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CLINICAL BRIEF

Type I Hyper IgM Syndrome with Novel Mutation from India

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Abstract Hyper IgM syndrome is a primary immunodeficiency disorder characterized by normal or raised levels of immunoglobulin (Ig) M with low or absent IgG, IgA, and IgE. Five genetic causes of Hyper IgM have been identified. *CD40L* is deficient on T cells in Type I Hyper IgM, leading to defective interaction between T and B lymphocytes and consequently an inability to switch from production of IgM to other classes of antibodies. This manuscript reports a patient with X linked Hyper IgM (XHIGM) syndrome caused by a novel mutation in the CD40 Ligand (*CD40L*) gene and a favorable outcome after bone marrow transplantation.

Keywords Hyper IgM · CD40 Ligand · Hematopoietic stem cell transplantation

Introduction

Hyper IgM syndrome (HIGM) is a rare heterogeneous group of primary immunodeficiences (PIDs) characterized by normal or raised levels of IgM and low or absent IgG, IgA, and IgE. Five subtypes of HIGM have been described, but X linked recessive HIGM (CD40 Ligand deficiency) is the most common [1]. This manuscript describes a case of X-linked HIGM with a novel mutation.

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Case Report

A 3-y-old boy, born of a non-consanguineous marriage, was referred for evaluation of recurrent infections and failure to thrive. He had repeated oral ulcers and fever requiring enteral antibiotics almost every month after 7 mo of age. Past blood reports showed normal leukocyte and platelet counts but reduced neutrophils (ANC range 1500 to 2000/μl) and eosinophilia (10–15 %). At 1.5 y, he was admitted in the ICU with pneumonia, acute respiratory distress syndrome and multi-organ dysfunction requiring prolonged ventilation. His neutrophil count remained low at that time (ANC 500 to 1200/μL) with eosinophilia (AEC 500 to 1500/μL), and bone marrow examination showed depressed myeloid series with eosinophilia and normal megakaryopoiesis. He had normal lymphocyte subset with depressed immunoglobulin IgG, A, E (63, 13, 1 mg/dL respectively) and normal IgM (148 mg/dL). GM-CSF and intravenous Ig substitution given at that time had no effect on his neutropenia. Two months after discharge from the hospital, the child developed a gluteal abscess requiring incision and drainage. When he presented to the authors at 3 y of age, he was developmentally normal without any organomegaly or candidiasis, but his weight and height were <3rd centile. His serum Ig panel at 3 y showed IgG 88.3 mg/dL (normal 443–916), IgA 5.4 mg/dL (20–100), IgE 0.1 mg/dL (20–100), and IgM 429 mg/dL (19–146). This clinical presentation and pattern of immunoglobulin levels suggested Hyper IgM syndrome. His activated T lymphocytes (confirmed by *CD69* expression) did not express CD40 ligand (*CD40L*, also called *TNFSF5* or *CD154*) after stimulation, thus confirming the diagnosis of Type I HIGM (Fig. 1).

