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A novel mutation of *LYST* and haemophagocytic lymphohistiocytosis as the first symptom in children with ph+ALL: A case report and literature review

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder. This study sheds light on a rare and intriguing case of HLH as the initial symptom in a child with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ph+ALL). This case report, accompanied by a comprehensive literature review, highlights the diagnostic challenges and treatment complexities encountered in the management of such rare manifestations. Moreover, the identification of a novel mutation in the *LYST* gene adds a unique genetic perspective to the understanding of HLH pathogenesis, potentially opening avenues for further research in this area.

1. Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterised by fever, hepatosplenomegaly, pancytopenia, and the presence of haemophagocytosis in the bone marrow and reticuloendothelial organs. HLH can be classified as primary and secondary; primary HLH occurs in patients with genetic abnormalities related to the killing function of natural killer (NK) and T cells, such as perforin1 (*PRF1*), syntaxin binding protein 2 (*STXBP2*), lysosomal trafficking regulator (*LYST*), *AP3B1*, and X-linked inhibitor of apoptosis (*XIAP*). Secondary HLH is an acquired disease associated with infections, malignancies, or autoimmune disorders, and has no obvious genetic characteristics [1–3]. However, patients with ph+ALL with HLH as the initial symptom are extremely rare.

Here, we report a child diagnosed with ph+ALL in April 2022, who presented of onset HLH. Exome sequencing results suggested digenic heterozygous *LYST* (NM_000081.4) c.2647C>G(p.Pro883Ala) mutations. Our literature and database searches yielded no reports related to HLH associated with these mutations.

2. Case

An 11-year-old female was admitted to the Affiliated People's Hospital of Ningbo University in April 2022, due to dizziness and recurrent high fever (> 39 °C) for 3 days. Clinical examination on admission revealed pallor, petechial spots on the trunk and limbs, hepatomegaly (3 cm below the costal margin), and splenomegaly (4 cm below the costal margin). Laboratory tests revealed the following: leukocytosis 35.59 × 10^9/L, with lymphocytes comprising 91.2 % of white cells. The red blood cell count was 2.14 × 10^12/L, haemoglobin was low at 59 g/L, platelet count was reduced at 31 × 10^9/L, and 15 % of cells were immature. Elevated levels of serum ferritin (9878 μg/L; normal range, 23.9–336.2 μg/L) were detected. A reduced level of fibrinogen (Fg 1.4 g/L; normal range, 2-4.0 g/L) and increased levels of lactate dehydrogenase (LDH 1500 U/L; normal range, 120–246 U/L), triglycerides (3.33 mmol/L; normal range, 0–1.7 mmol/L) and D-Dimer (16,163 ng/ml; normal range, 0-256 ng/mL) were detected. Serum antibodies to Epstein-Barr virus were negative, and other aetiological tests were also negative, including HIV, HAV, HBV, HCV, tubercle bacillus, and haemococcidium. The repeated blood culture results were negative. Bone marrow (BM) aspirates showed abnormal proliferation of primitive, immature lymphocytes (approximately 76 %). Flow cytometric immunophenotypic analysis showed that the abnormal B primitive lymphocyte population accounted for 91.9 % of the nuclear cells expressing CD34, HLA – DR, CD19, CD38, CD10str, cCD79a, partly expressing CD20, not expressing cCD3, CD7, CD117, MPO, CD13, and CD33, in accordance with B-cell ALL (B-ALL). The copy number of the BCR-ABL fusion gene was 81.415 % with negative gene mutations and IKZF1. Karyotype analysis revealed 48,XX,+8, ider (9)(q10)t(9;22)(q34;q11.2)+der (22)t(9;22)(g34;q11.2)[18]/46,XX[2] (Fig. 1A) , CT scan examination revealed splenomegaly. The levels of serum soluble interleukin 2 (IL-2) receptor (sCD25) in the plasma of PB were 11,150 μ/mL (normal levels, 223–710 μ/mL), while NK cell activity was 2.7 % (normal range, 31.54–41.58 %). Exome sequencing suggested a novel mutation, *LYST* c2647C.G(p.Pro883Ala) (Fig. 1B).

Based on both clinical and laboratory findings (fever, splenomegaly, cytopenia, hyperferritinaemia, elevated serum sCD25 levels, decreased NK-cell activity, and elevated levels of serum ferritin), the patient was diagnosed with ph+All complicated by haemophagocytic syndrome.

