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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.

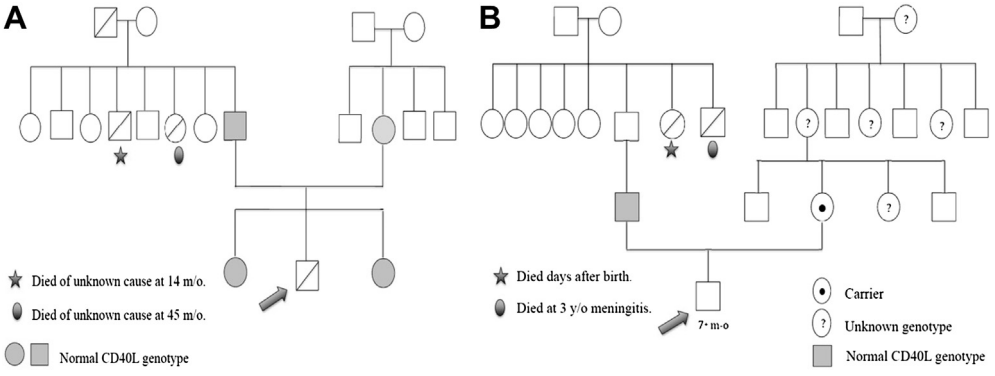

Figure 1. Pedigrees and clinical phenotypes of (A) Patient 1 and (B) Patient 2. Bar indicates mortality. The proband is indicated by an arrow.