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CASE REPORT

X-linked hyper-IgM syndrome with *CD40LG* mutation: Two case reports and literature review in Taiwanese patients

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Hyper-IgM syndrome (HIGM) is a rare primary immunodeficiency disorder characterized by elevated or normal serum IgM and decreased IgG, IgA, and IgE due to defective immunoglobulin class switching. X-linked HIGM (XHIGM, HIGM1) is the most frequent type, is caused by mutations in the CD40 ligand gene, and is regarded as a combined T and B immunodeficiency. We report an 18-year-old male who was diagnosed initially with hypogammaglobulinemia in infancy, but developed repeated pneumonia, sepsis, cellulitis, perianal abscess, pericarditis, and bronchiectasis despite regular intravenous immunoglobulin replacement therapy. The patient died at age 18 years due to pneumonia and tension pneumothorax. Mutation analysis revealed CD40L gene mutation within Exon 5 at nucleotide position 476 (cDNA 476G > A). This nonsense mutation predicted a tryptophan codon (TGG) change to a stop codon (TGA) at position 140 (W140X), preventing CD40L protein expression. Sequence analysis in the family confirmed a *de novo* mutation. The second case of 6-month-old male infant presented as *Pneumocystis jiroveci* pneumonia and acute respiratory distress syndrome. Gene analysis of the CD40L gene revealed G to C substitution in Intron 4 (c.409 + 5G > C) and mother was a carrier. Hematopoietic stem cell transplantation, the only cure for XHIGM, was arranged in the second case.

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Introduction

The hyper-IgM syndromes (HIGM), first described in 1960, are a heterogeneous group of genetic disorders characterized by elevated or normal serum IgM and severely deficient serum concentrations of IgG, IgA, and IgE, with normal numbers of peripheral B cells.[1] Defective immunoglobulin class-switch recombination (CSR) and somatic hypermutation (SHM) in HIGM can be caused by molecular defects in the CD40 ligand/CD40-signaling pathway or by defects involving the enzymes required for CSR and SHM.[2] Currently, HIGM can be classified into eight genetically defined types. Defects in CD40 ligand (CD40L, CD154) result in the most common hyper-IgM syndrome (HIGM1 or XHIGM), which is inherited as an X-linked recessive trait, and accounts for 65% to 70% of cases.[3] CD40L is expressed primarily on activated $CD4^+$ T cells, and interacts with CD40 expressed on B cells, monocytes, macrophages, and dendritic cells. CD40L-CD40 interactions provide a costimulatory signal for T cells, and lead to T cell activation.[4] The engagement of CD40 by CD40L on B cells leads to B cells proliferation and CSR,[5] The combined T and B immunological defect is clearly illustrated by the susceptibility of patients with HIGM1 to recurrent pyogenic and opportunistic infections.[6]

Patients with HIGM are highly susceptible to recurrent sinopulmonary infections, *Pneumocystis jiroveci* pneumonia (PJP), and chronic diarrhea due to *Cryptosporidium* infection that may lead to sclerosing cholangitis. They are also prone to intermittent or persistent neutropenia, autoimmune diseases, and malignancies.[6] Most patients with XHIGM present in infancy. Here we report two male XHIGM patients and further identified mutation in the *CD40L* gene.

Case reports

Case 1

An 18-year-old male patient was diagnosed with hypogammaglobulinemia at age 3 years. The family history was unremarkable (Fig. 1A). Starting at age 4 months, he suffered from bronchopneumonia, recurrent upper respiratory tract infections, occipital cellulitis (at age 7 months), recurrent acute otitis media, cellulitis, and pneumococcal pneumonia with pleural effusion (at age 3 years). Immunological evaluation showed normal blood cell counts, serum immunoglobulin levels: IgA $<$6.67 mg/dL, IgG $<$33.3 mg/dL, IgM 266 mg/dL, and IgE $<$10 IU/mL. Lymphocyte subsets showed $CD19^+$ B cells 37%, $CD3^+$ T cells 63%, $CD3^+CD8^+$ T cells 15%, $CD3^+CD4^+$ T cells 52%. With a diagnosis of hypogammaglobulinemia, he received regular intravenous immunoglobulin (IVIG) replacement therapy every 3 weeks with trough serum IgG levels of 500 to 800 mg/dL; however, at age 6 years, the patient developed *Pseudomonas aeruginosa* sepsis, urinary tract infection with *Candida albicans*, perianal abscess, and pericarditis. Intermittent severe neutropenia (absolute neutrophil count $\leq 200 \times 10^6$ cells/L) responsive to granulocyte-colony stimulating factor was also noted during infectious episodes.

