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Genetic analysis of a female patient with X-linked lymphoproliferative disease type 2: a case report

Yalin Sun[1], Shu Teng[1], Wen Li[1], Huaping Wang[1] and Zhenghong Qi[1*]

Abstract

Background X-linked lymphoproliferative syndrome type 2 is a relatively rare primary immunodeficiency disease caused by mutations in *XIAP*. X-linked lymphoproliferative syndrome type 2 typically occurs in male individuals, while female individuals are carriers of the pathogenic gene mutations. Furthermore, X-linked lymphoproliferative syndrome type 2 has a complex clinical phenotype. We aimed to explore the pathogenesis of X-linked lymphoproliferative syndrome type 2 through genetic testing of a family to provide a basis for clinical diagnosis.

Case presentation The clinical data of a female patient with X-linked lymphoproliferative syndrome type 2 and her family were collected and analyzed. The patient was 2 years 1 months old and of Han Chinese descent. Methylation-sensitive restriction enzyme amplification and capillary electrophoresis were used to detect X chromosome inactivation in the family. A novel mutation, c.910G > T (guanine to thymine), was identified in *XIAP* in the patient and her brother, but was not detected in the patient's parents. The proportion of chromosomal inactivation in the female children was 86%, which indicates a moderate inactivation shift and paternal inactivation shift.

Conclusion Close attention should be paid to shifts in X-chromosome inactivation in female children. When a pathogenic gene variant is not detected in a mother with a normal phenotype, gonadal mosaicism cannot be ruled out, and prenatal genetic diagnosis should be performed in the next pregnancy.

Keywords *XIAP*, Gonad mosaicism, X-chromosome inactivation offset

Background

X-Linked lymphoproliferative syndrome (XLP) is a relatively rare primary immunodeficiency disease that can be of the following two types: XLP-1, caused by mutations in *SH2D1A*, and XLP-2, caused by mutations in *XIAP*. Children with XLP are highly susceptible to Epstein–Barr virus (EBV) infection and lack the ability to mount an effective immune response following infection, which often leads to hemophagocytic lymphohistiocytosis (HLH). XLP-2 accounts for 20–40% of all XLP cases. XLP-2 typically occurs in male individuals, while female individuals are carriers of the pathogenic gene mutations.

XLP-2 has a complex clinical phenotype. EBV-associated HLH is the most common phenotype of XLP-2, which also includes splenomegaly, inflammatory bowel disease, and abnormal gammaglobulinemia, among others [1]. Most patients with XLP-2 die during childhood. Even with timely chemotherapy, the survival rate remains low. Currently, bone marrow hematopoietic stem cell transplantation is the key treatment to promote the long-term survival of patients [1, 2].

The aim of this study was to analyze the genetic characteristics of a female patient with XLP-2 and her family and provide a reference for the diagnosis of inherited

*Correspondence:
Zhenghong Qi
Huoyanyan333@163.com
[1] Department of Pediatric Infectious Diseases, Hangzhou Children's Hospital, Hangzhou, China

diseases and the prevention and control of birth defects in similar families.

Case presentation

We retrospectively analyzed the clinical characteristics of a female patient with XLP-2 who was admitted to our institution and presented with HLH as the first manifestation.

A girl, aged 2 years 1 month, of Han Chinese descent, was admitted to our department in October 2021 with a fever persisting for 14 days and edema in both eyelids lasting up to 4 days. A physical examination on admission showed a body temperature of 39 °C, respiration rate of 20 breaths/min, and a heart rate of 132 beats/min.

Furthermore, her blood pressure was 103/68 mmHg, and blood oxygen saturation was 97%. Both eyelids were swollen, and the bilateral cervical lymph nodes were enlarged. The liver was 4 cm below the subcostal margin and soft; the spleen was 3 cm below the subcostal margin. The heart, lung, and nervous system were normal.

