A Novel Activation-Induced Cytidine Deaminase Mutation in an Adult with Hyper-IgM Syndrome

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The hyper-immunoglobulin M (HIGM) syndromes are a group of immunodeficiencies that exhibit low or absent levels of immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin E (IgE), and normal to high levels of immunoglublin M (IgM) [1]. These syndromes are characterized by inherited defects in genes encoding for the CD40L or CD40 molecule, or defects in class-switch recombination (CSR) in B cells [2]. Activation-induced cytidine deaminase (AID) is a protein that is required for CSR in B cell differentiation [3,5]. A mutation in the activation-induced cytidine deaminase (AICDA) gene that encodes AID, causes the autosomal recessive (AR) form of HIGM syndrome known as HIGM2 [2,4]. This syndrome results in recurrent sinopulmonary infections by encapsulated bacteria, meningitis, gastrointestinal infections, lymphoid hyperplasia, and autoimmune conditions [2]. We report a case of a novel autosomal dominant (AD) mutation in the AID gene that has not been previously reported.

A 38-year old female with asthma, chronic obstructive pulmonary disease (COPD) and untreated HIGM syndrome, was transferred to our facility for extra-corporeal membrane oxygenation (ECMO) therapy. She was treated for pneumonia one week prior and had attempted to use a nebulizer at home without significant improvement. She presented to an outside emergency room with shortness of breath and productive cough, and was diagnosed with multi-lobar community acquired pneumonia. She initially failed bilevel positive airway pressure (BiPAP) and was intubated. She decompensated, went into pulseless electrical activity arrest, and was resuscitated. She developed refractory hypoxemia, hypercarbia, and distributive shock resulting in transfer to our facility for ECMO. Upon arrival, she was treated with broad spectrum antibiotics and pressors, and begun on ECMO. Due to her critical condition and reported HIGM syndrome, she also received 40 grams of intravenous (IV) Gamunex 10%, (600mg/kg). In time, her medical history revealed a long history of recurrent infections including several pneumonias, hospitalizations, and intubations at multiple facilities in recent years. Additionally, two of her sons had a history of recurrent severe infections, including sepsis, osteomyelitis, otitis media, and pneumonia, and had been receiving intravenous immunoglobulin (IVIG) infusions monthly for reported HIGM syndrome. In the past, due to cost, the patient had deferred her own recommended IVIG therapy in favor of treatment for her sons. Her sons had only recently been genetically diagnosed with a HIGM syndrome at an outside pediatric hospital. Eventually she was weaned from ECMO, followed by weaning from a persistent invasive ventilation requirement via percutaneous tracheostomy, and ultimately discharge to home.

A limited immunodeficiency work up revealed IgG less than 300 mg/dL, IgA less than 50 mg/dL, and an elevated IgM of 767 mg/dL. Total serum IgE was normal. Flow cytometry revealed a normal T-cell population. Extended B-cell flow revealed normal CD19 cells but reduced CD27+ cells, reduced CD38+IgM- cells, and elevated CD19+IgM+ cells. Mitogen lymphocyte stimulation response to ConA was normal. Further genetic workup revealed heterozygous c.552T>A (Y18X) mutations in the AICDA gene. The heterozygous mutation and affected parent and children supported an AD inheritance of a dominant-interfering mutation in the AICDA gene.

There are currently six known forms of HIGM [6]. HIGM1 is the most common type and is due to an X-linked mutation in the gene encoding CD40L leading to recurrent bacterial infections, opportunistic infections, chronic diarrhea, and liver damage [4,6,10]. HIGM3 is the second most common type and is due to an AR mutation in the CD40 gene, resulting in bacterial and opportunistic infections [6,10]. HIGM4 is a genetically undefined type with no defect seen in CD40L, CD40, AID, or UNG, and presents with a milder clinical phenotype [6]. HIGM5 is the third most common type and is due to an AR mutation in the UNG gene, solely affecting CSR and resulting in increased bacterial infection and lymphoid hypertrophy [6]. HIGM6, is due to an X-linked mutation in the NEMO gene, resulting in the development of inflammatory diseases [6,10].

HIGM2 is the least common type and is due to a mutation in the AICDA gene, affecting both CSR and SHM [6]. These patients typically present with sinopulmonary and gastrointestinal infections [10], but rarely with opportunistic infections [2]. This defect in CSR and SHM also results in lymphoid hyperplasia due to enlargement of germinal centers with proliferating B cells [6,10]. However, this finding has also been seen in HIGM patients, with or without defects in AID [9]. The usual cause of HIGM2 is a homozygous, or less commonly a compound

heterozygous mutation in the AICDA gene [3]. Since 2003, single point heterozygous mutations have been found in the C-terminal part of AID, which changes Arg190 to a stop codon in exon 5 of the AID gene (R190X) [3]. This results in a defect with CSR, but not SHM [3]. [3]. In Brazil, a new recessive mutation in HIGM2 was seen in two sisters with consanguineous parents [7]. In Finland, a founder mutation for AID deficiency due to a rare recessive allelic variant in the AID gene was found [8]. In our literature review, patients have not been found with this patient's single point mutation.

Here we describe a mother and her two sons who presented with a HIGM diagnosis. A genetic work up revealed a genotypically novel activation-induced cytidine deaminase (AID) mutation in the patient and her sons, which has not been reported previously in the literature. This mutation is predicted to cause premature termination of the C-terminal portion of the protein. Since our patient shares a heterozygous mutation with clinical symptoms of immunodeficiency, these findings support the notion that the Y184X mutation in AICDA acts in a dominant negative mode. In the future, finding additional AD HIGM patients with AICDA mutations may help clarify the clinical spectrum of this disorder and further define the functional consequences of this mutation. We hope to show this biochemically with other collaborators.

Table I. Immune Assessment Cell Subsets

Quantitative Immunoglobulins	Level	Reference
IgG	<300 mg/dL	700-1600
IgA	<50 mg/dL	70-400
IgM	767 mg/dL	40-230
T Cells	Level	Reference
CD3+	1161 cells/mcL	550-2202
CD3+ (%)	82%	58-86%
CD4+	565 cells/mcL	365-1437
CD4+ (%)	40%	32-64%
CD8+	639 cells/mcL	171-846
CD8+ (%)	45%	15-40%
CD45+ (total lymphocyte count)	1.42 thou/mcL	0.82-2.84
B Cells	Level	Reference
CD19+	225 cells/mcL	90-539
CD19+ (%)	15.7%	2.8-11.74%
CD20+	229.6 cells/mcL	95-580.8
CD20+ (%)	16.2%	3.2-16.8%
CD21+	205.8 cells/mcL	85-533
CD21+ (% of CD19+ cells)	92.5%	92.1-99.6%
CD27+IgM-IgD-	7.3 cells/mcL (low)	18-145
CD27+ (%)	0.2% (low)	2.3-26.5%
CD38+IgM-	0 cells/mcL (low)	7-153
CD38+IgM- (%)	0% (low)	4.1-42.2
CD19+IgM+	214.3 cells/mcL	37-327
CD19+IgM+ (% of CD19+ cells)	96.3% (high)	26-78

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