (pg)	20	15
MCHC (g/dL)	22.2	15
Platelet count (/mm3)	40,000	9,000
Urea/Creatinine (mg %)	27/0.8	40/2
Bilirubin Total/Direct (mg/dL)	3/2.7	11.5/10.5
AST/ALT (IU/L)	106/44	340/100
ALP (IU/L)	968	1,460
PT/INR	14/1.2	24/1.9

*Days of treatment; MCV- Mean corpuscular volume, MCH-Mean corpuscular hemoglobin, MCHC-Mean corpuscular hemoglobin concentration, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, ALP- Alkaline phosphatase, PT/INR- Prothrombin time/ International normalized ratio.

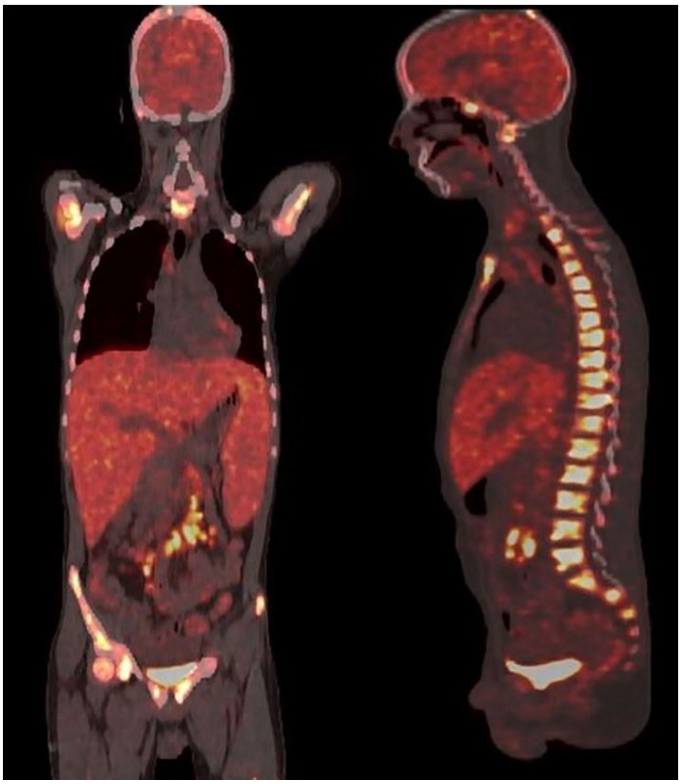

Figure 2. ^{18}FDG-PET CT scan (coronal and sagittal images) showing hepatomegaly (22.7 cm) and splenomegaly (17.9 cm), metabolically active with multiple FDG-avid abdominal and pelvic nodes. Significant FDG uptake in axial and appendicular skeleton and the presence of FDG-avid, hypodense, bilateral, thyroid masses. PET-CT: positron emission tomography-computed tomography.

revealed sterile blood and urine cultures; negative serology for brucellosis, leishmaniasis and enteric fever; negative tuberculin skin test; and negative viral and autoimmune markers.

A bone marrow biopsy revealed hypercellular marrow showing dense histiocytic infiltration with evidence of hemophagocytosis as well as an atypical T-cell infiltrate. Flow cytometry of bone marrow aspirate for malignant cells, staining for acid-fast bacilli, as well as cartridge-based nucleic acid amplification test (CBNAAT) assay for tuberculosis were negative. A liver biopsy showed interface hepatitis. ^{18}FDG-positron emission tomography-computed tomography (PET CT) scan showed hepatomegaly (22.7 cm) and splenomegaly (17.9 cm), which was metabolically active with multiple FDG-avid abdominal and pelvic nodes. There was also significant FDG uptake in the axial and appendicular skeleton and the presence of FDG-avid, hypodense, bilateral, thyroid masses (Figure 2).

With the above findings, the possibility of acquired HLH secondary to a lymphoproliferative malignancy was the best working diagnosis. However, given the strong family history, the possibility of FHL was also considered. The patient was managed in accordance with the HLH-94 protocol with dexamethasone and weekly etoposide, along with broad-spectrum antibiotics and modified anti-tuberculosis therapy. Over the next 10 days, the patient deteriorated with continuous fever spikes, worsening liver function tests, and pancytopenia. Hepatotoxic drugs were discontinued, blood products were transfused, and an empirical anti-fungal cover was added. The search for an HLA-matched sibling and an unrelated bone marrow donor was attempted but was unsuccessful. On day 12 of admission, the patient developed Type 1 respiratory failure with new-onset lung consolidation, mandating mechanical ventilation. Antibiotics were upgraded for likely hospital-acquired pneumonia. The patient succumbed on day 14 of hospitalization with refractory shock and renal shutdown.