Blood test results were as follows: white blood cell count, 24.72×10^9/L (reference value: 4–12×10^9/L); lymphocyte proportion, 74% (reference value: 20%–40%); hemoglobin level, 108 (reference value: 110–155) g/L; platelet count, 141×10^9/L (reference value: 100–400×10^9/L); and abnormal lymphocyte proportion, 6% (reference value: 0). Biochemical tests revealed the following: alanine aminotransferase level, 146 (reference value: < 50) U/L; aspartate aminotransferase level, 248 (reference value: 15–60) U/L; and triglyceride level, 2.55 (reference value: < 1.7) mmol/L. Serum EBV DNA level was 1.19×10^4 (reference value: < 400) copies/mL, and EBVCA-IgM level was > 160 (reference value: < 40 U/mL). Furthermore, the EBV-NK DNA level was 1.27×10^3 (reference value: $<4\times10^2$) copies/mL, EBV-B DNA level was 1.67×10^3 (reference value: $<4\times10^2$) copies/mL, EBV-T DNA level was 4.47×10^2 (reference value: $<4\times10^2$) copies/mL, EBV DNA level was 6.46×10^2 (reference value: $<4\times10^2$) copies/mL, and ferritin level was > 1500 (reference value: 11–306) μg/L. Blood coagulation function was normal, with D-dimer level of 8.76 (reference value: < 0.55) mg/L, and normal prothrombin level, activated partial thromboplastin clotting time, and fibrinogen level. The soluble CD25 level was 8796.4 (reference value: < 6400) pg/mL. Bone marrow cytology revealed hemophagocytic syndrome. Regarding an immunological diagnosis of leukemia, no obvious clones were found in the blood. Indeed, children with XLP2/XIAP deficiency do not develop lymphoma as a result of their condition. Abdominal ultrasonography showed hepatosplenomegaly. Ultrasonography of cervical lymph node B revealed bilateral cervical lymph node enlargement. Chest computed tomography (CT) showed bilateral pneumonia; abdominal CT showed hepatosplenomegaly, hydrops in the Greenson's sheath of the liver, and hydrops in the gallbladder fossa. Echocardiography revealed mild tricuspid regurgitation.

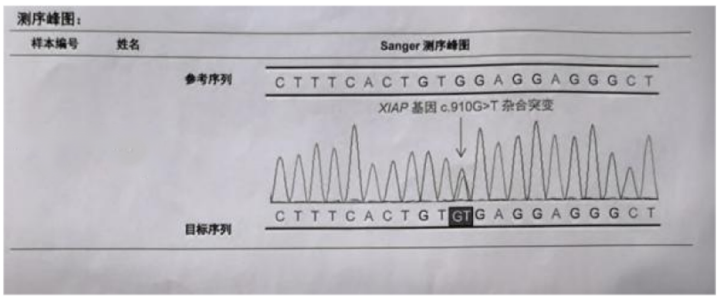
The child was diagnosed with HLH, EBV infection, and liver dysfunction. The patient was treated with ganciclovir antiviral therapy, high-dose dexamethasone pulse therapy, gamma-globulin support, albumin supplementation, and liver protection. On day 13 of admission, her body temperature returned to normal. On day 26 of admission, routine blood test results, liver function test results, ferritin level, and coagulation function test results were normal.

Genetic testing revealed a hemizygous mutation in *XIAP* (c.910G > T chrX: 123022501 p.G304X) in the patient's elder brother, who died of HLH in 2016, but not in their parents. A prenatal diagnosis of mutant *XIAP* was performed following amniotic fluid extraction during the next pregnancy, and the results showed that the fetus harbored an XIAPc.910G > T heterozygous mutation. The disease was considered to show X-linked recessive inheritance, and the sex of the fetus was female; therefore, the fetus was considered a carrier. Combined with the medical history, genetic testing of the patient and her family showed that the patient and her brother had the same gene mutation, c.910G > T in *XIAP*, which was not detected in their parents (Figs. 1 and 2). Female individuals are generally carriers; however, because of their clinical phenotype, a chromosome inactivation test was performed. The proportion of chromosome inactivation was 86%, indicating a moderate inactivation shift with paternal inactivation predominance (Fig. 3).

Discussion

XIAP is located on q25 of the X chromosome [3] and is the pathogenic gene implicated in XLP-2 [4]. XIAP can directly inhibit activated caspases-3, -7, and -9, and inhibit the apoptosis of effector T cells [5]. It also participates in innate immune functions through the pattern recognition receptors nucleotide-binding and oligomerization domain 1/2 (NOD1/2) and dectin-1 [6]. Additionally, XIAP is involved in the inhibition of inflammasome signaling pathways. Therefore, if there is a gene mutation, XIAP will fail to inhibit the apoptosis of activated T cells, while NOD2 signaling impairment leads to the release of large amounts of pro-inflammatory factors, causing diseases such as HLH and colitis.

