Familial Hemophagocytic Lymphohistiocytosis secondary to UNC13D mutation: a report of two cases

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by some clinical signs (e.g., non-remitting fever, hepatosplenomegaly) and laboratory findings (e.g., cytopenia, increased ferritin level, hypofibrinogenemia, lipid disorders, coagulopathy, and multiple organ failure). Depending on the etiology, HLH is divided into familial (i.e., primary) and acquired (i.e., secondary) forms. Familial HLH (FHL), an autosomal recessive condition, is classified into five subtypes based on underlying genetic defects. The PRF1, STX11, UNC13D, HPLH1, and STXBP2 are the most well-known genes of this type which are related to granule-mediated cytotoxic T and Natural killer (NK) cells. The treatment is based on the HLH-2004 protocol.

Case presentation: The current report presents two cases of HLH with presentations different from each other and previously reported cases. Case 1 was a 15-month-old boy with fever, skin rash, splenomegaly, and bicytopenia, raised triglyceride levels, AST (aspartate transaminase), and ALT (alanine aminotransferase), normal ferritin, and abundant hemophagocytic cell in bone marrow aspiration. He was diagnosed with HLH and received HLH protocol as treatment. The patient had a homozygous intronic mutation; NM_199242: c.2448-13G > A in UNC13D. The associated disease was Familial Hemophagocytic Lymphohistiocytosis 3 (FHL3). Case 2, a 37-day-old female presented with fever, a history of neonatal cholestasis, and huge hepatosplenomegaly. Her whole-exome sequencing report manifested that the patient had the same mutation as case 1. Unfortunately, both patients passed away.

Conclusion: The sequencing of the entire UNC13D gene (coding and non-coding regions) is an applicable and valuable diagnostic procedure for the detection of deep intronic splicing variants and large inversions in patients with atypical manifestations of HLH (such as normal ferritin or triglyceride and cholesterol).

Keywords: Case report, FHL (familial Hemophagocytic lymphohistiocytosis), HLH (Hemophagocytic lymphohistiocytosis), UNC13D

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Natural killer (NK) cells, and histiocytes is considered the leading cause of this disease.

Depending on the etiology, HLH can be divided into familial (i.e., primary) and acquired (i.e., secondary) forms [4–6]. Familial HLH (FHL), an autosomal recessive condition, is classified into five subtypes based on underlying genetic defects. The PRF1, STX11, UNC13D, HPLH1, and STXBP2 are the most well-known genes of this type.

Mutations associated with restrained cytotoxic responses of cytotoxic T and NK cells to B cells infected by Epstein-Barr virus (EBV) inducing X-linked lymphoproliferative syndrome (SH2D1A, XIAP) are the third reason. Nevertheless, other primary immunodeficiencies, including combined immunodeficiency, chronic granulomatous disease, autoinflammatory diseases, and antibody deficiencies, have been described to cause HLH [4–8]. Acquired or secondary HLH, also known as macrophage activation syndrome, mainly occurs after severe viral, bacterial, or fungal infections, metabolic disorders, malignancies, and rheumatologic and immune diseases, such as autoimmune or autoinflammatory diseases [4–6, 9–11].

The treatment is based on HLH-2004 protocol, including chemoimmunotherapy (corticosteroids, etoposide, cyclosporin A, and/or intrathecal methotrexate), supportive therapy, prophylactic antibiotics, and intravenous Ig (IVIG). Hematopoietic stem cell transplantation is recommended in selected patients with refractory and/or relapsed disease after appropriate chemoimmunotherapy [12–14]. This treatment is modified regarding the classification and pathophysiology of HLH.

T-cell-directed immunotherapy could be advantageous in patients with primary HLH. In contrast, strong immunosuppression therapy is contraindicated in patients with severe proceeding infections or some primary immunodeficiency diseases other than familial HLH and X-linked lymphoproliferative syndrome [3]. In addition, more T-cell targeting therapies, such as anti-thymocyte globulin, etoposide, and alemtuzumab, can be beneficial to patients with primary HLH due to overactivated T cells [4, 5].