AUTOPSY FINDINGS

On the opening of the thoracoabdominal cavity, there were gross ascites, pleural and pericardial effusions, generalized visceral lymphadenopathy, marked hepatosplenomegaly, and thyromegaly. On the

opening of the cranial cavity, the dura and brain were grossly unremarkable, and multiple sections from the brain were histologically normal. The gross thyroid examination showed a thick and adherent capsule. On serial slicing, the thyroid parenchyma was solid and firm, with the absence of colloid. The microscopic examination depicted a diffuse effacement of the follicular architecture with dense T-cell-rich infiltrate along with histiocytes destroying the thyroid follicles and forming diffuse lymphoepithelial lesions. Infiltrating T-cells displayed mild atypia. The follicular rupture was present; however, Hürthle cell change was absent. The thyroid capsule was thickened, with areas of capsular spill extending into the surrounding fat tissue (Figure 3).

Infiltrating T-cells showed immunopositivity predominantly for CD3 and CD4, and a sprinkling pattern of immunoreactivity for CD7, CD8, and CD5. CD 20 immunoreactivity was noted in a few of the dispersed larger cells. Granzyme and CD 56—the markers of activation—were positive in the T-cells. EBV-LMP1 staining was present in 2–5 cells/high-power field (Figure 4).

On microscopy, the architecture of the lymph nodes was maintained; however, sinus histiocytosis with evidence of erythrophagocytosis, and the presence of sinus T-cell infiltrates were present. Occasional multinucleated giant cells were also found (Figure 5A–C). Liver sections showed maintained architecture with dilated sinusoids and portal infiltrates comprised of T-lymphocytes and histiocytes (Figure 5D). Sections from the spleen showed a loss of lymphoid follicles, marked red pulp congestion, T-cell rich lymphoid infiltrates, and dense histiocytosis (Figure 6A and 6B).

Sections from the lung showed the histomorphological features of diffuse lobar pneumonia with alveolar exudate rich in histiocytes and T-cells. Bone marrow was hypercellular (Figure 7A) with near total replacement of normal hematopoietic