Bruton agammaglobulinemia tyrosine kinase (*BTK*) gene mutation analysis showed wild type. By flow cytometry, CD40 ligand expression on $CD3^+CD8^-$ T cells after stimulation with PMA (20 ng/ml) and inomycin (1 mg/ml) for 4 hours was 0.43%, compared with 85.2% in a healthy control (Fig. 2).[7] Subsequently, mutation analysis of the CD40L gene revealed G to A substitution within Exon 5 cDNA at nucleotide position 476 (cDNA 476G $>$ A) (Fig. 3). This nonsense mutation led to a tryptophan (W) codon (TGG) change to a stop codon (TGA) at position 140 (W140X), preventing CD40L protein expression (Fig. 2). DNA analysis of his mother and two sisters showed normal sequence. Therefore, the patient was thought to have a *de novo* mutation of the CD40L gene. The diagnosis of X-linked HIGM was confirmed.

From age 15 years, the patient had recurrent pneumonia typically presenting with hemoptysis and dyspnea, and complicated by bronchiectasis. At age 16 years, he developed pulmonary valve regurgitation with pulmonary hypertension, and col pulmonale. Furosemide was started. Pulmonary function testing revealed a moderate to severe mixed ventilatory defect, predominantly obstructive type. Bronchiectasis and recurrent pneumococcal pneumonia precipitated his progressive lung dysfunction. He had received bi-level positive airway pressure ventilation since age 17 years. The patient died at age 18 years, due to pneumonia with mixed infection of *Pseudomonas aeruginosa* and *Candida albicans*, complicated by tension pneumothorax, and ultimately by respiratory failure.

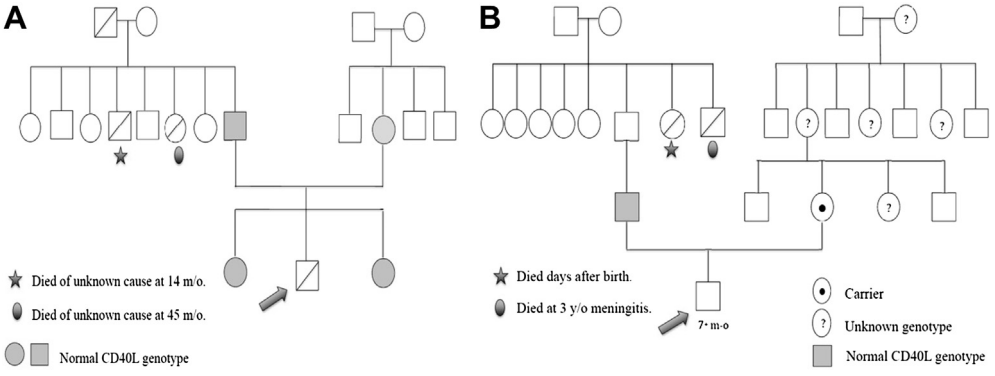

Figure 1. Pedigrees and clinical phenotypes of (A) Patient 1 and (B) Patient 2. Bar indicates mortality. The proband is indicated by an arrow.

