



Letter

Hyper immunoglobulin M syndrome in a 15-year-old boy caused by a Gly219Arg missense mutation

Introduction

Hyperimmunoglobulin M syndrome is a primary immunodeficiency disorder characterized by low or absent immunoglobulin (Ig) G, IgA, and IgE, with normal or elevated IgM levels.¹ X-linked hyper-IgM syndrome (X-HIGM or HIGM1) is the most frequent subtype of HIGM, which is caused by mutations in CD40 ligand (CD40L or CD154) gene encoding for the CD40L expressed on activated T cells.¹ CD40L plays an important role in class switching and maturation of B-lymphocytes by interacting with its receptor CD40 on B-cells. CD40L is also important for activation of T-cells. Mutations of CD40L result in a combined T- and B-cell immunodeficiency. Thus, patients with X-HIGM are susceptible to bacterial, fungal, and opportunistic microorganisms.^{1–3} We report a case of X-HIGM caused by a c.655G>A missense mutation, resulting in decreased but not absent CD40L expression and function on activated T-cells.

A 15-year-old boy was evaluated for a chronic purulent productive cough present for more than 2 years. He also reported fatigue, nasal congestion with purulent rhinorrhea, chronic gingivitis, and weight loss. His medical history included 5 hospitalizations for pneumonia requiring parenteral antibiotics. He also had a history of recurrent sinusitis, otitis media, severe varicella as an infant, and herpes zoster at age 10 years. He had myringotomy and tympanostomy tubes placed. There was no history of fungal infections. He had aplastic anemia at age 5 years and Crohn's disease diagnosed at age 8 years. No family history of primary immune deficiency or cystic fibrosis was present. Physical examination was notable for scarring of the tympanic membranes, purulent postnasal drainage, small tonsils, bibasilar rales, splenomegaly, and clubbing. Chest computed tomography scan showed extensive bronchiectasis of the lungs bilaterally.

As seen in Table 1, the immunologic evaluation showed decreased IgG, but normal IgM with decreased antibody titers to diphtheria, *Haemophilus influenza* type B antibody, *Streptococcus pneumoniae* antibody. Peripheral blood flow cytometry revealed decreased CD3+ T cells, CD4+ T cells, CD8+ T cells, and memory CD19+CD27+ B cells. Lymphoproliferative responses to stimulations with phytohemagglutinin, concanavalin A, pokeweed mitogen, *Candida albicans*, tetanus toxoid, and alloantigens were normal. CD40L expression on stimulated T cells was decreased at 39% (normal, 79%–96%; Cincinnati Children's Diagnostic Immunology Laboratory). A gene sequencing study identified a missense mutation 655G>A at exon 5, located in Xq26.3 resulting in amino acid change gly219arg (Correlagen Diagnostics Laboratory). Because controversy exists as to whether this mutation results in a functional CD40L defect, CD40 binding assay was performed with

Table 1

Immunologic studies in a 15-year-old boy with 655 G>A gly219arg missense mutation in X-HIGM syndrome

Study	Patient	Normal for 15-Year-Old
IgG, mg/dL	397	600–1,606
IgA, mg/dL	144	46–287
IgM, mg/dL	188	57–237
IgG1, mg/dL	273	350–900
IgG2, mg/dL	75	70–450
IgG3, mg/dL	6	20–90
IgG4, mg/dL	<1	3–90
Anti-diphtheria toxoid, µg/mL	0.0	≥0.05
Anti-tetanus toxoid, µg/mL	1.6	≥0.50
Anti-HiB, µg/mL	0.3	≥1.0
Anti- <i>S. pneumoniae</i> , % protective	43% (9/23)	≥1.3 µg/mL in ≥70% serotypes
ALC, cells/mm ³	1,260	1,400–3,300
CD3 cells/mm ³	882	1,000–2,200
CD4 cells/mm ³	516	530–1,300
CD8 cells/mm ³	302	330–920
CD19 cells/mm ³	151	110–570
CD56 cells/mm ³	63	70–480
CD19+CD27+, %	0	25–40
CD19+CD27+IgD-, %	0	≥6
PHA, %NR	131.7	≥50
Con A, %NR	107.7	≥50
PWM, %NR	215.3	≥50
<i>Candida albicans</i> , SI	7.4	≥3.0
Tetanus toxin, SI	20.9	≥3.0
Alloantigens, %NR	42.2	≥50
CD40L expression, %	39 ^a	79–96 ^a
Trap 1 mo ab	22.6 ^b	72.4 ^b
24–31 mo ab	29.7 ^b	43.7 ^b
CD40-Ig binding, %	19.1 ^b	71.1 ^b