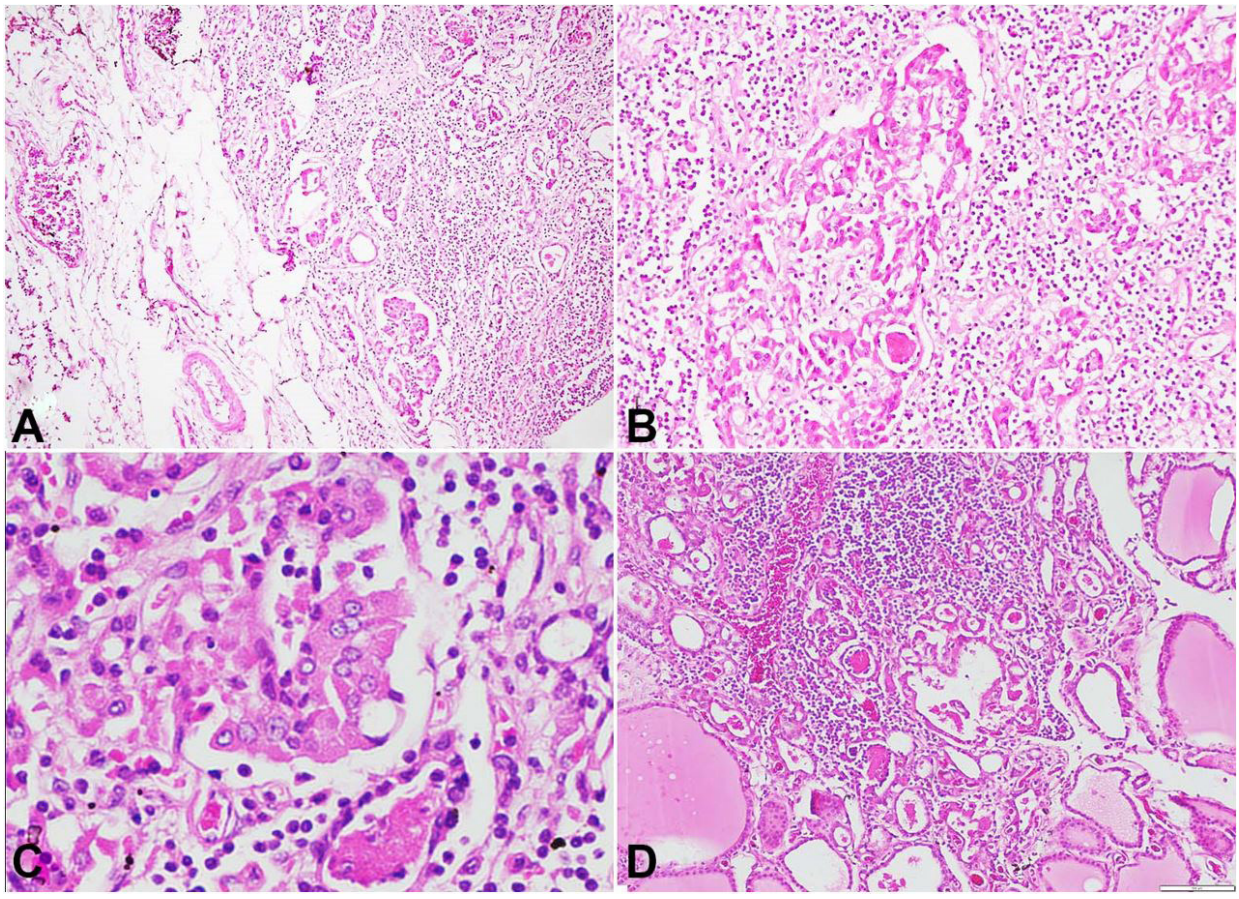

Figure 3. Photomicrographs of the thyroid. **A –** The capsular spill and infiltrative border (H&E, 100X); **B** & **C –** Diffuse infiltrate of T-cells destroying the thyroid follicles and forming lymphoepithelial lesions (H&E, 200X & 400X, respectively); **D –** Occasional ruptured follicles were also noted (H&E,100X).

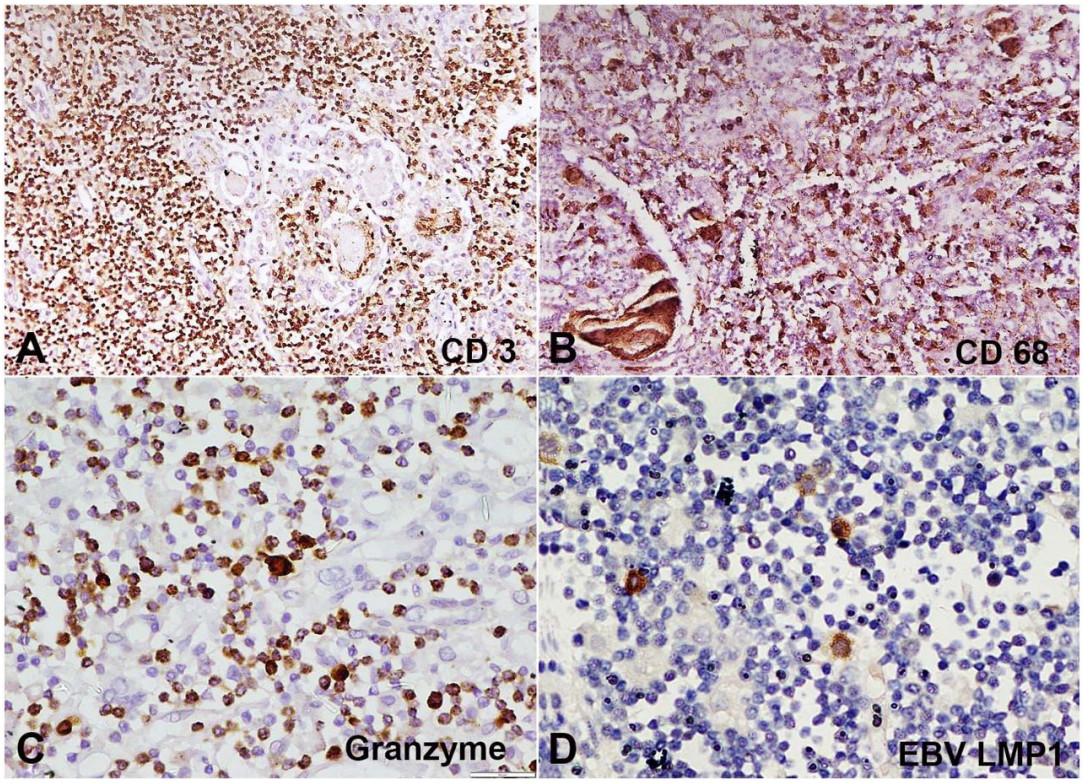

Figure 4. Photomicrographs of the thyroid. **A –** The majority of infiltrating lymphocytes stained for CD3 (100X). **B –** CD68 positive histiocytes (200X). **C –** T-cells immunopositive for granzyme-B (200X). **D –** EBV-LMP1 staining large atypical lymphoid cells (200X).