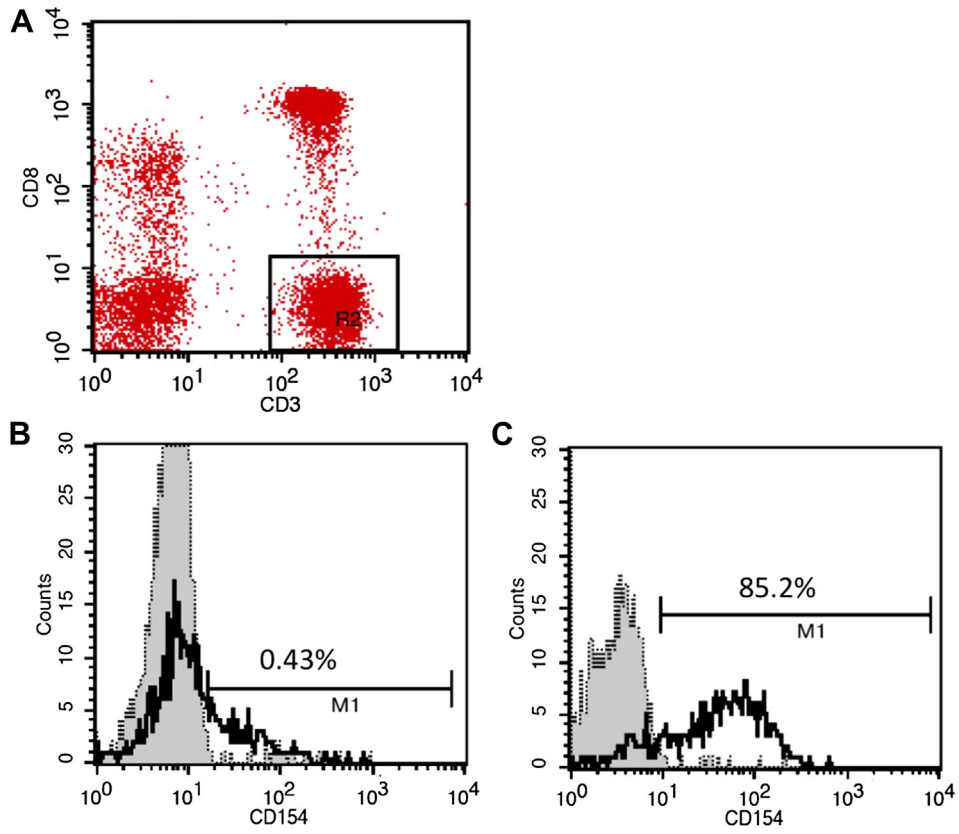

Figure 2. (A) A $CD3^{PE}$ versus $CD8^{APC}$ dot plot showing the "R2" gate set around the $CD3^{+}/CD8^{-}$ lymphocytes. Histograms from "R2" gates of (B) the patient and (C) control using unstimulated (shaded peaks) and stimulated cells (unshaded peaks) labeled with $CD3^{PE}/CD8^{APC}/CD154^{FITC}$ antibodies. CD154 expression on stimulated $CD3^{+}/CD8^{-}$ lymphocytes was 0.43% in Patient 1 and 85.2% in the control.

Case 2

A 6-month-old boy was admitted to our hospital for bronchopneumonia with cough, rhinorrhea and short of breath for one week. Fever was noted after admission. Dyspnea with diffuse wheezing and rales rapidly progressed under empirical antibiotics. He was intubated 8 days after admission due to progression to acute respiratory distress syndrome (ARDS) (Fig. 4A). Sputum PJP PCR was positive. Under the support of high frequency oscillator ventilation and the treatment of co-trimethoxazole/sulfamethoxazole (Sevatrim), ARDS improved and he was extubated 2 weeks later. Immunological evaluation showed elevated white blood cell counts 23.5×10^9/L, neutrophils 44.5%, lymphocytes 45.8%, serum immunoglobulin levels: IgA $<$22.6 mg/dL, IgG 13.5 mg/dL and IgM 68 mg/dL. Lymphocyte subsets showed $CD19^{+}$ B cells 52%, $CD3^{+}$ T cells 44%, $CD3^{+}CD8^{+}$ T cells 8%, $CD3^{+}CD4^{+}$ T cells 35%, NK cell 1%. Mitogen test for T cell function showed normal proliferation response using phytohaemagglutinin and pokeweed mitogen stimulation and decreased proliferation response using CD3/CD28 stimulation. CD40 ligand expression on stimulated $CD3^{+}CD8^{-}$ T cells of patient was 7.1%, compared with that of normal control 67.8%. Gene analysis of the CD40L gene revealed G to C substitution in Intron 4 (c.409 + 5G > C, IVS4 + 5G > C) (Fig. 4B). This splice site mutation is predicted to destroy the donor site of Intron 4 and produce abnormal RNA and protein. DNA analysis of his mother confirmed the mother as carrier. The diagnosis of X-linked HIGM was confirmed. He was discharged smoothly and received regular IVIG replacement therapy every 3 weeks with trimethoprim-sulfamethoxazole prophylaxis during follow-up. Hematopoietic stem cells transplantation was arranged.