Abbreviations: HiB, *Haemophilus influenzae* type B; ALC, absolute lymphocyte count; PHA, phytohemagglutinin; Con A, concanavalin A; PWM, pokeweed mitogen; %NR, percent normal response; SI, stimulation; NK, natural killer cell.

^aPerformed by Cincinnati Children's Diagnostic Immunology Laboratory.

^bPerformed by Seattle Children's Immunology Diagnostic Laboratory.

CD40-Ig fusion protein (Seattle Children's Immunology Diagnostic Laboratory), as previously described by Lee et al.⁴ Repeat CD40L expression was performed as previously described⁴ and demonstrated decreased CD40L expression of CD4+ T cells with the TRAP 1 monoclonal antibody, 22.6%, and normal with the 24–31 monoclonal antibody, 29.7% (Table 1). CD40 binding CD40-Ig fusion protein was decreased compared with control, 19.1% versus 71.1% (Table 1; Fig 1).

Patients with X-HIGM are susceptible to aplastic anemia associated with parvovirus infection.⁵ The patient had detectable antibody to parvovirus but was negative for viral antigen by polymerase chain reaction, which confirms the previous parvovirus infection.

Disclosures: Authors have nothing to disclose.

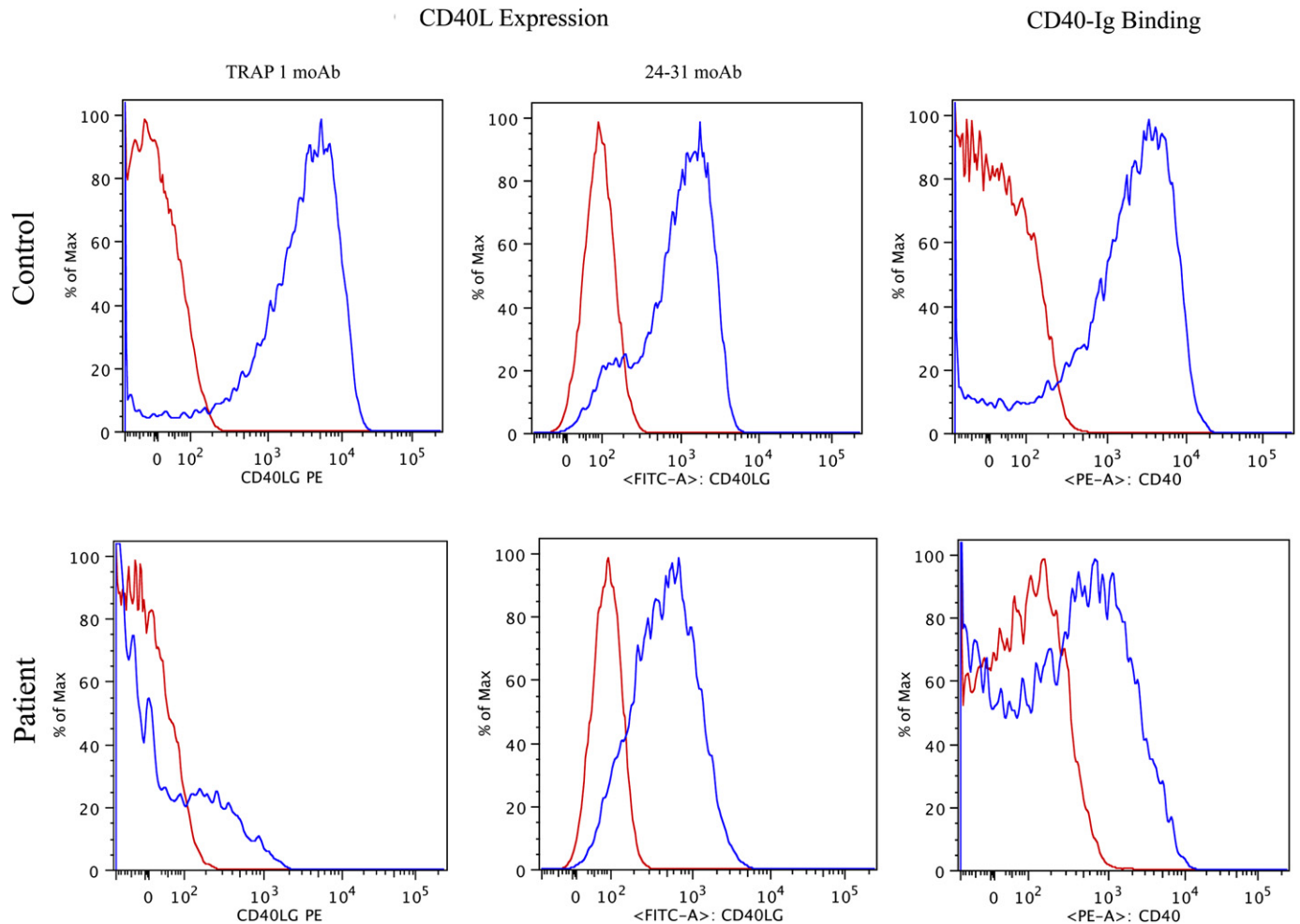


Figure 1. CD40L expression and CD40-Ig fusion protein binding. CD40L expression and CD40-Ig fusion binding was measured on unstimulated (red line) and on activated T cells (blue line). CD40L expression was measured using 2 different monoclonal antibodies that recognize different epitopes. CD40L expression was decreased on activated CD4⁺ T cells with the TRAP 1 monoclonal antibody, 22.6%, and normal with the 24–31 monoclonal antibody, 29.7%. CD40-Ig functional binding was decreased, 19.1%.

Discussion

After initial immunologic evaluation, common variable immune deficiency seemed most likely in this patient; however, we suspected CD40L deficiency given the medical history of parvovirus-induced aplastic anemia.⁴ The laboratory investigation indicated a CD40L gly219arg missense mutation, decreased CD40L expression on activated T cells, and decreased CD40-Ig binding, consistent with a milder form of X-HIGM syndrome.