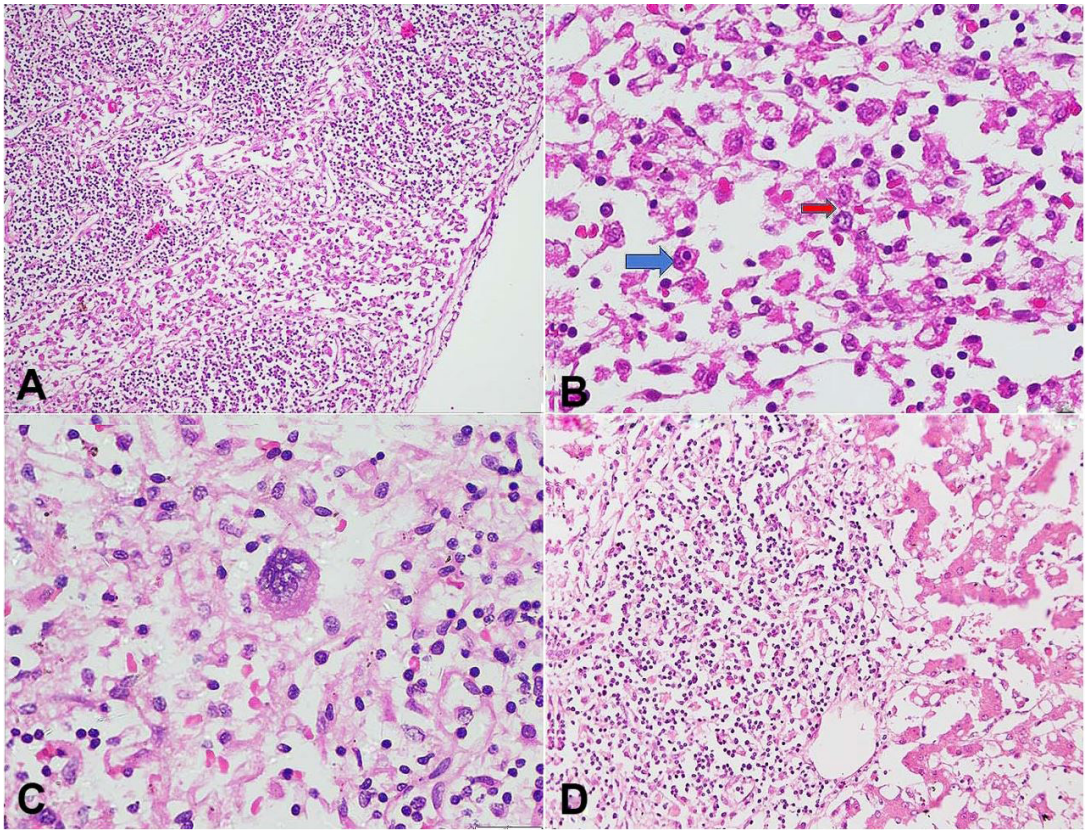

Figure 5. Photomicrographs of the lymph node (**A**, **B**, and **C**) and liver (D). **A –** Lymph node architecture maintained and marked sinus histiocytosis (H&E,100X). **B –** Macrophages displaying emperipolesis (blue arrow) and sinus histiocytes (red arrow) (H&E, 200X). **C –** An occasional multinucleated giant cell (H&E, 200X). **D –** Sinusoidal dilation and portal hepatitis comprising T-cells and histiocytes (H&E, 100X).

