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Case Report
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Familial Hemophagocytic Lymphohistiocytosis Type-2 Prior to Onset of Childhood Acute Lymphoblastic Leukemia in a Chinese Child with a Novel Compound Heterozygous Mutation in PRF1

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Abstract

Mutations of the PRF1 gene have been identified in Familial Hemophagocytic Lymphohistiocytosis type-2 (FHL-2), and may play a role in susceptibility to Acute Lymphoblastic Leukemia (ALL). Here, we present the case of a 9-year-old Chinese female with FHL-2 who developed ALL. The patient was compound heterozygous in PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M). This mutation resulted in deletion of almost the entire C2 domain and carboxyl terminal of perforin, which seriously affected protein function. Our findings should raise awareness among physicians that patients with FHL who present with abnormalities in natural killer cell function may be predisposed to malignancies.

Keywords: Familial hemophagocytic lymphohistiocytosis type-2; Childhood acute lymphoblastic leukemia; PRF1

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but potentially life-threatening hyperinflammation syndrome caused by excessive immune activation. Primary HLH (Familial Hemophagocytic Lymphohistiocytosis [FHL]) refers to HLH caused by mutations in several genes, including perforin/PRF1, Munc 13-4/UNC13D, or Munc 18-2/STXBP2.

Perforin is a cytotoxic pore-forming protein stored in the lysosome-like secretory granules of Cytotoxic T Lymphocytes (CTLs) and Natural Killer Cells (NKCs) [1,2]. In combination with granzymes, perforin is crucial for killing transformed cells and pathogen-infected cells by inducing target-cell apoptosis [3,4]. The spectrum of pathologies associated with perforin deficiency indicates that perforin is essential for immune homeostasis and tumor immune surveillance [5]. In humans, mutations in the Perforin (PRF1) gene confer susceptibility to early-onset melanoma, a malignancy in which CD8+ T cells limit disease progression and metastasis [6], and mono- and biallelic PRF1 gene mutations occur in patients with Hodgkin and non-Hodgkin lymphomas [2,7,8].

Here, we present the case of a 9-year-old Chinese female with a diagnosis of FHL-2 who developed pre-B Acute Lymphoblastic Leukemia (ALL). The patient was compound heterozygous for two novel mutations in the PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M). The patient had markedly reduced NKC cytotoxic activity. Our findings add to the evidence base showing that patients with FHL who present with abnormalities in NKC function are susceptible to malignancies [9].

Case Presentation

A 9-year-old Chinese female with a diagnosis of FHL-2 presented to our institution with persistent high fever of unknown origin, pancytopenia, and coagulopathy. Physical examination revealed lethargy, pallor, cervical lymph node swelling, and hepatosplenomegaly. Laboratory evaluations showed: Hemoglobin, 7.3 g/dl; hematocrit, 19.7%; platelets, 59K/µl; white blood cells, 1.67 K/µl; ferritin, 6250 ng/ml; triglyceride, 414 mg/dl; alanine aminotransferase, 65 U/L; aspartate aminotransferase, 140 U/L; Lactate Dehydrogenase (LDH), 812 U/L; fibrinogen, 109 mg/dl; partial thromboplastin time/activated partial thromboplastin time, 19.5/67.4 sec; thrombin time 45.6 sec; D-dimers 1841 ng/L; albumin 40.4 g/L; and soluble CD25 25774.65 pg/ml. Flow cytometry

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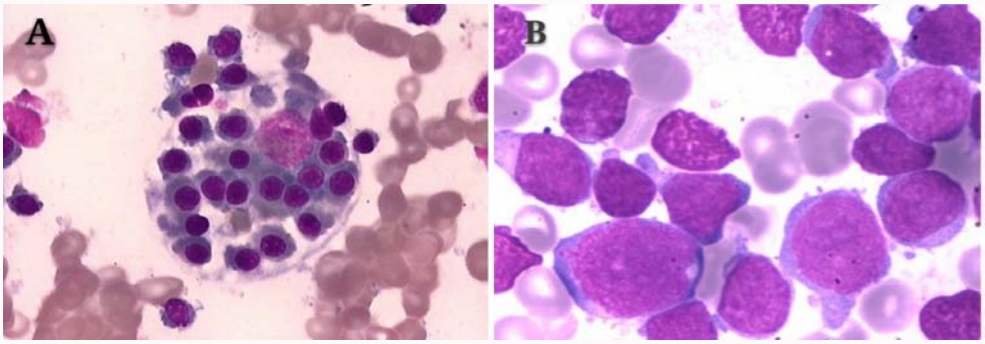

Figure 1: (A) Bone marrow biopsy specimen demonstrating hematophgocytosis as a diagnostic criterion for HLH; (B) Bone marrow biopsy specimen indicating ALL.

