Peripheral T-cell lymphoma in adult-onset familial hemophagocytic lymphohistiocytosis type 2 and heterozygous *LRBA* mutation

Here, we present an unusual case of a patient with late-onset familial hemophagocytic lymphohistiocytosis (FHL) type 2 and concurrent heterozygous *LRBA* mutation presenting with hemophagocytic lymphohistiocytosis (HLH), peripheral T-cell lymphoma, severe infectious complications with atypical pathogen spectrum and progressive hyperbilirubinemia.

FHL is a rare and life-threatening disorder characterized by uncontrolled immune activation leading to hyperinflammation and hemophagocytosis. In most cases, patients develop FHL, also called primary HLH, in the first 2 years after birth, although a subset of patients develop symptoms of FHL later (late-onset FHL). FHL-associated inflammation is often triggered by infection. In adults HLH usually develops secondary to viral infections, neoplasia, most commonly lymphoma or autoimmune disorders.[1,2]

The most common FHL subtype FHL2 is caused by hereditary biallelic mutations of the perforin gene *PRF1*. Perforin is involved in the immune system's cytotoxic function and plays a crucial role in the elimination of infected or abnormal cells by pore formation, facilitating the entry of cytotoxic molecules leading to cell death. Mutations in *PRF1* disrupt the function of perforin, impairing the cytotoxic activity of T lymphocytes and natural killer (NK) cells.[3,4]

Until now, best treatment option for patients with clinically manifested FHL remains allogenic hematopoietic stem cell transplantation (alloHSCT), with survival rates after alloHSCT of ~70%.[5]

Mono- and biallelic *PRF1* mutations were associated with the development of lymphoma with or without concurrent clinical evidence of FHL.[6] Homozygous lipopolysaccharide-responsive beige-like anchor protein (*LRBA*) mutations lead to a rare immune disorder known as *LRBA* deficiency. Some cases may present with an autoimmune lymphoproliferative syndrome (ALPS)-like phenotype. *LRBA* is involved in regulating immune cell function and mutations lead to immune dysregulation, autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenia (ITP), autoimmune enteropathy, and susceptibility to infections. AlloHSCT may be considered in severe cases.[7,8]

A 31-year-old male patient was administered to our tertiary care center with suspected HLH. In the previous 4 weeks the patient had shown recurrent episodes of fever and malaise. Histopathologically confirmed linear IgA dermatosis was known for 3 years and treated with dapsone. The patient's sister showed multiple demyelinating manifestations of the central nervous system (CNS) at adult-onset of unclear origin and was diagnosed with recurring episodes of ITP, AIHA, direct hyperbilirubinemia, and lymphoproliferation. In childhood, she developed prolonged infectious mononucleosis with large cervical

Table 1. Patient characteristics according to the hemophagocytic lymphohistiocytosis-2004 diagnostic criteria.

HLH-2004 criteria	Patient	Normal range
Fever >38.5°C	Recurring fever >38.5°C	Absent
Splenomegaly	Splenomegaly detected	Normal
Cytopenia ≥2 lineages* Leukocytes/nL Neutrophils/nL Hemoglobin g/dL Thrombocytes/nL	 1.53 0.32 8.4 36	 3.6-9.2 1.7-6.2 13.7-17.2 140-320
sIL2R ≥2,400 units/mL	40,908	220-700
Ferritin ≥500 µg/L	21,749	22-322
Triglycerides >265 mg/dL or fibrinogen ≤1.5 g/L	268 1.16	<200 1.88-3.84
NK-cell activity testing	Not performed	Normal
Morphologic hemophagocytosis	Found in bone marrow	Absent

Normal ranges are displayed as defined by the local laboratory. *Lineages are defined as neutrophil count, hemoglobin concentration and thrombocyte count. HLH: hemophagocytic lymphohistiocytosis; sIL2R: soluble interleukin 2 receptor; NK: natural killer.

histologically benign lymph nodes, that showed spontaneous regression. ALPS was suspected; *in vitro* apoptosis reaction test was positive; sequencing of the *FAS* gene showed no pathogenic mutations. She died at the age of 26 of fungal sepsis confirmed *post mortem* from gastric autopsy. A second sister was diagnosed with oligoclonal band negative multiple sclerosis at the age of 30 and was alive 16 years later under immunosuppression. Currently, a third sister of similar age showed no symptoms. Both non-consanguineous parents did not show any phenotype. HLH was diagnosed according to the HLH-2004 criteria, characteristics are summarized in Table 1.