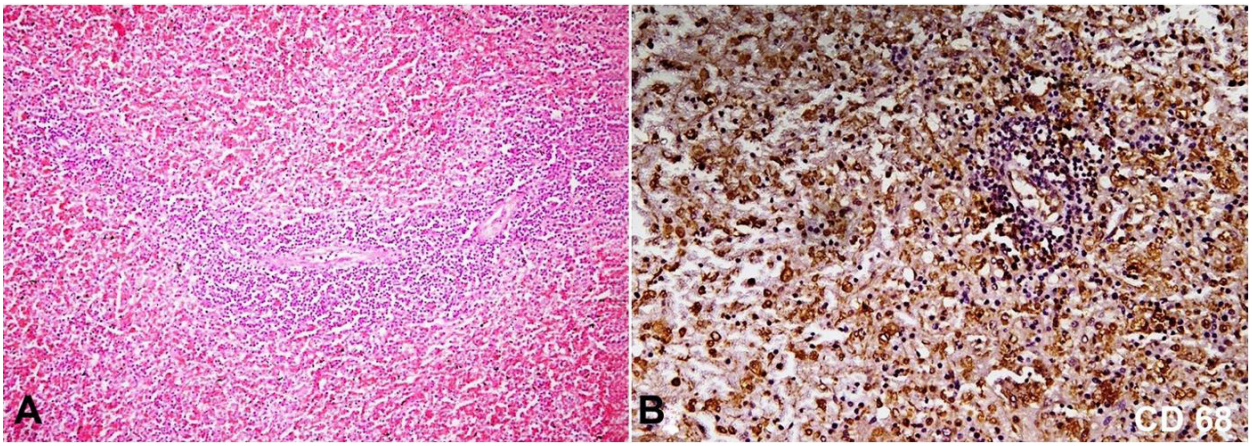

Figure 6. Photomicrographs of the spleen. **A –** Marked red pulp congestion with infiltrates rich in histiocytes and T-cells (H&E, 200X). **B –** CD 68 immunostaining highlights predominant histiocytic infiltration (H&E, 200X).