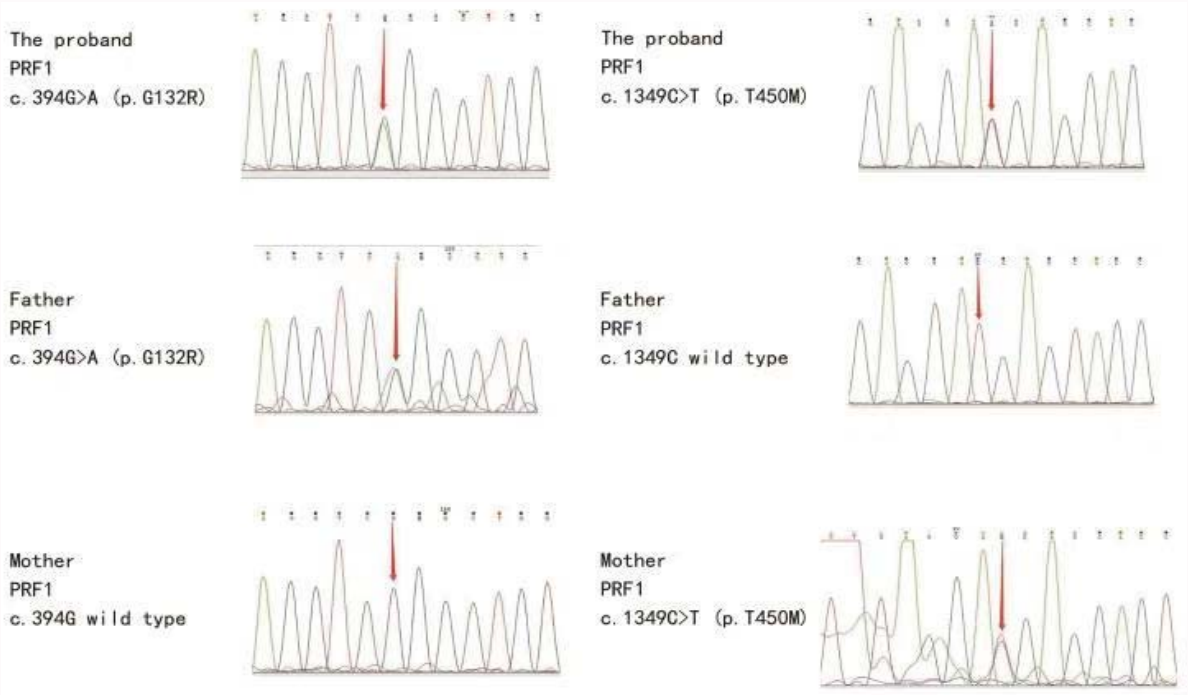

Figure 2: Sequence chromatograms showing the patient was compound heterozygous for two mutations in the PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M).

demonstrated decreased intracellular perforin expression on the patient's CTLs and NKCs , and markedly reduced NKC cytotoxic activity (2.7%) compared to levels observed in a healthy individual. The patient had defective degranulation on the CD107a assay. Viral markers of Epstein-Barr virus (EBV) were negative. Evaluation of bone marrow aspirates showed hemophagocytic Histiocytes (HS), consistent with hemophagocytic syndrome (Figure 1). Cytogenetic analysis demonstrated the patient was compound heterozygous for two mutations in the PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M); the patient's father was heterozygous for the c.394G>A (p.G132R) mutation and her mother was heterozygous for the c.1349C>T (p.T450M) mutation (Figure 2). The c.1349C>T (p.Thr450Met) mutation was inherited from her father and is known to be pathogenic. The c.394G>A (p.G132R) mutation was inherited from her mother and is previously unreported. The c.394G>A (p.G132R) mutation has a PolyPhen-2 predictive value of 0.926 (probably damaging).The c.1349C>T (p.Thr450Met) mutation has a Sorting Intolerant from Tolerant (SIFT) predictive value of -4.921 (deleterious variant) and a Polymorphism Phenotyping v2 (PolyPhen-2) predictive value of 1.000 (probably damaging).

The patient was diagnosed with hemophagocytic syndrome and treated with dexamethasone and etoposide. She achieved partial remission after 4 weeks of treatment. Hematopoietic cell transplantation was planned, but the patient experienced fever, seizure, leukocytosis, anemia, diffuse lymphadenopathy, and elevated LDH (1701 U/L) during the sixth week of treatment. Evaluation of bone marrow aspirates showed 26% lymphoblasts, no evidence of HS (Figure 1), and a 46.XY karyotype. Flow cytometry demonstrated that 72.4% of leukocytes were positive for CD19, CD10, CD22 and HLA-DR, indicating a pro-B cell phenotype. The patient was treated with a Berlin-Frankfurt-Muenster 95-protocol for standard risk pre-B ALL. She remained in clinical remission after induction therapy, but soon relapsed and died of multiple organ failure.