Discussion

We report the case of a young man with XHIGM who suffered from repeated infections of the respiratory tract, lungs, and skin, complicated by early-onset bronchiectasis despite regular IVIG replacement therapy. The male infant with XHIGM was diagnosed soon after the recognition of PJP pneumonia and ARDS as opportunistic infection. Either X-linked agammaglobulinemia (*BTK* gene mutation) or XHIGM (*CD40LG* gene mutation) could present with a hypogammaglobulinemia phenotype; however, susceptibility to opportunistic infection should raise the suspicion of abnormal cellular immunity, as in XHIGM. CD40 ligand expression in *in vitro*-activated lymphocytes should be assayed in patients with low serum IgG, normal or elevated serum IgM, and opportunistic infections or family history consistent with X-linked inheritance. In addition, sound CD40L-CD40 signaling enhances the development of memory-B cell

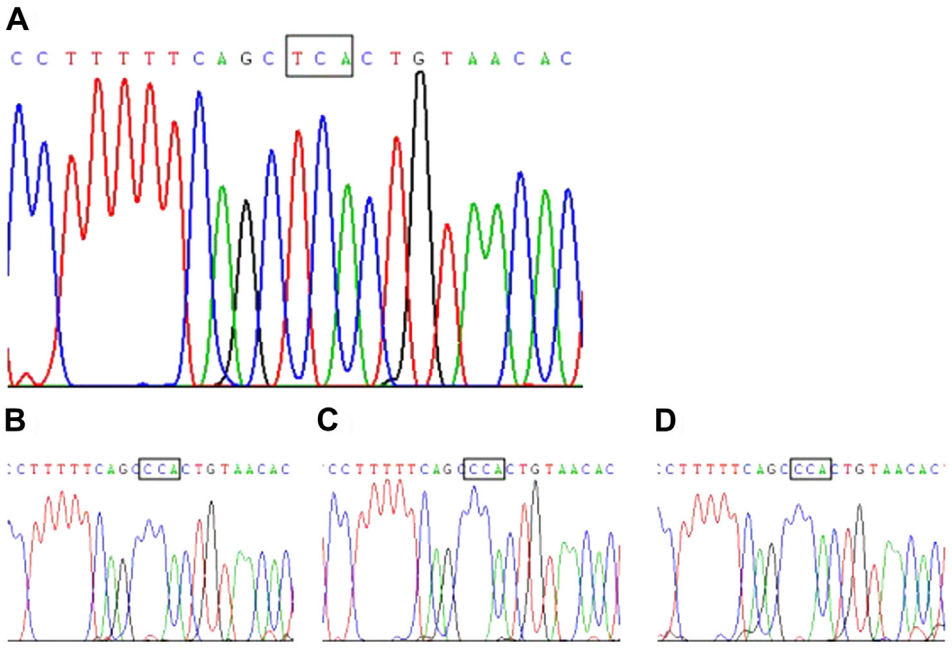

Figure 3. Sequence analysis in genomic DNA of Patient 1, and his mother and two sisters. (A) A nonsense mutation in Exon 5 (c.476G > A) changes a tryptophan (W) codon (TGG) into a translation termination (X) codon (TGA) at amino acid position 140 (W140X). (B) The mother and (C,D) two sisters had wild type gene sequences.

from naïve B cell. Absence of $IgM^{-}IgD^{-}CD27^{+}$ memory B cell population in peripheral blood was also found in X-linked hyper-IgM syndrome.[8,9] The high IgM concentrations have been assumed to reflect chronic antigenic stimulation, and serum IgM levels may normalize after regular IVIG treatment.

The CD40 ligand gene product, a 39-kDa type II membrane glycoprotein, belongs to the family of TNF receptor molecules. The CD40 ligand monomer consists of four structural domains: a *N*-terminal intracellular tail (amino acids 1—22), a transmembrane domain (amino acids 23—46), a portion that forms the extracellular unique domain (amino acids 47—122), and the extracellular *C*-terminal TNF homology (TNFH) domain (amino acids 123—261).[10] Most *CD40LG* mutations are exonic single nucleotide substitutions, mainly in the extracellular TNFH domain, encoded by Exon 5 and part of Exon 4. According to the mutation registry for *HIGM1* (a former synonym for *CD40LG*, now withdrawn), CD40Lbase (http://bioinf.uta.fi/CD40Lbase),[11] only one previous study has reported a point mutation within Exon 5 at nucleotide position 476 (476G > T),[12] leading to an amino acid change (W140C) in the TNFH domain. The genetic mutation observed in our two cases has not been reported previously. Moreover,