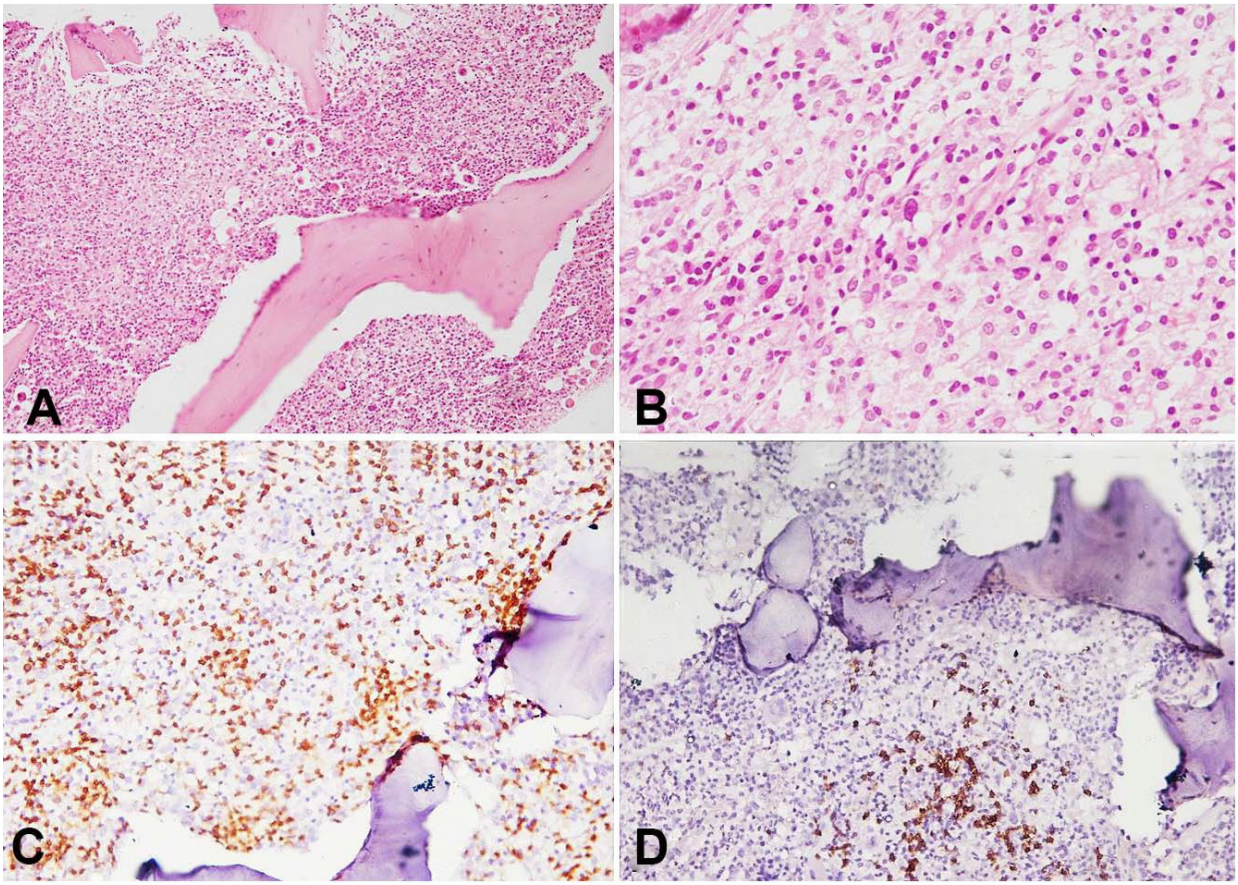

Figure 7. Photomicrographs of the bone marrow. **A –** The core of hypercellular bone marrow (H&E, 100X). **B –** Note the near total replacement of normal hematopoietic elements by sheets of histiocytes admixed with T-cells and a few large cells (H&E,200X). **C –** CD3 stain shows a predominant T-cell population (200X). **D –** Immunostaining for CD20 is positive in a few large interspersed B-cells (200X).

elements by sheets of histiocytes admixed with T-cells and a few large cells (Figure 7B). T-cells and a few interspersed CD20 positive lymphoid aggregates (Figure 7C and 7D). Few histiocytes displayed hemophagocytosis containing lymphocytes and leucocytes (Figure 8). CD68 immunostaining demonstrated a predominant histiocytic population (Figure 9A).

Immunohistochemistry for EBV-LMP1 and in-situ hybridization for EBV-encoded RNA (ISH EBER) was positive in a dispersed pattern in the infiltrating lymphoid cells (Figure 9B).

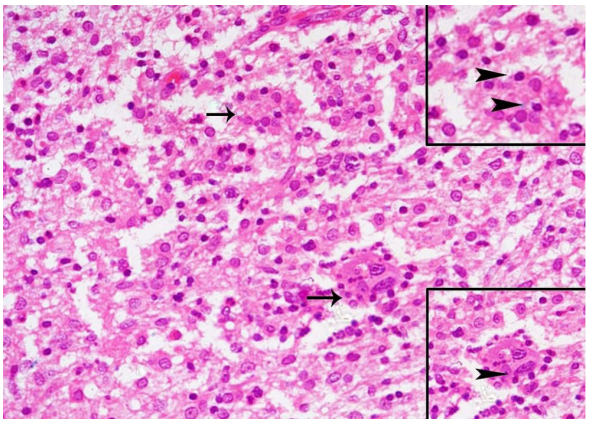

Figure 8. Photomicrographs of the bone marrow showing dense histiocytosis with evidence of hemophagocytosis. The black arrows show hemophagocytic histiocytes containing lymphocytes and leucocytes (H&E 20X). (Inset: multinucleated macrophages showing hemophagocytosis [arrowheads; H&E 40X]).

Based on the clinico-histopathological findings, a final diagnosis of HLH involving liver, spleen, lymph nodes, and bone marrow, with associated EBV-positive T-cell lymphoproliferative disorder of thyroid infiltrating liver, spleen, lung, and bone marrow was made. Whole exome sequencing (next-generation sequencing) performed on a bone marrow aspirate sample revealed a homozygous missense mutation in exon 3 of the perforin gene (*PRF1*) on chromosome 10 (chr10:72358128G>A) (Figure 10). This mutation resulted in the amino acid substitution of methionine for threonine at codon 450 (p.Thr450Met) and was pathogenic for autosomal recessive familial hemophagocytic lymphohistiocytosis-2 (FHL-2). Genetic counseling was provided for the two surviving siblings and parents, but they could not afford genetic testing.

