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CASE REPORT

X-Linked Hyper IgM Syndrome: A Report of the First Case in Thailand with a Confirmed Mutation of CD40 Ligand Gene

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SUMMARY **X-linked hyper IgM (XHIM) syndrome is a rare congenital immunodeficiency disease caused by failure of B cell to isotype switch from IgM to other classes of immunoglobulins in response to infections. Recently, a molecular cloning of the gene responsible for the syndrome, the CD40L gene has been accomplished and the gene was successfully mapped to the long arm of X chromosome at the position Xq26. We, herein, report the first case of molecular proven XHIM in a Thai boy with a classic presentation and with a confirmed mutation of the CD40L gene. Case Report: A.S. was a 1 year 7 month old boy referred from Buriram Provincial Hospital for a work up and treatment for his recurrent infections consisted of chronic respiratory tract infections with otitis media (since 6 months of age), chronic diarrhea (since 9 months of age) and malnutrition (marasmus) secondary to his longstanding illnesses. He was a product of a consanguineous marriage but without history of similar illness observed in his pedigree. Abnormal laboratory works up included IgG of 300 mg/dl, IgA 10 mg/dl, IgM 1,635 mg/dl, positive stool examinations for *Cryptosporidium*, chronic colitis on radiographic gastrointestinal follow through study, a positive acid fast bacillus (AFB) stain of gastric aspirate and multiple positive bacterial cultures from various body sources. His anti-HIV serology was negative. His hospital course was significant for several bouts of infections of gastrointestinal, respiratory, and genitourinary systems. His treatment consisted of multiple courses of antibiotics, antituberculous drugs and IVIG administrations. His hospital course was complicated with feeding problem from an esophageal stricture requiring several esophageal dilatations. The analysis of CD40L gene revealed a point mutation of exon 5 (A619T) of the CD40L gene resulting in a stop codon confirming that indeed he had XHIM. He died with *Pseudomonas* septicemia during the waiting period for a bone marrow transplantation from a cord-blood stem cell.**

X-linked hyper IgM syndrome is a rare congenital immunodeficiency syndrome caused by failure of B cells to isotype-switch from IgM-producing cells to cells secreting other classes of immunoglobulins in response to infections.[1] The syndrome is characterized by absence or low of serum IgG, IgA and IgE levels with a normal or more frequently elevated serum IgM level.[1,2] Affected patients are susceptible to recurrent sinopulmonary infections, recurrent opportunistic infections, neutropenia, autoimmune disease, lymphoma and cancer of the liver, pancreas or biliary tree.[2] The syndrome was first described by Rosen *et al.*[3] and by Burtin *et al.*[4] in 1961. Recently, a molecular cloning of a gene responsible to the syndrome, the CD40 ligand gene, has been reported and the gene was successfully mapped to the long arm of X chromosome at the position Xq26.[2,6] The gene contains 5 exons and 4 introns and there are several mutation patterns.[10,11] The CD40L expressed on activated T cells react with the CD40 on B cells causing the latter to isotype switch from IgM to the other class of immunolobulins.[5] B cells from patients with X-linked hyper IgM syndrome lacking in the expression of CD40L protein transcript secrete high level of IgM and

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low level of IgG, IgA and IgE. We, herein, reported the first case of classical X-linked hyper IgM syndrome in Thailand with a confirmed mutation of his CD40L gene.

CASE REPORT

A.S. was a 1 year and 7 month old boy referred from Buriram Hospital (Northeastern Thailand) to Siriraj Hospital in Bangkok for a work up and treatment for his recurrent infections. He was a product of a consanguineous marriage. Nevertheless, there was no family history of similar illnesses observed in his pedigree. He was born by normal vaginal delivery with a birth weight of 2,500 gm. His vaccination was up to date. His growth and development was normal until 6 months of age when he began to develop recurrent respiratory tract infections and otitis media in both ears along with chronic diarrhea. He had been admitted at Buriram Hospital on three occasions with pneumonia and severe diarrhea. On arrival to Siriraj Hospital he was febrile, cachectic and was in a state of malnutrition due to his long-standing illnesses. His body weight was 6.6 kg (below 3rd percentile) and his height was 75 cm (below 10th percentile). He was pale, weak and dyspnic. Perforation of both ear drums was observed with foul smell discharge. Oral thrush was present. Medium to coarse crepitations was heard on auscultation of both lungs. Liver was enlarged 3 cm below right costal margin. His routine laboratories consisting of complete blood count, urine examination and blood chemistry tests including blood sugar, electrolytes and liver function tests were normal. Stool examinations revealed numerous white blood cells with cyst of *Cryptosporidium* seen on 2 occasions. Nevertheless stool culture failed to grow any pathogenic bacteria. His gastric aspirates for *Mycobacterium tuberculosis* (TB) culture and a polymerase chain reaction (PCR) utilizing a 16S rRNA-based primers[12] were negative although acid fast staining for TB was positive for only 1 bacillus. His serology for HIV (gel particle agglutination) was negative. Delayed type hypersensitivity test panel yielded positive reaction only to *Corynebacterium diphtheriae* antigen. Immunoglobulin levels revealed IgG 300 mg/dl, IgA 10 mg/dl and IgM of 1,635 mg/dl. Lymphocyte enumeration by FACS revealed a B cell count of 2,077 cells/mm^3, CD4+ T cells of 1,850 cells/mm^3 and CD8+ T cells of 1,063 cells/mm^3. DNA analysis for the mutation of CD40 ligand gene was performed by a previously reported PCR and a single-stranded, conformational polymorphism (SSCP) technique.[10,13] A point mutation in the exon-5 (A 619 T, adenine at postion 619 being substituted by thymidine) of his CD40L gene was uncovered which resulted in a stop codon (Arg 200x) of the gene leading to nonproduction of the protein product. A