The patient underwent broad virology, autoimmunology, and morphological screening. Epstein-Barr virus viral reactivation with low viral load of 795 units/mL was detected. Autoimmunological assessment showed weakly positive antinuclear antibodies (1:160). Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging revealed multiple lymph nodes with high glycolytic activity (Figure 1A-D). Furthermore, a diffuse intensive glucose utilization of the bone marrow was found. A CNS lesion on the right cerebellar side was found as focal hypometabolism and showed enhancement of gadolinium in magnetic resonance imaging (MRI). Microbiological and virological cerebrospinal

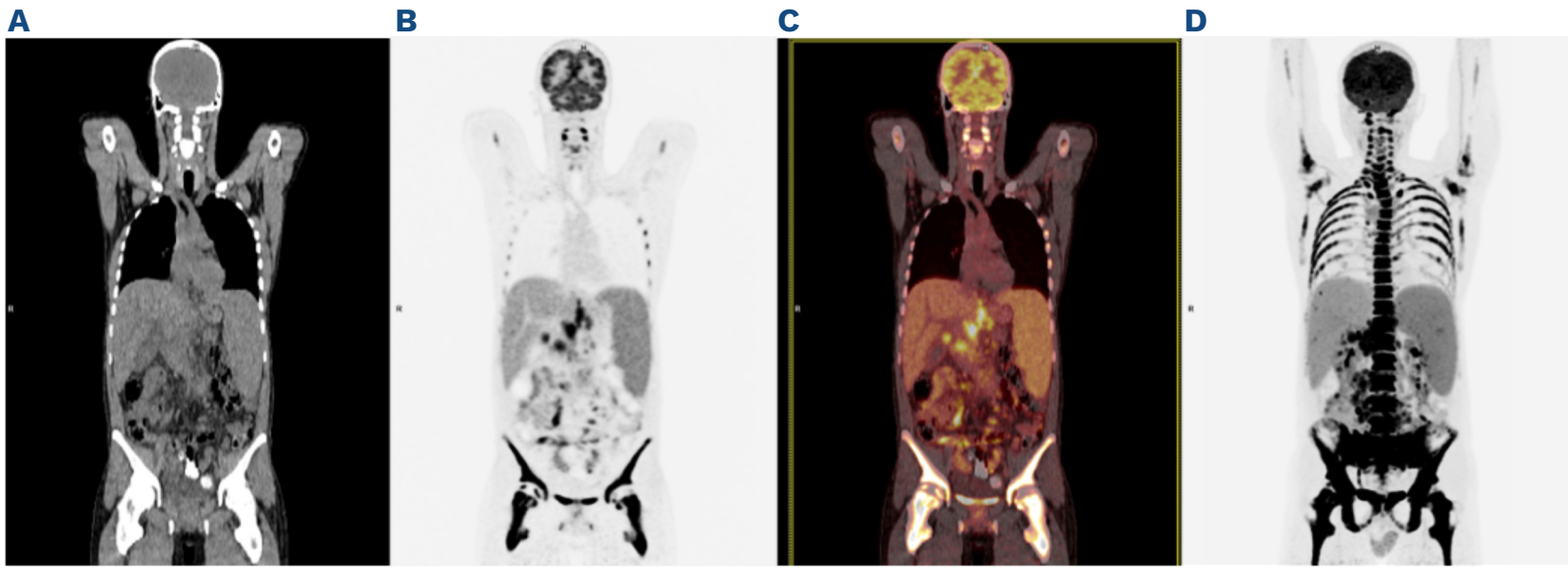

Figure 1. Diagnostic findings: imaging, tissue histology, and molecular genetic results. (A-D) Positron emission tomography-computed tomography imaging demonstrating increased fluorodeoxyglucose uptake in lymph nodes along the right thoracic internal mammary chain, hepatic hilum, portal venous system, retroperitoneum, and mesentery, with concomitant diffuse bone marrow uptake. (E, F) Histopathology of T-cell lymphoma in (E) hematoxylin and eosin stain and (F) anti-CD3-immunhistochemistry. (G) Schematic representation of *PRF1* mutations both detected in exon 3 by whole-exome seuquencing. (H) Confirmation of the compound heterozygous *PRF1* genotype by allele specific polymerase chain reaction with gel electrophoresis, products amplified with Amplitaq-Gold (1: 253Glu/356Arg [negative], 2: 253Glu/356Trp [positive], 3: 253Lys/356Arg [positive], 4: 253Lys/356Trp [negative], C1-4: negative controls of 1-4). The figure was created in BioRender (https://BioRender.com/xabycto and /r1w4pz4).

fluid findings were unremarkable, oligoclonal bands were negative, meningeosis lymphomatosa was excluded. After laparoscopic retroperitoneal lymphadenectomy histology confirmed peripheral T-cell lymphoma, not further specified according to latest World Health Organization 2022 classification with an EBER$^-$/CD3$^+$/CD5$^+$/CD30$^-$/CD56$^-$/TCL1$^-$/bF1$^+$/partial