In this study, neither of the parents carried the *XIAP* mutation, and the mother was a non-mutant carrier; however, she gave birth to two consecutive children with the same mutation. One reason for this may be that the same de novo mutation occurred twice on the same maternal X chromosome during meiosis, which is



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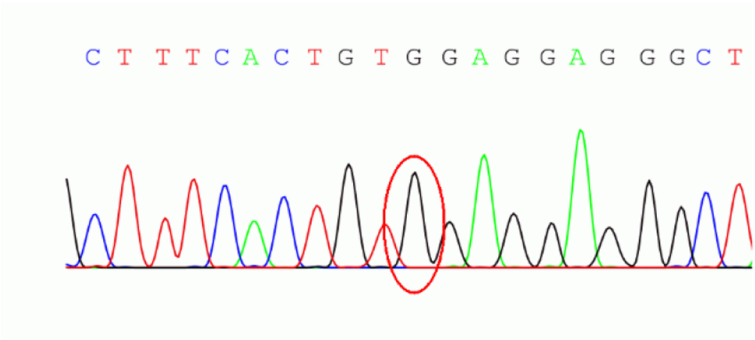

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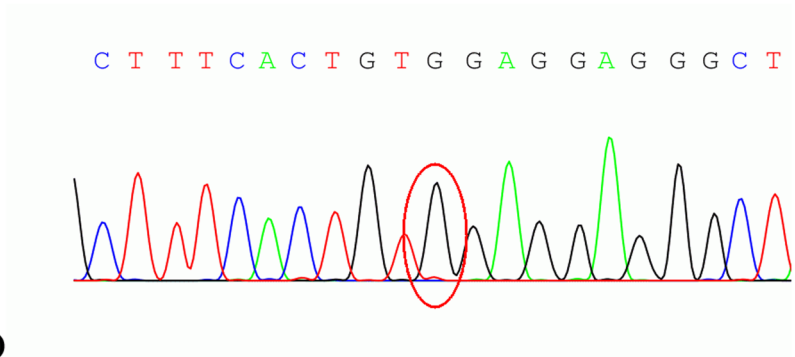

D

Fig. 1 Sanger sequencing results of the XLP-2 female child, her parents, and brother. **A** A heterozygous mutation c.910G > T was found in the *XIAP* gene of the female child. **B** The elder brother of the patient had a hemizygous mutation c.910G > T in *XIAP* gene. **C** The mutation was not detected in the patient's father. **D** The mutation was not detected in the mother