Discussion

In 1999, Stepp et al. [10] described PRF1 as the first gene for

FHL2. Since then, PRF1 mutations have been identified in 15% to 50% of patients with primary HLH [11]. Specifically, Wang et al. [12] identified mutations in 18/252 (7.1%) adolescent and adult patients with a clinical diagnosis of HLH, with PRF1 being the most common.

PRF1 is located at 10q21–22. It has 3 exons, and all coding sequences are in exons 2 and 3. Mutations in PRF1 lead to a deficiency in perforin protein, diminished lymphocyte cytotoxicity, uncontrolled immune activation, and extreme inflammation, which cause the onset of HLH symptoms [13]. Primary HLH has been associated with mutations in at least 9 genes. Among these, an estimated 70 mutations occur between exons 2 and 3 in PRF1.

p.W374X is the most common single PRF1 mutation in patients with primary HLH; however, PRF1 mutations may be distributed according to geographical region and ethnicity [5,14]. c.1090_1091delCT is the most prevalent PRF1 mutation in Korean and Japanese infants with typical HLH [15,16], p.S168N and p.T450M have been reported in adolescent and adult patients with a clinical diagnosis of HLH in China [12], and the compound heterozygous mutation c.65delC has been found in Asian infants with primary HLH [17,18]. Other PRL1 mutations such as c.949G>A, c.1228C>T, c.1349C>T, or p.A91V delay the age of onset or lead to mild symptoms, possibly because they occur in a functionally unimportant region of the protein [14].

The child in the present study had a diagnosis of FHL-2 and developed pre-B ALL. She was compound heterozygous for two mutations in the PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M). These variants have not been previously reported in individuals with primary HLH or as predisposing factors for ALL. Despite this, an increasing body of evidence in animal models and humans is linking mutations in PRL1 with increased susceptibility to hematologic malignancies, including leukemia and lymphoma [19]. In mice, perforin-deficiency substantially increased susceptibility to malignancy in distinct lymphoid cell lineages [20]. In patients with lymphoma, biallelic mutations of the perforin gene were associated with the development of Hodgkin or non-Hodgkin lymphoma; one patient with T-cell lymphoma had a sibling carrying the same mutations who developed HLH [21-23]. A small study linked the perforin polymorphism A91V to childhood ALL [24], but this finding was not confirmed in a larger cohort [25]. However, a subset of patients with ALL who also had a BCR-ABL translocation was more likely to carry A91V [26].

In conclusion, findings from the present study indicate that common genetic variants in the perforin locus may be associated with HLH and susceptibility to ALL. In this case, a 9-year-old Chinese female with a diagnosis of FHL-2 developed pre-B ALL. She was compound heterozygous for two mutations in the PRF1 gene: c.394G>A (p.G132R) and c.1349C>T (p.T450M). Physicians should be aware that patients with FHL who present with abnormalities in NKC function may be predisposed to malignancies.