3. Treatment

The patient received chemotherapy for ALL(ZJCH-ALL-2019):DXM (6 mg/m^2 i.v., four times a day for 28 days), CTX (400 mg/m^2, days 1-3), VDS (3 mg/m^2, qw), VP16 (100 mg/m^2, days 1-3) and dasatinib (80 mg/m^2/d) orally,four times a day. On the 8th day of treatment, the white blood cell differential count showed 32 % lymphocytes, and immature lymphocytes were 3 % in BM aspirates. On day 14, minimal residual disease (MRD) was assessed at 9.48 %, and bone marrow examination showed hyperplasia with 2 % immature lymphocytes. Subsequent tests showed MRD reduced to 0.141 %. One month later, the patient achieved bone marrow remission, and MRD turned negative, and

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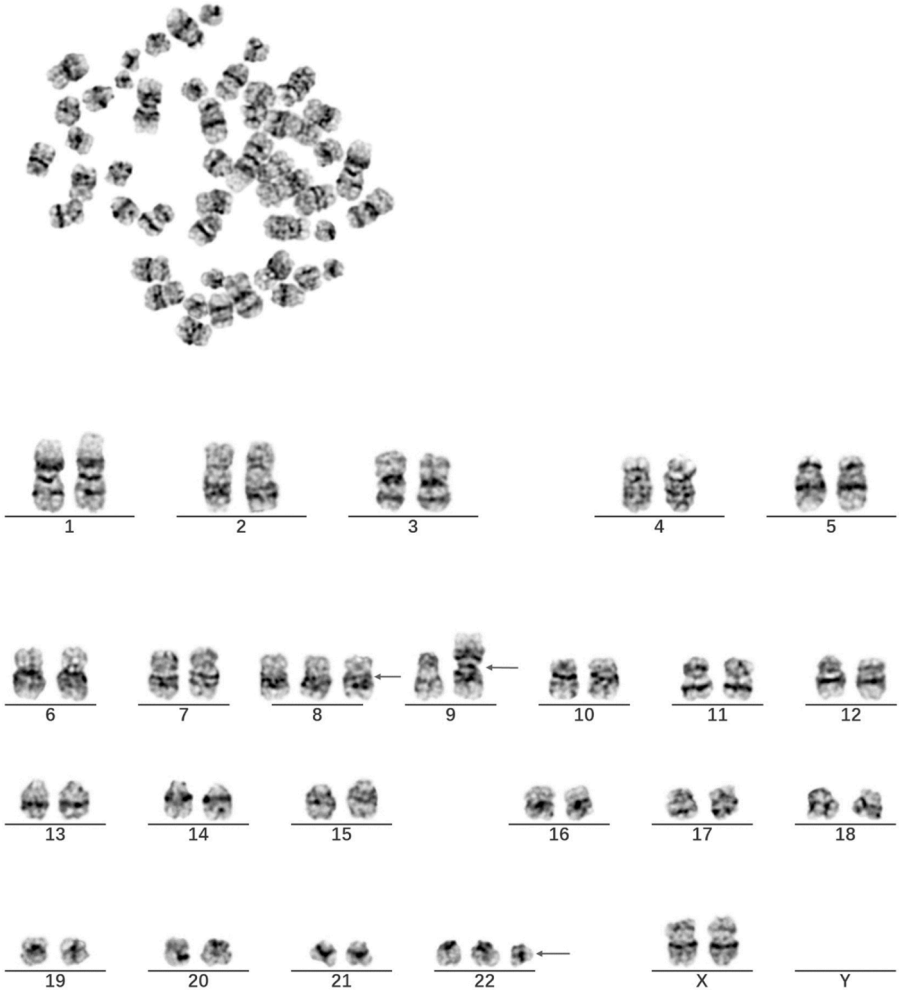

Fig. 1A. Karyotype analysis revealed:48,XX,+8,ider(9)(q10)t(9;22)(q34;q11.2),+der(22)t(9;22)(q34;q11.2)[18]/46,XX[2].

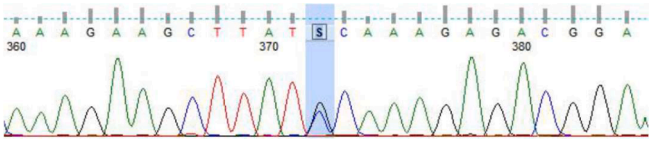

Fig. 1B. LYST(NM_000081.4) c.2647C>G(p.Pro883Ala)(heterozygous mutation).

BCR/ABL1 was negative (Fig. 1C). Haemophagocytic syndrome was ameliorated after the first cycle of chemotherapy. The patient achieved BM remission without haemophagocytosis. After the second cycle, the patient received chemotherapy, according to ZJCH-ALL-2019. Unfortunately, the patient died of septic shock after the last chemotherapy session.