PD1$^+$ immune-phenotype (Figure 1E, F). Bone marrow aspiration and biopsy showed hemophagocytosis and 30% infiltration of the lymphoma with concurrent monoclonal VJ-recombination of the TRG locus. Flow cytometry showed 30% CD3$^+$/CD4$^+$ lymphocytes. Peripheral blood showed 65% lymphocytes with a concurrent immunophenotype. Chromosomal banding analysis showed a normal 46,XY karyotype in 27 metaphases.

Whole-exome sequencing (WES) (Twist Human Core Exome, Ilumina NextSeq) was performed from whole blood and genes associated with FLH (14 genes), ALPS or ALPS-like phenotype (14 genes) and neurofibromatosis (*NF1, NF2*) were assessed. WES analyzed gene panels included (i) HLH: *CD27, HAVCR2, IFNGR1, LYST, PRF1, RAB27A, RAG1, RAG2, SLC29A3, SLC7A7, STX11, STXBP2, UNC13D, XIAP; (ii) ALPS: CASP10, CASP8, CTLA4, FADD, FAS, FASL, ITK, KRAS, LRBA, MAGT1, NRAS, PIK3CD, PRKCD, RASGRP1* and (iii) NF: *NF1, NF2*; whereas the lymphoma somatic next-generation sequencing panel included (i) full sequences of *ASXL1, BCOR, CALR, CEBPA, ETV6, EZH2, IKZF1, NF1, PHF6, PRPF8, RB1, RUNX1, SH2B3, STAG2, TET2, TP53*, and *ZRSR2*; (ii) mutational hot spots of *ABL1, BRAF, CBL, SF3R, DNMT3A, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, MYD88, NPM1, NRAS, PTPN11, SETBP1, SF3B1, SRSF2, U2AF1*, and *WT1*.

Two heterozygous pathogenic and likely pathogenic missense variants in *PRF1* were detected (NM_001083116.3:c.757G>A and NM_001083116.3:c.1066C>T) leading to the amino acid substitutions p.Glu253Lys and p.Arg356Trp detected in variant allele fractions (VAF) of 47 % and 52% likely reflecting a germline heterozygous state (Figure 1G). Allele-specific polymerase chain reaction confirmed compound heterozygosity of the *PRF1* mutations (Figure 1H). *PRF1* p.Ala91Val polymorphism was excluded. Additionally, a likely pathogenic heterozygous *LRBA* missense variant NM_006726.4:c.3913C>G leading to the amino acid change p.Arg1305Gly was present in VAF of 41 % without signs of copy number loss in exome-based copy number variant analysis.