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References

1. Podack ER, Young JD, Cohn ZA. Isolation and biochemical and functional characterization of perforin 1 from cytolytic T-cell granules. Proc Natl Acad Sci U S A. 1985;82(24):8629-33.
2. Clementi R, Locatelli F, Dupre L, Garaventa A, Emmi L, Bregni M, et al. A proportion of patients with lymphoma may harbor mutations of the perforin gene. Blood. 2005;105(11):4424-8.
3. Chinn IK, Eckstein OS, Peckham-Gregory EC, Goldberg BR, Forbes LR, Nicholas SK, et al. Genetic and mechanistic diversity inpediatric hemophagocytic Lymphohistiocytosis. Blood. 2018;132(1):89-100.
4. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. Annu Rev Pathol. 2018;13:27-49.
5. Terrell CE, Jordan MB. Perforin deficiency impairs a critical immunoregulatory loop involving murine CD8(+) T cells and dendritic cells. Blood. 2013;121(26):5184-91.
6. Trapani JA, Thia KY, Andrews M, Davis ID, Gedye C, Parente P, et al. Human perforin mutations and susceptibility to multiple primary cancers. Oncoimmunology. 2013;2(4):e24185.
7. Mhatre S, Madkaikar M, Desai M, Ghosh K. Spectrum of perforin gene mutations in Familial Hemophagocytic Lymphohistiocytosis (FHL). Blood Cells Mol Dis. 2015;54(3):250-7.
8. Ding Q, Yang LY. Perforin gene mutations in 77 Chinese patients with lymphomas. World J Emerg Med. 2013;4(2):128-32.
9. Chang TY, Jaffray J, Woda B, Newburger PE, Usmani GN. Hemophagocytic lymphohistiocytosis with MUNC13-4 gene mutation or reduced natural killer cell function prior to onset of childhood leukemia. Pediatr Blood Cancer. 2011;56(5):856-8.
10. Stepp SE, Dufourcq-Lagelouse R, Kumar V. Pillars article: Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999. 286: 1957-1959. J Immunol. 2015;194(11):5044-6.
11. Ishii E. Hemophagocytic lymphohistiocytosis in children: Pathogenesis and treatment. Front Pediatr. 2016;4:47.
12. Wang Y, Wang Z, Zhang J, Wei Q, Tang R, Qi J, et al. Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood. PLoS One. 2014;9(9):e107386.
13. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lympho-histiocytosis. Hematology Am Soc Hematol Educ Program. 2015;2015:177-82.
14. Mancebo E, Allende LM, Guzman M, Paz-Artal E, Gil J, Urrea-Moreno R, et al. Familial hemophagocytic lymphohistiocytosis in an adult patient homozygous for A91V in the perforin gene, with tuberculosis infection. Haematologica. 2006;91(9):1257-60.
15. Seo JY, Song JS, Lee KO, Won HH, Kim JW, Kim SH, et al. Founder effects in two predominant intronic mutations of UNC13D, c.118-308C>T and c.754-1G>C underlie the unusual predominance of type 3 Familial Hemophagocytic Lymphohistiocytosis (FHL3) in Korea. Ann Hematol. 2013;92(2):357-64.
16. Hori M, Yasumi T, Shimodera S, Shibata H, Hiejima E, Oda H, et al. A CD57+ CTL degranulation assay effectively identifies familial hemophagocytic lymphohistiocytosis type 3 patients. J Clim Immunol. 2017;37(1):92-9.
17. Kim JY, Shin JH, Sung SI, Kim JK, Jung JM, Ahn SY, et al. A novel PRF1 gene mutation in a fatal neonate case with type 2 familial hemophagocytic lymphohistiocytosis. Korean J Pediatr. 2014;57(1):50-3.
18. Chiang GP, Li CK, Lee V, Cheng FWT, Leung AWK, Imashuku S, et al. Perforin gene mutation in familial haemophagocytic lymphohistiocytosis: The first reported case from Hong Kong. Hong Kong Med J. 2014;20(4):339-42.
19. Chia J, Yeo KP, Whisstock JC, Dunstone MA, Trapani JA, Voskoboinik I. Temperature sensitivity of human perforin mutants unmasks subtotal loss of cytotoxicity, delayed FHL, and a predisposition to cancer. Proc Natl Acad Sci US A. 2009;106(24):9809-14.

20. Abdalgani M, Filipovich AH, Choo S, Zhang K, Gifford C, Villanueva J, et al. Accuracy of flow cytometric perforin screening for detecting patients with FHL due to PRF1 mutations. Blood. 2015;126(15):1858-60.

21. Clementi R, Emmi L, Maccario R, Liotta F, Moretta L, Danesino C, et al. Adult onset and atypical presentation of hemophagocytic lymphohistiocytosis in siblings carrying PRF1 mutations. Blood. 2002;100(6):2266-7.

22. Strenger V, Merth G, Lackner H, Aberle SW, Kessler HH, Seidel MG, et al. Malignancy and chemotherapyinduced haemophagocytic lymphohistiocytosis in children and adolescents-a single centre experience of 20 years. Ann Hematol. 2018;97(6):989-98.

23. Sepulveda FE, Garrigue A, Maschalidi S, Garfa-Traore M, Ménasché G, Fischer A, et al. Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice. Blood. 2016;127(17):2113-21.

24. Santoro A, Cannella S, Trizzino A, Nigro LL, Corsello G, Aricò M. A single amino acid change A91V in perforin: A novel, frequent predisposing factor to childhood acute lymphoblastic leukemia? Haematologica. 2005;90(5):697-8.

25. Mehta PA, Davies SM, Kumar A, Devidas M, Lee S, Zamzow T, et al. Perforin polymorphism A91V and susceptibility to B-precursor childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. Leukemia. 2006;20(9):1539-41.

26. Yang L, Liu H, Zhao J, Da W, Zheng J, Wang L, et al. Mutations of perforin gene in Chinese patients with acute lymphoblastic leukemia. Leuk Res. 2011;35(2):196-9.