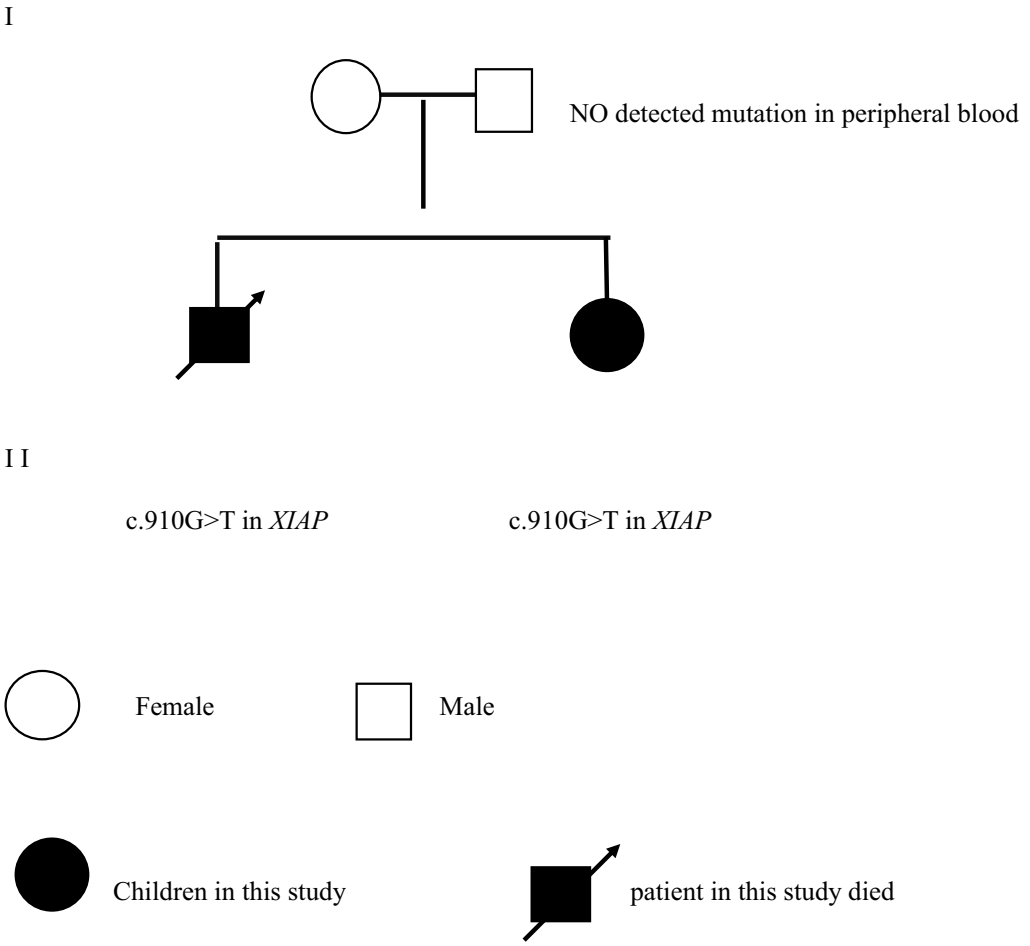

Fig. 2 Pedigree of the patient's family

extremely rare. Another reason may be that the mother of the child had a gonadal chimera with a gene mutation.

Genetic mutations can occur at different stages of embryonic development. If a gene mutation occurs during the initial stages of embryonic development, the individual has two or more cell lines, termed mosaicism. The occurrence of this kind of mosaicism in the gonads is called gonadal mosaicism [7]. A common cause of gonadal mosaicism is heterologous mosaicism, in addition to de novo mutations (Fig. 4). Therefore, gonad mosaicism has a certain effect on offspring; however, it is difficult to predict the risk of recurrence in the offspring because the probability of recurrence is related to the proportion of mutant cells, and the proportion of mutant cells in germ cells is closely related to the time of mutation occurrence. Studies worldwide have identified many cases of paternal or maternal gonad mosaicism leading to disease in the offspring [8–10]. In the case of our patient, the parents of the child were normal and noncarriers, but they had two consecutive children with the same gene mutation in *XIAP*; therefore, the mother of the child was highly likely to have gonadal mosaicism.

XLP-2 is an X-linked recessive genetic disease that usually occurs in male individuals, while female individuals

(See figure on next page.)

Fig. 3 X-chromosome inactivation test in the female patient. **A** Before X chromosome restriction in the female patient. **B** In female children, after X chromosome restriction. **C** Before enzyme digestion of the X chromosome of the father of the female child. **D** After enzyme digestion of the X chromosome of the father of the female child. **E** Mothers of female children before X chromosome restriction. **F** Mothers of female children after X chromosome restriction. The arrow indicates the amplification product of the reference gene, which was absent after complete digestion. Numbers in the figure indicate fragment length and peak area