Treatment according to the HLH-94 protocol was initiated (Figure 2).[9] Initially, laboratory findings improved during the first 4 weeks of treatment. However, the patient developed severe infectious complications consisting of recurring neutropenic fever with blood stream infections of *S. haemolyticus* and *E. faecium*, prolonged diarrhea, progressive dysphagia with diffuse distal esophagitis de-

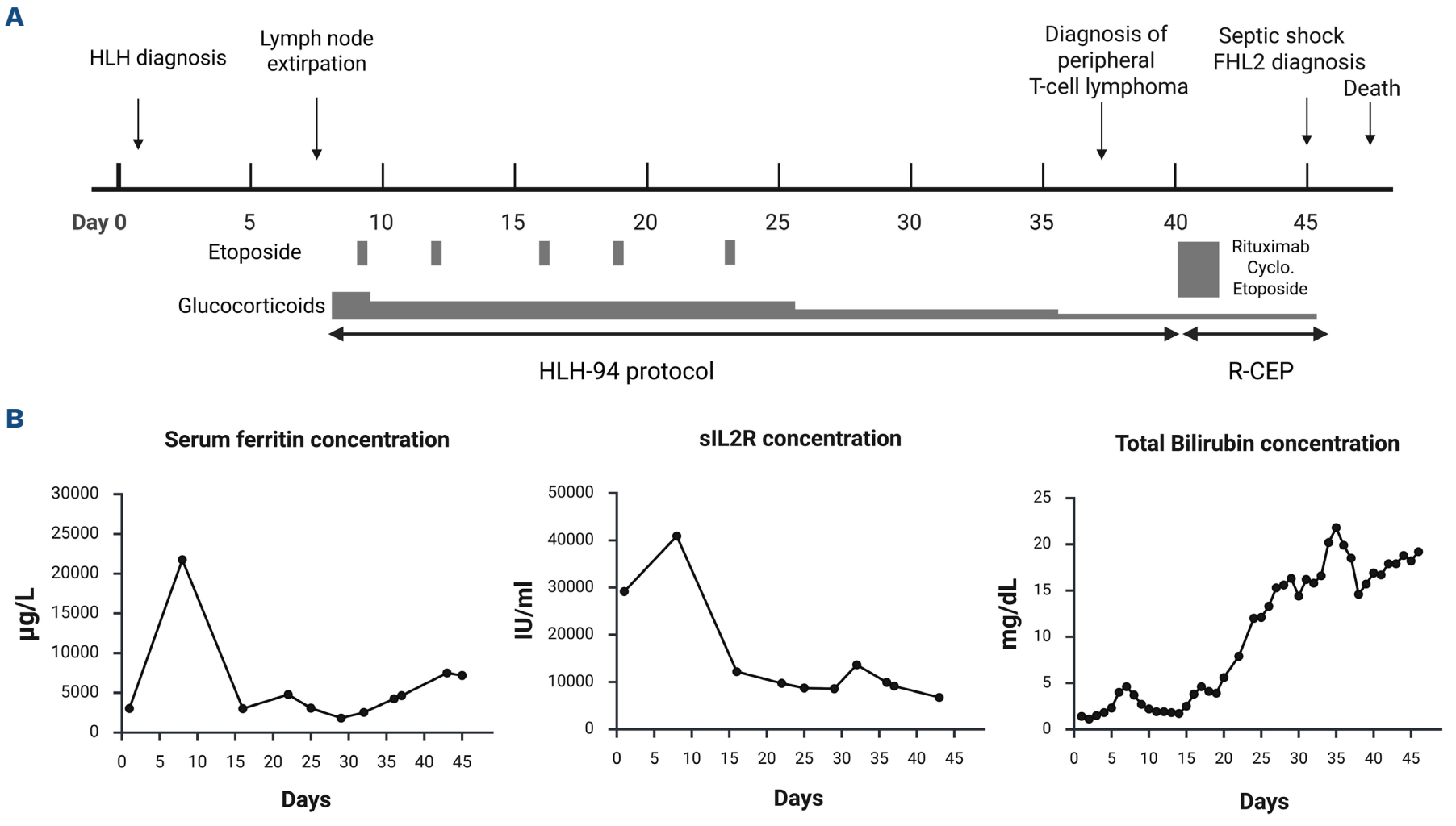

Figure 2. Clinical course of the patient. (A) Timeline from initial diagnosis till death including treatment regimens. (B) Selected laboratory parameters (serum ferritin, soluable interleukin 2 receptor [sIL2R], total bilirubin). HLH: hemophagocyitc lymphohistiocytosis; FHL: familial hemophagocyic lymphohistiocytosis subtype 2; Cyclo: cyclosporin; R-CEP: Rituximab, Cyclosporin, Etoposide. The figure was created in BioRender (https://BioRender.com/xabycto and /r1w4pz4).