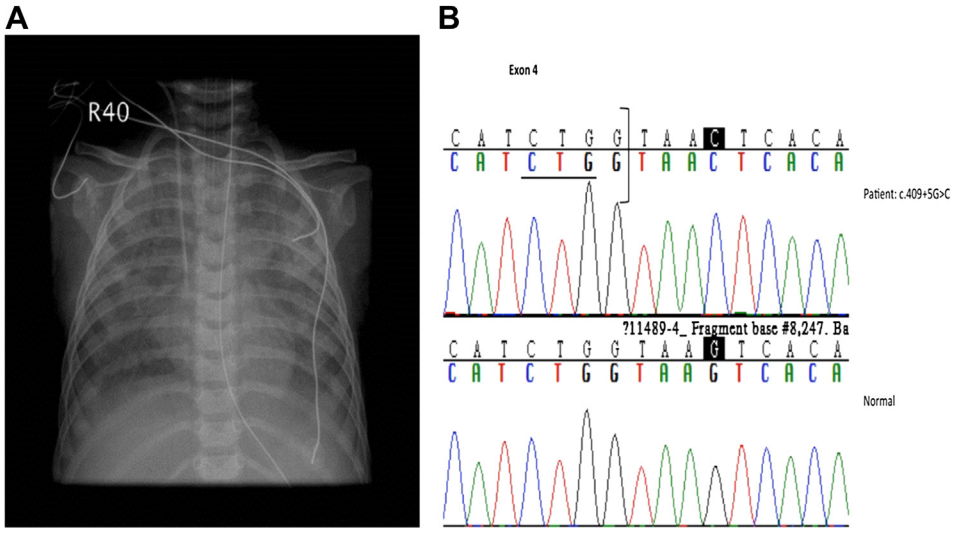

Figure 4. (A) Chest x-ray showed diffuse hazy density with clinically low arterial oxygen levels in patient 2. (B) Gene analysis of the CD40L gene in patient 2 revealed G to C substitution in Intron 4 (c.409 + 5G > C).

Codon 140 is a hot spot for *CD40LG* gene mutation, with 11 mutations affecting Codon 140, including six missense mutations (2 W140G, 2 W140C, 2a W140R), and five nonsense mutations W140X recorded in CD40Lbase.[11,12] The nonsense mutations W140X cause truncation of the extracellular domain of CD40 ligand and are expected to result in large deletions of the TNF homology region. The 12 patients with XHIGM mutations in Codon 140 (including our case) represented a variety of ethnicities. There were six Europeans, one Australian, one Korean, three Japanese, and one Han-Chinese (our case). These patients experienced *Pneumocystis jiroveci* pneumonia (one patient), bacterial sepsis (three patients), diarrhea due to *cryptosporidium* (three patients), neutropenia (seven patients), oral ulcers (four patients), arthritis (one patient), hepatitis (three patients), liver cirrhosis (one patient), and hepatocellular carcinoma (one patient). Bronchiectasis was seen only in our patient. None of them received a bone marrow transplant. The splice site mutation in Intron 4 (g.IVS4 + 1G > C) of CD40L gene in two families had been reported by Seyama et al.[13] This mutation caused Exon 4 skip and inframe deletion of 21 amino acids with frameshift.

HIGM with CD40L and CD40 mutations has been classified into combined T and B immunodeficiency, not predominantly antibody deficiency. Only 20% of patients with XHIGM survive beyond 25 years of age.[1] The major causes of death are PJP early and liver disease later in life. Winkelstein et al[6] reported that 59% of patients with pneumonia of XHIGM had PJP compared with 27% having unknown pathogens. The use of trimethoprim-sulfamethoxazole for prophylaxis of PJP may also be beneficial.[14] Therapy for HIGM is monthly infusions of IVIG that reduce the frequency and severity of infections. However, IVIG did not prevent the development of sclerosing cholangitis or bronchiectasis.[15] In a previous report, 68% of XHIGM patients had neutropenia and 45% were chronic. If neutropenia is severe, it may respond to G-CSF. [16] Bone marrow transplantation performed early in life may cure XHIGM.[1,17] Hematopoietic stem cell transplantation was curative in 58% of patients with XHIGM and successful in 72% of patients without preexisting hepatic disease in a review of 38 patients in Europe.[17] In our first patient, lack of anti-PJP and anticandida prophylaxis might contribute to the development of cor pulmonale because of T cell defects. When T cell defects are found, stem cell transplantation should be considered as early as possible. Among 13 published cases with HIGM in Taiwan, only one received HLA-matched sibling donor bone marrow transplantation successfully.[18]