Table 1 Serial immunoglobulin levels of the patient, before and after treatment with IVIG (Venoglobulin S, Alpha Therapeutics, Co, Los Angeles, CA)

Date	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	Date and doses of IVIG
19 March 98	405	36	1,665	27 March 98 (2.5 gm)
7 April 98	260	9	1,450	8 April 98 (2.5 gm)
17 April 98	340	20	960	24 April 98 (5 gm)
12 May 98	365	5	570	3 June 98 (5 gm)
18 June 98	660	13	425	7 July 98 (5 gm)
17 July 98	660	9	645	

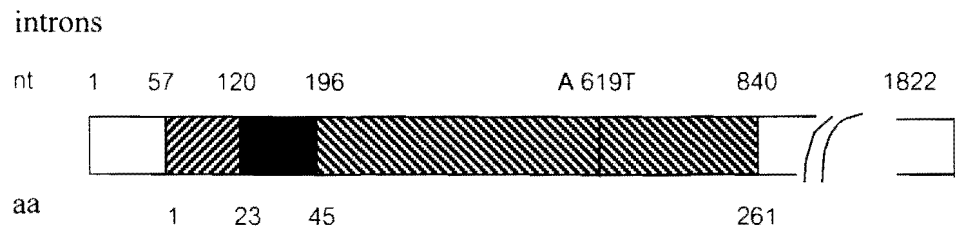

Fig. 1 An illustration showing CD40L gene with a site of mutation found in the currently reported case of XHIM patient (point mutation in the exon 5[A 619 T]).

definitive diagnosis is X-linked hyper IgM syndrome was made. During his admission, the patient had several bouts of infections of gastrointestinal, respiratory and genitourinary systems included *Candida* septicemia and *Pseudomonas* urinary tract infections. He was treated with amphotericin B, appropriate antibiotics and intravenous immunoglobulins (5% Venoglobulin S, Alpha Therapeutics Co., Los Angeles, CA). After several courses of IVIG administrations, his IgM level declined but he continued to develop several recurrent infections (see Table 1 for serial IgM levels). Cord blood stem cell transplantation was contemplated but he expired from *Pseudomonas* septicemia before the procedure had been possible.

DISCUSSION

Although cases with similar presentations have been observed in Thailand,[14] our patient is the first to be proven a case of XHIM by a gene analysis. XHIM syndrome results from mutations of a gene encoding for a membrane glycoprotein CD40L, belonged to the tumor necrosis factor (TNF) gene superfamily which mainly expressed on activated T cells.[11] In the absence of CD40L, normal cooperation between T and B cells is impaired and B-cell immunoglobulin-switch from IgM to other isotypes fails to occur.[5] The CD40L gene is located on the X chromosome at the position of Xq26 and the disorder is usually inherited in an X-linked recessive manner. The definitve diagnosis of XHIM is the identification of a CD40L gene mutation.[15,16] Nonoyama[10] reported several mutation patterns in 13 Japanese patients with XHIM. Affected patients experienced early-onset infections, usually within the first year of life, upon a decline of maternally-derived antibodies. Although most infections are of bacterial origin, XHIM patients are also unusually susceptible to infections with opportunistic pathogens and often suffer from *Pneumocystis carinii* pneumonia and *Cryptosporidium* intestinal infection, conditions frequently observed with T-cell immunodeficiencies but not with other forms of hypogammaglobulinemia.[8] Isekil[7] reported two siblings with hyper IgM syndrome whom the elder brother died with disseminated *Cryptococcosis* but the younger brother with CD40L gene analysis revealed a point mutation (at nucleotide 475, tryptophane [TGG] to cause a stop codon [TAG]), survived with the normal level of IgM after IVIG treatment. Our patient had the typical characteristics[2,6,9] and laboratory findings[9] of hyper IgM syndrome. Patients with XHIM can develop recurrent respiratory tract infections, chronic diarrhea, urinary tract infections including the opportinistic infections such as from *Cryptosporidium*, *Candida* species and from *Mycobacterium tuberculosis*. Although some patients with XHIM had neutropenia, thrombocypenia, or anemia which may result from autoantibodies or from chronic inflammation,[2,17] our patient had near normal white blood cell and platelet counts. B cell numbers which were normal in this patient can be used to differentiate from classical X-linked agammaglobulinemia (XLA).[1] Normal numbers of T cells and T-cell subsets with normal proliferation to mitogens have been observed in some XHIM patients presenting with *P. carinii* infection in contrast to patients with severe combined immunodeficiency or HIV patients.[2,6] Treatment of XHIM is mainly based on regular administration of intravenous immunoglobulins (IVIG) at appropriate dosages. Administration of IVIG provide adequate functional levels of IgG and could also decrease serum level of IgM.[18-22] This may result from the reduction in the number of infections and possibly involving the regulatory effect of IgG molecules on IgM production. Infections are treated with specific antimicrobial administrations and neutropenia, if severe, can be treated with G-CSF.[23] Bone marrow transplantation can cure XHIM and may be feasible if an HLA-matched sibling is available.[24] Since our patient was the only child in the family, a cord blood stem cell transplantation (from a planned sex-oriented, *in vitro* fertilization) was contemplated. Unfortunately, the child did not survive his last severe septicemia from *P. aeruginosa*. The patient represents the first case of XHIM in Thailand proven with a confirmed mutation of his CD40L gene.

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