The differentiation between the two mentioned types of HLH is sometimes tricky, particularly in the beginning; moreover, diagnosis at the right time is critical for initiating appropriate and indicated treatment. Therefore, we performed whole-exome sequencing on two separate patients with relatively different symptoms to find the same homozygous intronic UNC13D mutation.

Case presentation
In this study, we present the case of two children with rather different clinical symptoms hospitalized almost at the same time in two different centers affiliated with Tehran University of Medical Sciences. Their ages, symptoms, and signs were different, especially at the beginning; nonetheless, whole-exome sequencing was employed due to the uncertainty surrounding the underlying etiology. Written informed consent was obtained from their parents.

Case 1
The first case was a 15-month-old male infant born to consanguineous parents via normal vaginal delivery. He had normal growth and development until admission due to prolonged fever for 40 days with no specific pattern, vomiting, and maculopapular rash on his face. His physical examination revealed huge splenomegaly (diameter 120 mm) and fever. Liver function tests demonstrated a rise in aspartate aminotransferase (AST) of 88 IU/L and alanine aminotransferase (ALT) of 52 IU/L. His Complete blood count (CBC) showed bicytopenia (white blood cell count of 10.8 thousand/mm³, anemia with hemoglobin of 10.8 g/dl, and thrombocytopenia with a platelet count of 106 *10³/μl). Triglyceride (TG) level was initially 425 mg/dl, which increased to 644 mg/dl. The cholesterol level was initially 86 mg/dl, which increased to 182 mg/dl. The c-reactive protein (CRP) was high (73 mg/dl) with a normal erythrocyte sedimentation rate (ESR) at the same time (14 mm/h). Remarkably, the value of serum ferritin was normal throughout all his disease period (150 μg/l).

His abdominal sonography illustrated splenomegaly with a diameter of 120 mm and homogenous echogenicity. Bone marrow aspiration (BMA) performed from the iliac crest appeared normal. He was diagnosed with macrophage activating syndrome in the context of systemic juvenile idiopathic arthritis by a consultant rheumatologist. He received intravenous methylprednisolone pulse therapy (30 mg/kg) and intravenous immune globulin (IVIG). He was discharged from the hospital with oral prednisolone at a dose of 1 mg/kg/day and readmitted with intermittent fever and vomiting after 45 days. He had bicytopenia, increased ALT and CRP during hospitalization, and his ferritin level was 248 μg/l. Antibody assessment against cytomegalovirus (CMV) and Epstein-Barr virus (EBV) displayed no abnormality.

The patient underwent BMA again, and bone marrow revealed abundant hemophagocytic cells. He was treated with cyclosporine A, etoposide, and dexamethasone according to HLH protocol 2004. After 1 month of treatment, CBC turned normal; CRP and TG decreased. Upon the completion of induction therapy with HLH protocol
and initiation of maintenance therapy, the patient experienced a disease flare-up and was readmitted with fever and status epilepticus. Laboratory data revealed pancytopenia and increased levels of TG, AST, and ALT again; however, ferritin level was in the normal range, and brain computed tomography (CT) scan showed ventriculomegaly and Mega Cisterna Magna (Table 1).

In the last course of hospitalization, the patient passed away because of progressive brain involvement and hydrocephalus, and the whole-exome sequencing (on genomic DNA extracted from peripheral blood cells through an Agilent SureSelect V7 kit and Genome Analyzer HiSeq 4000 (Illumina, USA)) revealed a homozygous intronic UNCI3D (NM_199242: c.2448-13G > A), probably affecting splicing. Although Sanger sequencing is not a routine survey for parents, since this mutation is transferred from parents or is a de novo mutation for the assessment of the next child, it was performed and confirmed that his parents were heterozygous carriers for this mutation (Fig. 1). The associated disease was Familial Hemophagocytic Lymphohistiocytosis 3 (OMIM 608897) with autosomal recessive inheritance.