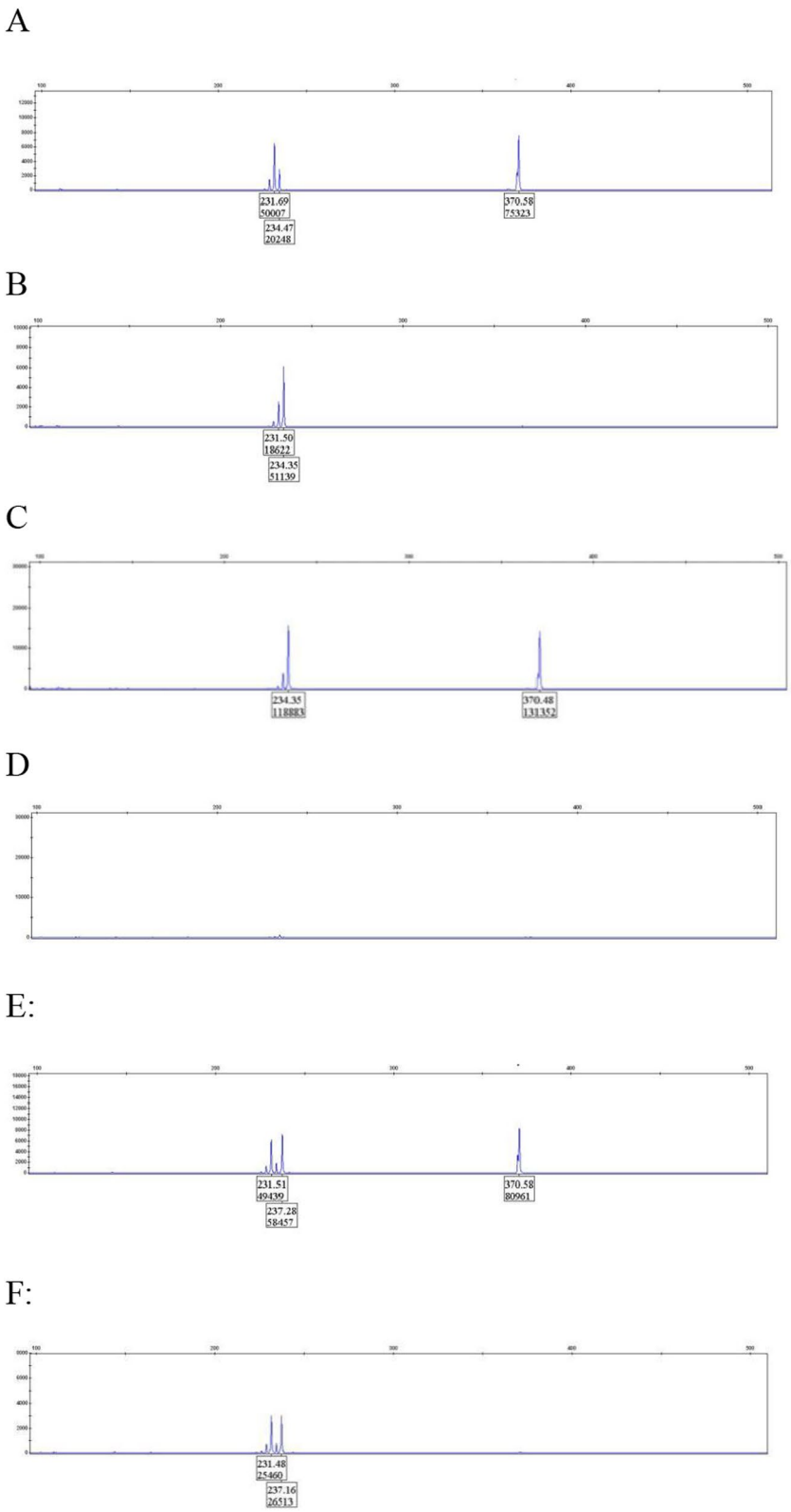

Fig. 3 (See legend on previous page.)

