Pediatric secondary Chronic myelogenous leukemia in a patient with Hemophagocytic lymphohistiocytosis carrying UNC13D , LYST and ITK variant

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Abbreviation	The full term
HLH	Hemophagocytic lymphohistiocytosis
CML	Chronic myelogenous leukemia
VP16	Etoposide
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
MDS	Myelodysplastic syndromes
PIOL	Primary intraocular lymphoma
Tr-CML	Treatment-related chronic myelogenous leukemia
DLBCL	Diffuse large B-cell lymphoma

Letter to the editor

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by acute onset, criti-

cal condition, and high mortality rate[1]. Since the adoption of the HLH protocol, mortality rates associated with HLH have markedly decreased[2]. As survival rates increase in HLH, some individuals who initially had HLH subsequently develop long-term secondary leukemia, such as secondary acute myeloid leukemia(AML), secondary acute lymphoblastic leukemia (ALL) and secondary myelodysplastic syndromes(MDS)[3-5]. However, Chronic Myelogenous Leukemia (CML) is not reported as a common secondary leukemia in HLH. CML accounts for 2% to 3% of leukemia cases in the pediatric and adolescent population[6, 7]. Secondary CML in children is rare and has been reported in a few cases, including pineal germinoma, langerhans'cell histiocytosis(LCH), diffuse large B-cell lymphoma(DLBCL), nasopharyngeal carcinoma(NPC), B-ALL and AML[8]. In this study, we present the case of a patient who developed CML approximately two years post-completion of HLH treatment.

A 6-year-old Chinese male with no significant family history, was admitted to the hematology department due to a high fever of unknown origin and an abnormal blood test. Initial laboratory tests, including de novo heterozygous UNC13D, LYST and ITK variants (the significance of the gene variants is uncertain; functional assays of the gene were not performed), yielded positive results (Table 1). Flow cytometry analysis of the bone marrow did not indicate the presence of neoplastic lesions. Consequently, he underwent treatment with vp16 (1380 mg/m^2), steroids and cyclosporine, achieved complete remission in eight weeks and completing chemotherapy in twelve weeks. At an intermittent follow-up one year post-discharge, his symptoms had disappeared. Due to economic factors, the child didn't undergo hematopoietic stem cell transplantation (HSCT).

Two years later, the patient was readmitted to the hospital due to persistent fever, anemia, and leukocytosis, with no recurrence of HLH. Laboratory tests revealed a hemoglobin level of 92 g/dL and a WBC count of 105.4×10^9/mL with a differential count indicating neutrophils (25%), lymphocytes (10%), metamyelocytes (6%), basophils (6%), myelocytes (20%), stab granulocytes (18%), and blasts (3%). Bone marrow smear revealed myeloid hyperplasia without evidence of hemophagocytosis. Flow cytometry indicated that 81.5 % of leukocytes were positive for CD10, CD11, CD13, CD15, CD16, CD33, CD58 and CD64. Karyotyping of the bone marrow was positive for 46, XY, t (9; 22)(q34;q11). Polymerase chain reaction (PCR) analysis confirmed the presence of BCR-ABL (P210) positivity, so the patient was diagnosed with chronic phase CML. In accordance with standard treatment protocols, the patient was started on daily administration of 400mg imatinib tablets. At the follow-up appointment one month after discharge, the blood test results showed a decrease WBC count to 9.02×10^9/L. Within three months, the patient achieved hematological, cytogenetic, and molecular remissions. The patient continues to take imatinib as part of his ongoing treatment plan.

Treatment-related CML (Tr-CML) is associated with the administration of chemotherapy, radiotherapy, and immunotherapy, accounting for approximately 3% of the total 452 CML cases reported[9]. Vp16 is a critical component of the HLH-2004 protocol, serving as a topoisomerase II inhibitor cleaving the DNA chain, inducing gene rearrangement and DNA damage, and ultimately leading to the development of leukemia[10]. The development of secondary leukemia associated with vp16 is influenced by various risk factors, including a cumulative dose exceeding 3000 mg/m^2, the frequency of administration (weekly or twice-weekly dosing), and the concomitant use of platinum agents[11]. In our case, the patient with HLH received weekly or twice-weekly vp16 treatment, accumulating a dose of 1380 mg/m^2. Although this cumulative dose is lower than the threshold of 3000 mg/m^2; the frequency of administration and the specific treatment protocol used may have contributed to the development of secondary CML in this case.

Cytotoxic T lymphocytes and natural killer cells play a crucial role in eliminating malignant cells[12]. Genetic deficiencies in HLH can mediate cellular cytotoxicity pathways, affecting lymphocyte granule secretion and T cell cytolytic capacity[13]. Without the use of known leukemogenic agents, one patient carrying a heterozygous UNC13D variant developed AML[14]. One patient harboring a heterozygous PRF1 variant progressed to primary aggressive DLBL[15]. Additionally, mutations in the STX11 gene may be associated with secondary malignancies (MDS/AML)[16]. The patient with HLH had heterozygous variants in UNC13D, LYST, and ITK, which may weaken immune surveillance against malignant cells, contributing to CML development. Genetic studies primarily serve to assess the risk of HLH recurrence[2]. HSCT is performed to prevent potentially

fatal recurrences of HLH; HLA typing and preliminary donor searches be conducted early after diagnosis to HSCT if necessary[17]. Genetic risks are often unknown during the initial presentation of a patient with HLH. Unfortunately, the patient with HLH was unable to undergo HSCT treatment in the early stages.

In conclusion, the risk of secondary leukemia in patients with HLH is low but still exists. Genetic screening should be intensified, if possible, during the initial stages of HLH diagnosis. Additionally, it is essential to regulate the dose and frequency of essential drugs like vp16. The prompt administration of HSCT is essential for the treatment of primary HLH, while secondary CML requires meticulous identification and management during the follow-up period.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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TABLE1 Laboratory results from the hematology department

Parameters	Results	Reference
Blood examination		-
WBC(10^9/L)	1.45	4-10
ANC (10^9/L)	0.07	2.3-7.7
HB(g/L)	111	110-150
PLT(10^9/L)	72	100-450
SF(ug/L)	871.5	>500
TG(mmol/L)	3.66	<1.7
LDH(U/L)	12000	120-246
Fibrinogen(g/d)	1.2	2-4
Hemophagocytosis of bone marrow	Positive.	-
Mutational analyses		
UNC13D	C.321+19C>G in exon4	-
LYST	C.8368A>C in exon32	-
ITK	C.496-56G>A in exon6	-

Abbreviations: WBC, white blood cell; ANC, absolute neutrophil count; HB, hemoglobin; PLT, platelet; SF, serum ferritin; TG, triglyceride;LDH, lactate dehydrogenase.