Table 1  Timeline of clinical and laboratory presentation of case 1

| Clinical presentation | First admission | Second admission | Last admission |
|-----------------------|----------------|-----------------|---------------|
| CBC                   | Bicytopenia    | Bicytopenia     | pancytopenia  |
| ESR (mm/h)            | 14             | 21              | 16            |
| CRP (mg/dl)           | 73 reduced to 4| 46              | 5             |
| AST (IU/L)            | 88             | 36              | 74            |
| ALT (IU/L)            | 52             | 53              | 207           |
| TG (mg/dl)            | 425 increased to 644 | 386 | 972 |
| Chol (mg/dl)          | 86 increased to 182 | 127 | 155 |
| Ferritin (μg/l)       | 150            | 248             |               |
| Bone marrow aspiration| Normal         | hemophagocytic cells | |

Fig. 1  Sanger sequencing of c.2448-13G > A mutation in the studied families (Geneious software was used for sanger analysis)
Furthermore, prenatal diagnosis with chorionic villus sampling was implemented in the 12th week of gestational age for the next child of this family and demonstrated that the fetus was only a heterozygous carrier of UNC13D mutation.

Case 2
A 37-day-old female neonate born to consanguineous parents via cesarean section was admitted with fever (Temperature: 39°C), cough, and a history of neonatal cholestasis. Her physical examination revealed fever and huge hepatosplenomegaly (with spleen preference). She had normal growth before admission despite the previous admission for cholestasis. Her liver function tests resulted in an AST of 331IU/L that increased to 981IU/L and an ALT of 21IU/L that increased to 391IU/L in her admission process. Her CBC revealed pancytopenia (leukopenia with white blood cell (WBC) of 3.13 thousand/mm² and ANC of 210, anemia with hemoglobin of 5.1 g/dl, and thrombocytopenia with platelets of 41 *10³/μl).

The TG and cholesterol levels were 113mg/dl and 76mg/dl, retrospectively. Ferritin level was increased to 2050μg/l during her hospitalization. The CRP was 76 mg/dl, retrospectively. Ferritin level was increased a diameter of 144 mm and hepatomegaly with a diameter of 105 mm (both of homogenous echogenicity). The BMA and bone marrow biopsy were performed from the proximal tibia and appeared normal.

Her purified protein derivative (PPD) test turned negative, and a normal TORCH study (assessing antibodies against toxoplasmosis, rubella, CMV, and Herpes simplex virus [HSV]) was detected. The HIV ab was also negative. Metabolic screening tests, including MS/MS, ammonia, lactate, serum amino acid chromatography by HPLC, and urine reducing substance, all were normal. Nevertheless, the evaluation of Galactosemia, Gaucher’s disease, and Niemann-Pick’s disease were not feasible due to the previous history of blood transfusion. Furthermore, fibrinogen was in the normal range.

She was treated with prednisolone (4 mg/kg/day) and IVIG (2 g/kg Stat) as prescribed by a hematologist (with autoimmune thrombocytopenia and anemia diagnosis). Firstly, there was a rapid increase in platelet number and hemoglobin level. Nonetheless, the patient needed multiple blood transfusions and platelets due to sustained bicytopenia. Since the second case did not fulfill the criteria, she did not receive the 2004-HLH treatment protocol as suggested by a consultant rheumatologist. Finally, she died of severe sepsis by abdominal distention and jaundice, like some other manifestations of the disease, were observed in our cases to some extent [18, 21].
Moreover, the laboratory findings of these two cases were in line with the literature (except for ferritin level in case 1), suggesting that neutropenia, thrombocytopenia, lack of NK cell activity, reduced fibrinogen, increased ferritin, and high level of triglycerides should raise doubts about the diagnosis of FHL3 [11].