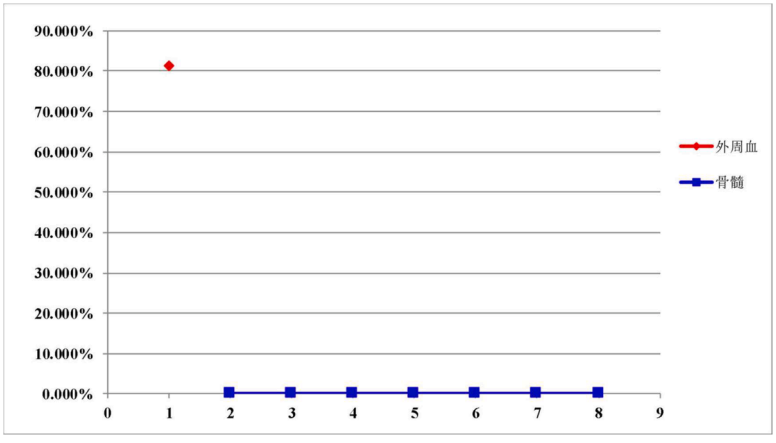

Fig. 1C. BCR-ABL1 dynamic curve of fusion gene quantification.

4. Discussion

The leading cause of malignant tumour-associated HLH in children is B cell and T cell lymphoma/leukaemia, which may be related to the imbalance of cytokines, such as IL-6 and TNF-α, and abnormal haematopoietic clone immune disorders [4,5]. Gadoury-Levesque et al. analysed the frequency of gene mutations in 1892 patients with suspected inherited HLH disorders, and a potentially causal genetic finding was observed in 12.0 % of samples. In total, 10.4 % of patients had a definite genetic diagnosis. Pathogenic or likely pathogenic variants of *PRF1* were the most frequent. Mutations in genes associated with degranulation defects (*STXBP2, UNC13D, RAB27A, LYST, and STX11*) are more common and collectively represent >50 % of all cases [3]. Zhang et al. found that in 128 (128/311) patients who were positive in genetic screening, the most frequently detected mutant gene was *UNC13D* (29 %), followed by *LYST* (21 %), *PRF1* (17 %), and *STXBP2* (10 %) [6]. *LYST*, a member of the *BEACH* family of proteins, is present in all eukaryotes. It is a molecule that regulates the fusion of intracellular vesicles, such as lysosomes, causing Chediak-Higashi Syndrome [7]. In particular, the *LYST* c2647C>.G(p.Pro883Ala) variant was found in this patient. Because the patient's parents refused further examination, it was not determined whether it was related to genetics. It was indicated that the patient developed HLH due to mutations in defective genes, with ph+gene as the trigger. Currently, the mutated gene has not been identified in the literature, and whether it will lead to hemophagocytic syndrome is unknown.

According to the current literature, hemophagocytic syndrome is mainly secondary to malignant tumours during treatment. Lehmberg and Pan et al. reported a case of tumour-associated HLH treated with the HLH-2004 protocol with slightly different outcomes, in which the ORR was 68.2 % [8,9], and Gopinathan et al. reported a case of ALL with HLH. According to the HLH protocol, the treatment effect is poor. During treatment, the patient was diagnosed with B-cell ALL by bone marrow examination, and then he was treated with chemotherapy, finally he has achieved complete remission [10]. Compared with other published cases, our case was novel in that it was characterised by haemophagocytosis. We did not treat this patient solely for HLH, but for a combination of leukaemia and HLH, so that the patient could achieve faster clinical symptom remission and haematological remission. Therefore, in this patient, leukaemia therapy was predominant, which in turn led to the resolution of haemophagocytosis. Moreover, haemophagocytosis did not occur during consolidation chemotherapy.

5. Conclusion

The possibility of primary malignancy as a trigger should always be considered when managing HLH in children, owing to an overlap in the clinical features of acute leukaemia and HLH. HLH treatment alone cannot solve this fundamental problem. Therefore, in clinical practice, establishing the correct diagnosis is the most effective treatment in such patients.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the ethics committee of the institution. Informed consent was obtained from this patient.

Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analysed.

CRediT authorship contribution statement

Tiantian Wang: Writing – original draft. **Xuhui liu:** Writing – review & editing. **Li Lin:** Software. **Renzhi Pei:** Writing – review & editing. **Ying Lu:** Methodology.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2024.100481.

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