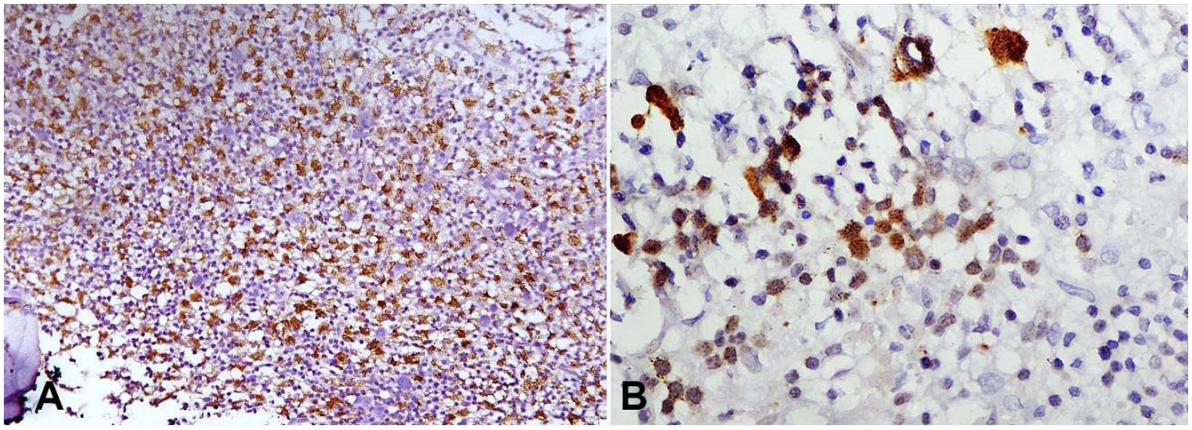

Figure 9. Photomicrographs of the bone marrow. **A –** Histiocytes immunopositive for CD68 (200X). **B –** EBV LMP-1 immunopositive in atypical lymphoid cells (200X).

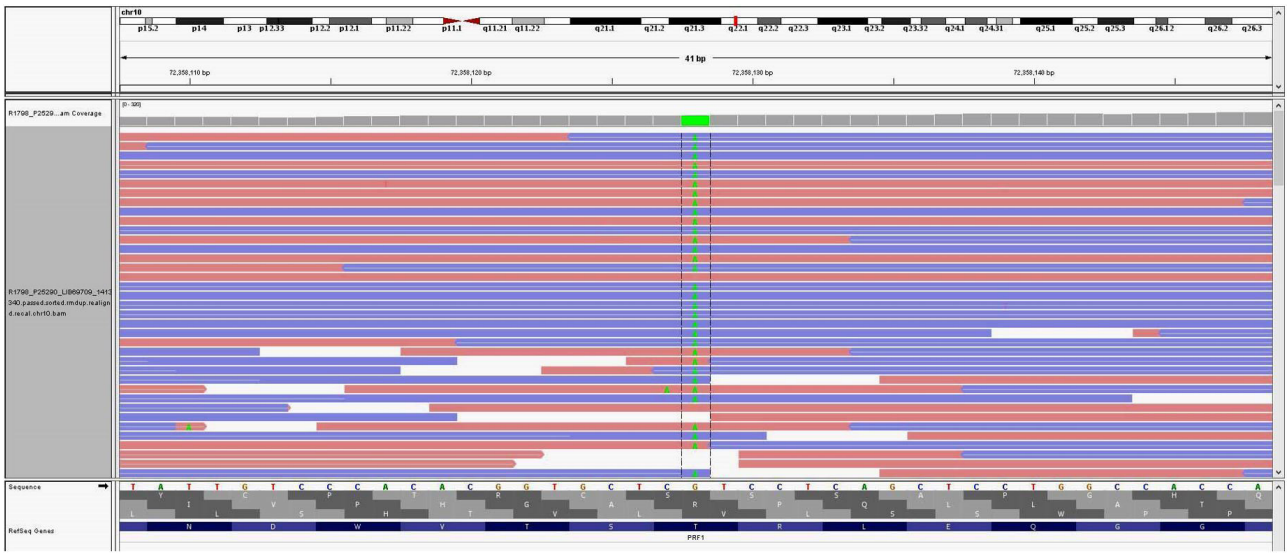

Figure 10. Mutation analysis: Whole exome sequencing performed on the bone marrow aspirate sample revealed a homozygous missense mutation in exon 3 of the perforin gene (*PRF1*) on chromosome 10 (chr10:72358128G>A).

DISCUSSION

In the index case of FHL in this family, clinical criteria for the diagnosis of FHL were met and there were similar presentations in five siblings who were undiagnosed. Pathogenic mutation in the *PRF1* gene was identified which explains the clinical manifestations. Diagnosing FHL can be a challenge when the disease presents in the first sibling with a conglomerate of non-specific signs and symptoms mimicking many infectious and autoimmune diseases, with biopsies often failing to demonstrate hemophagocytosis. The presence of a coexisting occult T-cell lymphoma further enhances the diagnostic conundrum, which often leads to therapeutic delay. The diagnosis of FHL can be established if biallelic pathological variants are present in any one of the following four loci: *PRF1, UNC13D, STX11,* or *STXBP2*[4] (Table 2); or if at least five of eight criteria listed in the guidelines of the Histiocyte Society are fulfilled (Table 3).[11]