The FHL3 mostly happens in the first year of life (with a median age of 3 months); nonetheless, the first case was older than 1 year [22]. Ferritin level has been reported high in most previous studies; however, it was interestingly normal in our first case, even during the active phases of the disease [23, 24]. A wide range of bacterial, viral, protozoal, and fungal infections are correlated with HLH [25]. Viral infections are supposed to provoke both primary and secondary types of HLH. Herpesviruses, particularly EBV, are the most prevalent viral infections [26], Rickettsia [27], Mycobacterium [28], and Histoplasmosis [29] are the most frequent bacterial and fungal infections, retrospectively. Although it could not be justified, the sepsis induced by *Pseudomonas aeruginosa* could trigger the incidence of HLH in the second patient.

The solitary treatment for familial and severe HLH is bone marrow transplantation [13]. Based on the HLH 2004 protocol, an 8-week monotherapy utilizing dexamethasone, Cyclosporine A, or etoposide is considered the first-line treatment. However, the second case did not receive any treatment due to a failure to fill in the HLH 2004 protocol. Due to the involvement of the central nervous system in readmission, intrathecal methotrexate was administered to our first case with fever and status epilepticus, and bone marrow transplantation was considered the next step to put the disease in remission [30]; however, the neurological involvement did not respond well to the treatment, and after a course of status epilepticus, the patient’s condition got worse, and finally, he passed away.

The HLH, as a challenging diagnosis, may have a wide diversity of clinical manifestations and laboratory findings. Sequencing the entire UNCI3D gene (coding and non-coding regions) is an applicable and valuable diagnostic procedure for detecting deep intronic splicing variants and large inversions in patients. Genetic assessment can significantly help in the event of HLH disease with atypical manifestation or situations when primary evaluations cannot detect etiology.

**Abbreviations**

HLH: Hemophagocytic lymphohistiocytosis; NK: Natural killer; FHL: Familial HLH; PRF1: Perforin 1; STX11: Syntaxin 11; UNCI3D: Unc-13 Homolog D; HPLH1: Hemophagocytic lymphohistiocytosis 1; STXBP2: syntaxin binding protein 2; EBV: Epstein-Barr virus; IVG: Intravenous immune globulin; PID: Primary immunodeficiency; WES: Whole exome sequencing; AST: Aspartate aminotransferase; ALT: Alanine Transaminase; CBC: Complete Blood Count; TG: Triglyceride; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; BMAs: Bone Marrow Aspiration; CMV: Cytomegalovirus; CT: Computed tomography; DNA: Deoxyribonucleic Acid; WBC: White Blood Cells; ANC: Absolute Neutrophil Count; BM: Bone Marrow Biopsy; PPD: Purified protein derivative; TORCH: Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes Simplex Virus; HSV: Herpes Simplex Virus; MS/MS: Tandem mass spectrometry; HPLC: High-performance liquid chromatography; FHL3: Familial HLH type 3; CTL: Cytotoxic T cell; CD 107: Cluster of differentiation, Cell markers in immunophenotyping.

**Acknowledgments**

We thank the parents for giving us their consent to report the cases.

**Authors’ contributions**

RM and PS admitted and monitored the patient in the first weeks. RM and PS followed the patients in follow-up. GG and RM drafted the manuscript. HR and MC analyzed WES data and wrote the parts of manuscript related to WES and prepared the sanger analysis and figure. All authors read and approved the final manuscript.

**Authors’ information**

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**Funding**

No person who participated in accomplishing the case report has been sponsored.

**Availability of data and materials**

Data of these two patients are available in the Children’s Medical Center hospital archive and can be public according to your request and The reported mutations in this study are submitted in ClinVar (Submission ID: SUB12176411).

**Declarations**

**Ethics approval and consent to participate**

An written informed consent was obtained from the individual parents whose identifying information is included in this paper. The whole research was done under the permission of the Ethics committee of Tehran University of Medical Sciences and also Genetic Testing for parents was done because of their desire to have next healthy child and it was done under the permission of Ethic committee of Tehran University of Medical Sciences.

**Consent for publication**

We obtained written informed consent from the parents of two cases for publication of their children’s personal or clinical details and images.

**Competing interests**

The authors declare that there is no competing interest.

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Received: 20 April 2022   Accepted: 10 November 2022

Published online: 19 November 2022

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