Clinical features and genetic mutation of 9 Taiwanese patients with HIGM in the literature are summarized in Table 1.[19–25] Sinopulmonary infection occurred in all patients, while bronchiectasis, chronic diarrhea, and septicemia were common presentations. Patient 1 with missense mutation (Thr254Met) in the CD40L gene had a less severe HIGM presentation, similar to common variable immunodeficiency phenotype. According to genomic DNA sequencing, Patients 2, 3, and 4 from the same family all had a missense mutation located at Tyr169Asn (526 T > A) in Exon 5 of the CD40L gene. Patient 2 developed severe diarrhea and interstitial pneumonia caused by coxsackievirus B4 at age 3 months. Patient 3 presented with recurrent pneumonia, sepsis, and recurrent herpetic

Table 1 Clinical features, immunoglobulin levels, protein expression and gene analysis of 9 male HIGM patients in Taiwan

No.	Onset age	Clinical presentation					CD40L gene mutation (exon/intron)	Predicted effect on protein (domain)	Immunoglobulins (mg/dL)			CD40L (%)[b]	FH	Ref
		Sinupulmonary infection	Bronchiectasis	Chronic diarrhea	Septicemia	Other			IgG	IgA	IgM			
1	22 y	+	+	−	−	—	782T > C (E5)	T254M (TNF)	48	83	109	29.6	−	19
2	3 mo	+	−	+	−	—	526T > A (E5)	Y169N (TNF)	190	2	34	<1	+	15,20
3	3 y	+	+	−	+	—	526T > A (E5)	Y169N (TNF)	175[a]	8	187	<1	+	15
4	3 y	+	−	+	+	Sclerosing cholangitis	526T > A (E5)	Y169N (TNF)	12	6	104	<1	+	15,21
5	5 mo	+	−	−	−	—	307A > T (E2)	K96X (EC)	18	4	128	0.5	−	22,23
6	2 y	+	−	−	−	Ileum perforation	—	—	184	<6.7	216	6.8	−	24
7	4 m	+	−	−	−	HIE	—	—	51.3	8.32	140	<1	−	25
8	4 m	+	+	−	+	Cellulitis, perianal abscess, pericarditis	476G > A (E5)	W140X (TNF)	<33	<6.7	266	<1	−	current study
9	7 m	+	−	−	−	PJP, ARDS	IVS4 + 5G > C (I4)	—	13.5	<22	68	7.1	−	current study

ARDS = acute respiratory distress syndrome; EC = extracellular domain; FH = family history; HIE = hypoxic ischemic encephalopathy; PJP = *pneumocystis jiroveci* pneumonia; Ref = reference; TNF = tumor necrosis factor homology domain.

[a] Post-IVIG IgG seral level.

[b] CD40L surface expression on activated CD4+ lymphocytes.

gingivostomatitis since age 3 years, and he developed bronchiectasis thereafter. Patient 4 presented with chronic diarrhea, recurrent pneumonia, salmonellosis, and herpetic gingivostomatitis since age 3 years. He developed sclerosing cholangitis at age 18 years despite regular IVIG supplement. Patient 5 presented with pneumonia at age 5 months. CD40L gene analysis revealed a nonsense mutation at nucleotide 307 A > T, resulting in a stop codon at Lys 96 position. He had painful recurrent oral ulcers and neutropenia. Patient 6 developed pneumonia and ileum perforation followed by peritonitis at age 2 years. Pathologic findings showed massive intestinal lymphoproliferation. Patient 7 presented with pneumonia and hypoxic ischemic encephalopathy at age 4 months. Patient 6 and 7 remained healthy during 1 year of follow-up.

In conclusion, we identified two patients with XHIGM, with mutations of the *CD40LG* gene (Patient 1 *de novo* mutation, Patient 2 X-linked transmission from carrier mother). Recurrent infections despite regular IVIG supplement ultimately led death in the first case. Early diagnosis, as in Patient 2, is essential for early hematopoietic stem cell transplantation before the onset of significant organ damage, which is the only cure for XHIGM.

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