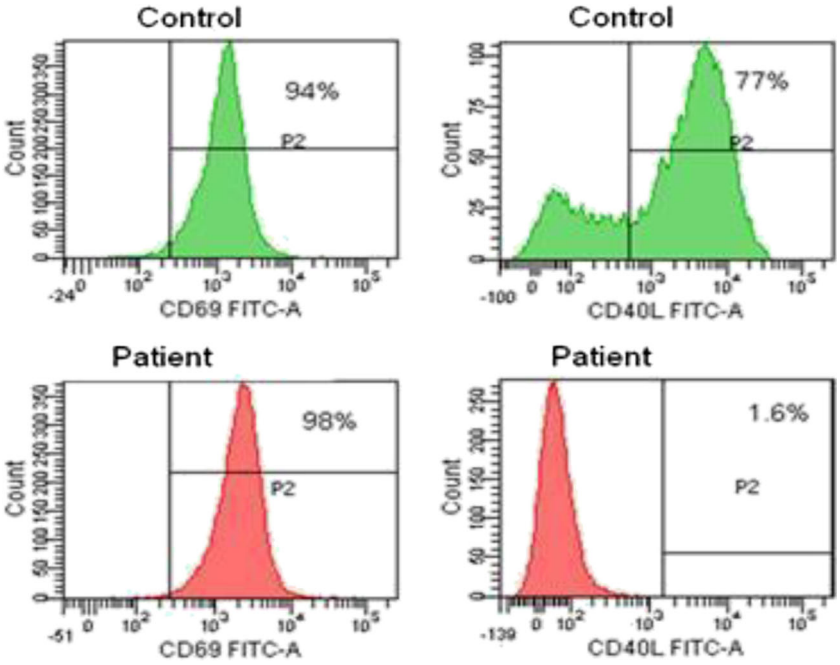

Fig. 1 Flowcytometric evaluation of the patient. Activated T blast cells (CD69) from healthy control (*green*) with normal expression of CD40 Ligand (CD154) and normal CD40 binding. Activated T blast cells (CD69) from patient (*red*) fail to express CD40 Ligand (CD154)

Gene *CD40LG* (OMIM: 300386) was amplified from genomic DNA (gDNA) using specific oligonucleotide primers and compared with gene bank, showed a novel nonsense mutation at exon 2 (nonsense mutation at nucleotide level c.229A>T and at protein level R77X), (Fig. 2) which has not been described previously. This is the first case report of a mutation study from India in a patient of *CD40L* deficiency. After initiating regular Immunoglobulin (IvIG) replacement therapy, the patient experienced a dramatic decrease in oral ulceration and infections along with remarkable increase in weight and height. Fortunately, he had a 6/6 HLA geno-identical matched sibling donor (sister) and was successfully transplanted with peripheral hematopoietic stem cells. Six mo after transplantation, he no longer requires immunoglobulin replacement with 81 % chimerism.

Discussion

During the primary immune response, B cells produce IgM class of antibodies with less avidity and specificity. The secondary immune response is T lymphocyte dependent and consists of class-switch recombination (switching from IgM to more specific IgG, IgA or IgE) and somatic hypermutation (introduction of point mutations in the V regions of the Ig genes). This requires CD40 Ligand (CD154) (expressed on activated T lymphocytes) and CD40 molecule (expressed on B lymphocyte) interaction which occurs in peripheral lymph nodes [1]. In X linked Hyper IgM (XHIGM) (Type I), *CD40L* is deficient, leading to defective "cross talking" between T and B lymphocytes and consequently no class switch response. Type I HIGM, is hence a T cell disorder because B cells are functionally normal. As CD40 is also expressed on dendritic cells and monocytes, this leads to defective cell mediated immunity, opportunistic infections and tumors. Various bacterial, viral (including JC virus induced multifocal leukoencephalopathy), protozoal (*Isospora*, *Cryptosporidium*) and fungal (*Cryptococcus*) diseases have been described [2]. *CD40* is required for granulopoiesis accounting for neutropenia which may be persistent, episodic or periodic. *CD40L–CD40* interaction also seems to have an important role in T regulatory cells explaining the high incidence of autoimmune disorders in its absence.

The majority of patients with Hyper IgM syndrome have an abnormal *CD40L* gene on Xq26.3. The *CD40L* gene has 5 coding exons and 4 introns [3]. Over 165 pathological *CD40L* mutations have been described in all 5 exons, commonly in the TNF-homology domain (exon 5). Missense mutations (26 %), nonsense mutations (20 %), partial or whole gene deletions/insertions, and splicing mutations have all been observed. A total of 5 types of HIGM have

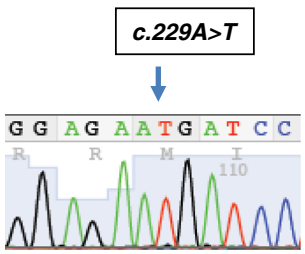

Fig. 2 The electropherogram of mutation *c.229A>T*

been described; mutations in the *AICDA* gene, *CD40* gene, *UNG* gene and an unidentified defect comprise the other four subsets. [4] Another X linked form is due to a mutation of the *NEMO* gene is characterized by associated anhidrotic ectodermal dysplasia. IvIG replacement therapy usually controls serious infections but cannot prevent tumors, autoimmune disorders, or neutropenia [5]. HSCT is the only cure available for Type I HIGM [6–8]. Genetic analysis is desirable for genetic counseling of future pregnancy. Fortunately, the patient described received his transplant before he could develop complications of infection, autoimmunity or malignancy.

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Conflict of Interest None.

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