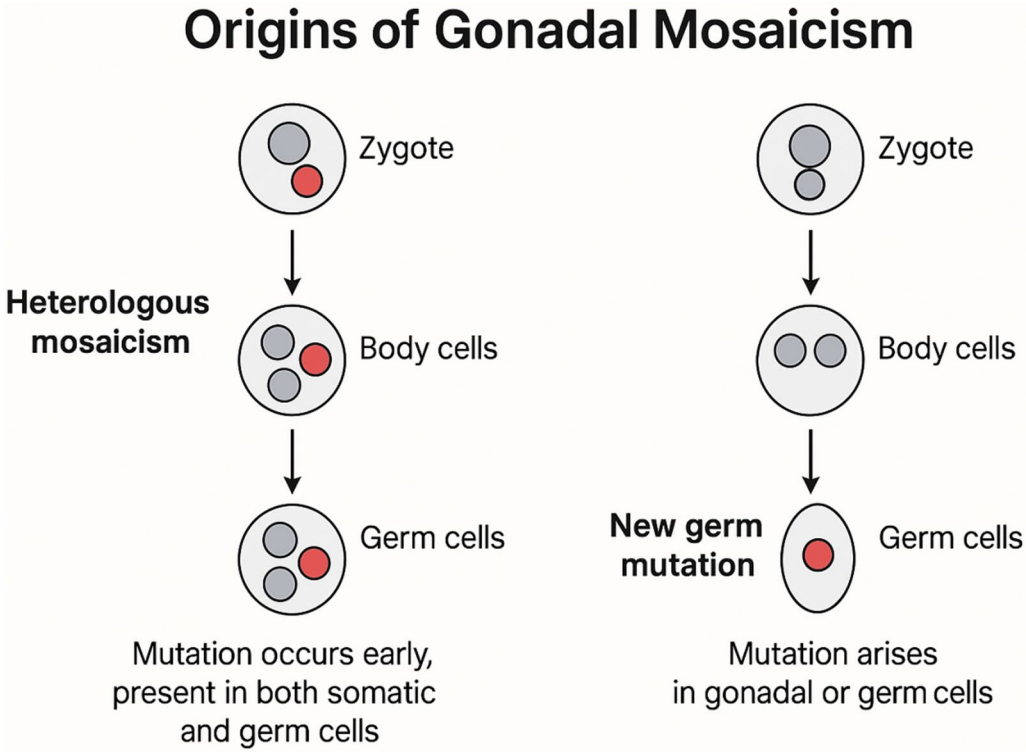

Fig. 4 Origins of gonadal mosaicism

are carriers of the gene mutations. Most female carriers do not show clinical manifestations, and the disease is primarily caused by excessive paternal inactivation of the X chromosome. In female individuals, one of the two X chromosomes is randomly inactivated in each cell early in development to compensate for the dosage difference between male (XY) and female individuals (XX). This inactivation is usually random, but in some cases, it can be skewed, that is, one X chromosome is preferentially inactivated or activated. Skewed X inactivation can have clinical implications, especially in female individuals who carry a disease-causing mutation on one of their X chromosomes. In a previous study, a small number of female individuals were found to have an X-chromosome inactivation shift [11]. Ishizaki *et al.* found that 51 out of 93 female patients with Duchenne muscular dystrophy (DMD) had an X-chromosome inactivation shift, which confirmed that female carriers with early-onset or severe disease mostly had a pathogenic X-chromosome inactivation shift [12]. In 2015, Yang *et al.* reported a Japanese family with a heterozygous mutation in the mother, among whom two boys and one girl presented with XLP-2; a chromosome inactivation study of the girl showed a highly skewed pattern [13]. Similarly, Dziadzio *et al.* found that, in a large Caucasian family, the clinical symptoms of XLP-2 presentation were not limited to male patients; they also manifested in several female carriers, with the most severely affected carriers showing random X-chromosome inactivation [14]. However, in 2008, Woon *et al.*, through genetic studies of a high-incidence lymphoma family, found that female individuals with *SH2D1A* mutations exhibited significant clinical manifestations related to X chromosome inactivation [15]. Chinese researchers also discovered that female patients with heterozygous missense mutations in *WAS* showed symptoms such as thrombocytopenia and bleeding. Upon examination, this was considered to be associated with complete paternal X chromosome inactivation [16]. It can be concluded that overexpression of the X chromosome carrying the mutant gene is the main genetic mechanism for female carriers of pathogenic gene mutations of X-linked recessive genetic diseases, such as DMD and XLP-2. Similarly, our study found that paternal X-chromosome inactivation was present in 86% of the female children. Therefore, this disease is considered to be related to paternal X-chromosome inactivation.

This study had some limitations and lacked direct evidence for the diagnosis of mosaicism. If *XIAP* detection is performed on multiple oocytes from the mother of a child before pregnancy, it could be used as a direct basis for the diagnosis of gonadal mosaicism. However, the procedure to obtain a sufficient gonad tissue sample by

ovarian puncture is traumatic for women; therefore, it is extremely difficult to perform genetic testing.

Conclusion

For timely diagnosis of XLP-2 patients, X-chromosome inactivation analysis should be routinely performed in female patients. Germ cell mosaicism should be considered in mothers with two children harboring the same gene mutation. As it is difficult to obtain germ cell tissue samples, it is difficult to confirm germ cell mosaicism. Digital polymerase chain reaction can be used to detect a very low proportion of germ cell mosaicism in easily obtained blood samples, and this helps identify the source of genetic variation and, thus, assists in genetic counseling. In women with children with XLP-2, even if peripheral blood genetic testing does not suggest that they are carriers of pathogenic gene mutations, prenatal genetic screening is still necessary in the next pregnancy to reduce the risk of disease recurrence.

Abbreviations

CT	Computed tomography
DMD	Duchenne muscular dystrophy
EBV	Epstein–Barr virus
HLH	Hemophagocytic lymphohistiocytosis
NOD1/2	Nucleotide-binding and oligomerization domain 1/2
XLP	X-linked lymphoproliferative syndrome
XLP-2	X-linked lymphoproliferative syndrome type 2

Supplementary Information

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Additional file 1.

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Author contributions

All authors have read and approved the final version of the manuscript. Yalin Sun: data case collection and manuscript writing. Shu Teng and Wen Li: literature search. Huaping Wang: created the charts. Zhenghong Qi: revised the manuscript.

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Availability of data and materials

All data and materials are accurate.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of our hospital (approval no. 2021-ER-CT-55), with consent to participate.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

All authors have no competing interests.

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