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LETTER TO THE EDITOR

A new SH2D1A mutation in a female adult XLP disease with hemophagocytic lymphohistiocytosis and NK-cell leukemia

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Dear Editor,

X-linked lymphoproliferative disease (XLP) is a rare primary immune deficiency characterized by Epstein–Barr virus (EBV) infection [1]. There are two subtypes of XLP [2]: (1) XLP1 caused by mutations in *SH2D1A* [3]; and (2) XLP2 caused by mutations or deletions in *BIRC/XIAP* [4]. XLP most commonly presents in childhood or early adolescence [5]. The most common presenting feature is hemophagocytic lymphohistiocytosis (HLH) mostly triggered by EBV-infection and which sometimes progresses to a lymphoproliferative neoplasm, usually a B-cell non-Hodgkin lymphoma [5, 6]. Progression to aggressive NK-cell lymphoma/leukemia is not reported.

Female carriers of XLP1 are usually asymptomatic. In contrast, female carriers of XLP2 are reported to have HLH, erythema nodosum (EN) and mild inflammatory bowel disease (IBD) [7–9]. We describe a female adult carrier with XLP1 developing an aggressive NK-cell leukemia and HLH after a EBV infection.

A 44-year-old woman presented with abdominal pain and a history of chronic diarrhea in 10 March 2018. A colon biopsy showed acute and chronic mucosal inflammation. In 20 March 2018, she began to have fevers, night sweats, weight loss, splenomegaly, and bilateral leg edema. The hemoglobin concentration was 89 g/L, WBC, 4.1 × 10E+9/L with 19% NK-cells quantified by flow cytometry (FCM), platelet 91 × 10E+9/L, EBV-DNA 4.25 × 10E+5 copies/mL, triglycerides, 2.03 mmol/L, fibrinogen, 1.21 g/L, ferritin, 565.5 ng/mL, and soluble CD25, 5160 pg/mL. NK cell activity analysis at the pretreatment showed that the activity of NK cell 19.04%, which was lower than normal control. The bone marrow showed diffuse infiltration by intermediate-size cytologically atypical cells with abundant histiocytes/macrophages (Fig. 1a–d). Immune histochemistry showed abnormal cells which were diffusely and strongly positive for CD56, TIA1, and granzyme B (Fig. 1e–i).

A bone marrow aspirate showed abnormal NK cell expressing CD56. CD8, CD2, CD7, CD94, CD161, and HLA-DR staining were moderate. Killer cell immunoglobulin-like receptor (KIR) analyses showed no expression of CD158a, CD158b, CD158e, or CD158i (Supplemental Fig. 1). Cytogenetic analyses showed 45,X,ins (x;2) (q11;q11q14), dup(1) (q25d32), − 4,del(9) (p13), add (11) (q23) [2]/46,XX[8].

Next-generation sequencing (MiSeq, Illumina Inc) of the coding region and adjacent intronic regions (± 8 base pairs) of 18 genes related to diseases of immune dysregulation (*AP3B1*, *ITK*, *LYST*, *PRF1*, *Rab27a*, *SH2D1A*, *ST11*, *STXBP2*, *UNC13D*, *XIAP*, *ARF6*, *CD27*, *SRGN*, *CORO1A*, *CTPS1*, *GNLY*, *GZMB*, *LAMP1*). We identified a *SH2D1A* mutation (position: Xq25: exon1:c.G7T:p. Ala3Ser; ratio 28.7%) in the subject and a similar mutation in her brother ratio 96.9%). Western blotting analysis showed no SAP protein was expressed in the patient (Supplement Fig. 2). A positron emission tomography/computed tomography (PET/CT) show activity in the spleen (maximal standard uptake value (SUVmax) = 3.0) and bone marrow (SUVmax = 4.0). Based on these data, the subject was diagnosed as having HLH (7 of 8 criteria of HLH 2004 [10] (Supplement Table 1) and aggressive NK-cell leukemia. She received chemotherapy but died on 23 August 2018.