Despite the genetic heterogeneity, patients with FHL have a similar phenotype. The perforin mutation is the most common mutation and accounts for 20%–40% of all FHL cases. The highest reported percentage is among African American families (>50%), followed by Turkey (43%), Japan (42%), and India (41%).[12] The mutations identified in those patients with the late clinical presentation are mostly missense compared to those harboring nonsense mutations.[13] *PRF1* encodes for the cytolytic effector perforin, expressed by cytolytic T-cells and NK-cells, which induces apoptotic cell death in response to granzyme.[8] An abnormal perforin gene product results in the dysregulation of apoptotic mechanisms and impaired antiviral mechanisms, resulting in inappropriate proliferation of T-cells and macrophages.[7,8] Malignancy-triggered HLH is well documented in the setting of viral infections, particularly EBV, where the former acts as a co-trigger. However, hematological malignancy co-existing with FHL is not well-defined, and data available in the literature are scarce. Mache et al.[6] reported two cases of FHL associated with T-cell lymphoma in siblings; however, the genetic testing for the presence of the

Table 2. Genetic mutations in familial hemophagocytic lymphocytosis (FHL)

Disease	Gene Mutation/Protein	Function
FHL-1	Not identified	
FHL-2	*PRF1*/perforin	Forms pores on target cell membrane, enabling NK-cell induced macrophage destruction
FHL-3	*UNC13D*/munc 13-4	Regulates cytolytic granule maturation
FHL-4	*STX11*/syntaxin 11	Controls cytolytic granule exocytosis
FHL-5	*STXBP2*/syntaxin binding protein 2	Promotes release of cytolytic granules

Table 3. Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH 2004 Protocol)

a - Molecular identification of an HLH-associated gene mutation* or

b - Five out of the eight following features:

1 - Fever ≥38.5°C

2 - Splenomegaly

3 - Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/mm^3; absolute neutrophil count <1000/mm^3

4 - Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)

5 - Hemophagocytosis in bone marrow, spleen, lymph node, or liver

6 - Low or absent NK-cell activity

7 - Ferritin >500 ng/mL

8 - Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms

*Children require documentation of homozygosity or compound heterozygosity. For adults, heterozygosity of mutated gene is sufficient, if clinical features are compatible.

specific FLH mutation was not performed. The present case presented with T-cell lymphoproliferative disorder (LPD) involving the thyroid, bone marrow, spleen, and liver, which often poses diagnostic difficulties in distinguishing it from EBV-HLH. The presence of high titers of the EBV viral-capsid antigen IgM probably represents a recent primary infection in this case, secondary to decreased immune surveillance. A T-cell lymphoproliferative disorder arising in the setting of acute EBV infection presenting with FHL is a rare association.[14,15] Infiltrating lymphocytes can be morphologically bland, displaying minimal to frank atypia depending upon the stage of the disease. Interestingly, the histological atypia is proportional to the stage of the disease; it can be polymorphous and polyclonal, polymorphous and monoclonal, or monomorphic and monoclonal.[14,15] Clonality studies—namely the TCR gene rearrangement and cytogenetic studies—differentiate LPD from EBV-HLH, but the major limitation relies on the detection of a false positive result in the reactive settings besides having no clinical impact on patient outcome.[14,15] Published literature shows that EBV-HLH and SE-LPD share similar clinicopathological findings and represent a continuous spectrum of the acute EBV-associated T- or NK-cell lymphoproliferative disorders.[15] FHL patients with genetic mutations may be prone to developing malignancy in the future, even if HLH resolves; therefore they require long-term follow-up.[6,16] Our case and previous studies[6,9,10,16] suggest that decreased perforin function and underlying genetic mutations lead to increased susceptibility for the development of HLH as well as lymphoma, since the pathogenesis involves common cytotoxic pathway mutations and possibly some additional genetic insult.

The treatment of HLH and FHL is focused on curbing the unchecked immune response and eliminating the trigger. HLH-94 and HLH-2004 therapy protocols are often not effective in FHL cases.[11] Hence, allogenic hematopoietic cell transplantation should be undertaken as early as possible in children with confirmed FHL.[4,17] FHL has an aggressive clinical course and a fatal outcome; therefore, a high level of suspicion, and a thorough clinical and genetic work-up will prompt early diagnosis and management.

CONCLUSION

Although FHL typically manifests under 1 year of age, childhood and/or adult FHL is also common. Hematological malignancy should always be searched in cases with primary HLH-related genetic mutations. If a pathogenic mutation is identified, genetic testing of asymptomatic first-degree relatives should be carried out, and the affected individuals may be considered for early bone marrow transplantation before the development of a full-blown multi-system disorder.

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