However, controversy exists over whether this missense mutation is responsible for X-HIGM syndrome, because this missense mutation may be found as a normal variant seen in 1% of the normal population (Correlagen Diagnostic Laboratory). Interestingly, this variant is present more commonly in healthy females but when compared among the affected individuals it is seen more commonly in male patients with X-HIGM than females. Recently, Martinez-Martinez et al⁶ reported that the gly219arg mutation was seen in the mother and grandmother of 2 siblings who were diagnosed with X-HIGM. Interestingly, these patients did not have this mutation, but their mother has this mutation that resulted in decreased CD40L function. Aghamohammadi et al⁷ also reported a 32-year-old male patient with X-HIGM who was also found to have gly219arg mutation. This patient was diagnosed with X-HIGM at the age of 25 years, and he also appeared to have a milder form of the disease. He is the oldest survivor with X-HIGM in this case series of 23 patients.

Barnhart et al⁸ and Rigard et al⁹ separately reported that this mutation caused changes in the amino acid sequence and was associated with decreased function of CD40L. Thusberg et al¹⁰ reported that the amino acid glycine (G219) plays an important role in complex stabilizing interactions in CD40L trimerization, and when it is substituted with arginine the protein function was affected. Thus, we propose that the gly219arg missense mutation results in protein conformational changes of CD40L that results in decreased expression and function.

In conclusion, we believe that in our patient; X-HIGM was caused by missense mutation gly219arg, resulting in decreased function of CD40L but not complete absence of the CD40L function, leading to a milder form of X-HIGM disease. He is currently being treated with intravenous immunoglobulin. Treatment of more severe form of X-HIGM includes immunoglobulin replacement, prophylactic antibiotics to prevent opportunistic infections, and immune reconstitution with hematopoietic stem cell transplantation.² However, in our patient, CD40L expression and function is reduced but not absent, and T cell function is intact. Therefore, stem cell transplantation may not be necessary, and intravenous immunoglobulin treatment is sufficient.

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