tected by esophagogastroduodenoscopy (EGD), PAS-positive signs of fungal infection in EGD biopsies and diffuse upper gastrointestinal bleeding. Endoscopic biopsies from the latest EGD showed caspofungin-resistant *Saccharomyces cerevisiae* besides Candida species (*C. crusei/albicans*) and *Bacterioides caccae*. Additionally, Herpes simplex virus 1 DNA was found in these biopsies but not prior to that in oropharyngeal washes and swabs. Later, the patient developed clinical jaundice, progressive ascites, and direct hyperbilirubinemia up to total bilirubin serum levels of 21.8 mg/dL. Cholestasis was excluded by sonography and MR-cholangiopancreatography. Ascites punctures excluded spontaneous bacterial peritonitis. Consecutive hepatitis testing remained negative. During the whole treatment, the patient was highly transfusion dependent. After diagnosis of peripheral T-cell lymphoma was confirmed, intensity reduced treatment with cyclophosphamide, etoposide and prednisolone was initiated. The patient rapidly developed a fulminant septic shock with multi organ failure, and died 3 days after admission to the intensive care unit. The study was performed in accordance with the ethical standards and regulations of the country in which it was conducted and in adherence to the Declaration of Helsinki. Consent for publication was not obtained because the patient deceased. Formal ethics committee approval was not obtained, as this is a descriptive single-patient case report.

FHL2 is associated with a wide spectrum of *PRF1* mutations. Our patient carried compound heterozygous *PRF1* mutations (Glu253Lys/Arg356Trp), a genotype not previously described, though both variants have been individually linked to FHL2. The Arg356Trp mutation has been associated with late-onset FHL2 and cases of peripheral T-cell lymphoma, with some patients initially presenting with neurological symptoms.[6,10] In contrast, the Glu253Lys variant has been predominantly described in early-onset cases of FHL2, often accompanied by CNS involvement and rapid progression.[11,12] The identification of compound heterozygous *PRF1* mutations in this 31-year-old patient aligns with increasing evidence regarding the genetic landscape of adult-onset HLH. Bloch *et al.*[13] recently demonstrated that variants of uncertain significance and pathogenic variants in FHL-related genes, such as *PRF1*, are significantly enriched in adults presenting with severe HLH, suggesting that these genetic predispositions may remain clinically silent until triggered by a secondary insult like malignancy or infection.

In addition, our patient harbored a previously unreported heterozygous *LRBA*^{Arg1305Gly} variant. However, a pathogenic variant at the same residue Arg1305His has been linked to *LRBA* deficiency, supporting a functional relevance in this highly conserved position.[14]

The complexity of our patient's genetic profile, involving both *PRF1* and *LRBA*, supports the 'synergistic defect' model proposed by Zhang *et al.*,[15] which illustrates how compound heterozygosity or multiple defects in cytotoxic pathways can converge to cross the threshold for clinical FHL.

The previously unreported genotype found in our patient may point toward a synergistic effect contributing to immune dysregulation and progression to lymphoma. Our findings underscore the clinical relevance of comprehensive genetic testing in atypical HLH presentations and highlight the need for further investigations into potential pathogenetic interactions between *PRF1* and *LRBA* variants in immune-mediated disorders and lymphomagenesis. As commercial panels for autoinflammatory and immunodeficiency syndromes become increasingly accessible, we anticipate that findings in multiple converging pathways of HLH and lymphoproliferation will become more frequently recognized. Our case adds to this growing body of literature and reinforces the argument that widespread HLH genetic testing is warranted in young adults with hyperinflammatory presentations.

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Contributions

MT wrote the manuscript with support from MH. TH performed the WES and allele specific PCR experiments. HCR and MH supervised the project. MT created the figures of the manuscript.

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Data-sharing statement

Data is available upon request.

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