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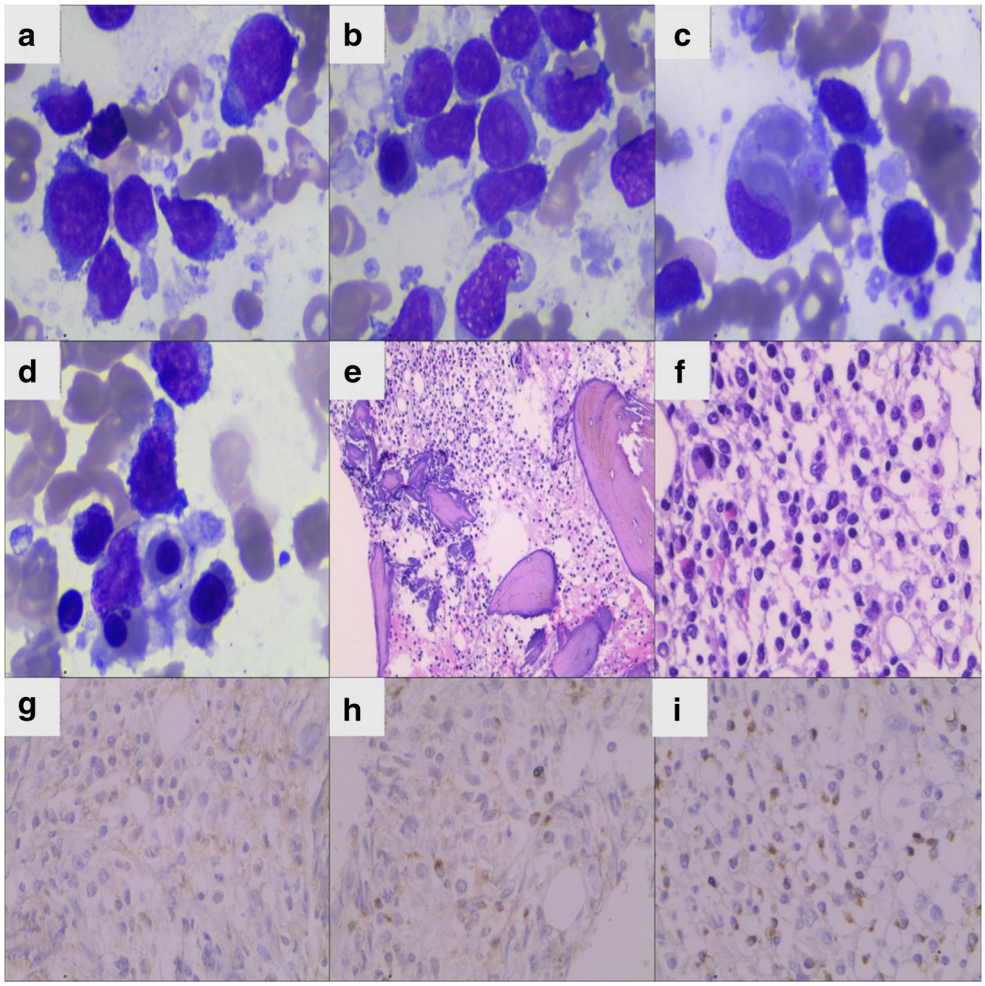

Fig. 1 Histology and immune histochemical staining (magnification, × 400) of bone marrow biopsy. **a**, **b** Diffuse infiltration by intermediate-size cytologically atypical abnormal cells. **c**, **d** Histiocytes/macrophages with phagocytosis of RBCs and granulocytes. **e** (HE × 100) and **f** (HE × 400) diffuse infiltration of abnormal cells. **g** Staining for CD56. **h** Staining for TIA1. **i** Positivity of granzyme B

Our case is remarkable in 2 regards: (1) we identified a new *SH2D1A* mutation (c.G7T:p.Ala3Ser) located within the SH domain, a highly conserved region of the protein; and (2) development of an aggressive NK-cell leukemia in a female adult carrier.

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Compliance with ethical standards

Ethics approval The ethics approval of this study was obtained from the Independent Ethics Committee of Nanjing Medical University. The subjects are given written informed consent completing the requirements of the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare that they have no competing interests.

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