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Case Report

A Case Report of Hyper-IgM Syndrome Patient with Normal Serum IgA Level

Amer Khojah[1*]; Lauren Gunderman[2,3]; Mohammad Binhussein[1]; Ameera Bukhari[4]; Imad Khojah[5]

[1]College of Medicine, Umm Al-Qura University, Saudi Arabia

[2]Division of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[3]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[4]College of Science, Taif University, Saudi Arabia

[5]Faculty of Medicine, King Abdulaziz University, Saudi Arabia

***Corresponding author: Amer Khojah, MD**
Pediatrics Department, College of Medicine, Umm Al-Qura University, Saudi Arabia, PO Box 715, Al Abdeyah, Makkah, 24381, Saudi Arabia.
Phone: +966 56 504 4998
Email: amkhojah@uqu.edu.sa

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Abstract

Hyper IgM syndromes are a group of disorders characterized by defective T and B cell interactions resulting in the lack of Immunoglobulin class switching. The most common hyper IgM syndrome is CD40 ligand (CD40L) deficiency. Patients with CD40L deficiency present with recurrent infection, neutropenia, and autoimmunity. These patients typically have absent serum IgA and IgG due to the class switch defect. Here we present a case of CD40L deficiency who presented with oral ulcers, failure to thrive, and recurrent fever. His laboratory evaluation was notable for intermittent neutropenia, elevated IgM (397mg/dl), normal IgA (78mg/dl) and low IgG (51mg/dl). Antibody responses to tetanus and measles were undetectable despite full vaccination. Whole exome sequencing showed a likely pathologic variant in CD40LG (c.674 T>C, p.L225S). This case highlights the importance of considering the diagnosis of hyper IgM syndrome in the appropriate clinical setting, even if the patient has a normal serum IgA level.

Keywords: Hyper IgM syndromes; IgA; CD40LG; Pneumatosis intestinalis

Abbreviations: CD40L: CD40 ligand; XHIGM: X-linked Hyper-IgM Syndrome; PJP: Pneumocystis Jiroveci Pneumonia; GI: Gastrointestinal; CRP: C - Reactive Protein; Hib: Haemophilus Influenzae Type b; IVIG: Intravenous Immunoglobulin; NK: Natural Killer, G-CSF Therapy: Granulocyte Colony Stimulating Factor Therapy; COVID-19: Corona Virus Disease of 2019; HSCT: Hematopoietic Stem Cell Transplantation

Introduction

Hyper IgM syndromes are a group of inborn error of immunity disorders that are characterized by the lack of Immunoglobulin class switching due to defective T and B cell interactions [1]. Hyper-IgM syndrome patients typically have markedly reduced serum concentrations of IgG and IgA with normal to elevated levels of IgM and normal B cell count [1,2]. The most common hyper IgM syndrome is CD40 ligand (CD40L) deficiency which is due to mutation in the CD40LG gene located at the X chromosome (Xq26.3-27) [3]. The estimated incidence of CD40L deficiency, also known as X-linked hyper-IgM syndrome (XHIGM), in the United States is around 1:1,030,000 live births [4]. CD40L is expressed on CD4+ T cells upon activation and interacts with CD40, which is expressed constitutively by B cells [5]. This interaction leads to B cell class switching and somatic hypermutation (Figure 1) [5]. Patients with XHIGM typically present with respiratory tract infections, including Pneumocystis Jiroveci Pneumonia (PJP) in infancy [3,4,6]. In addition to typical bacterial infections, XHIGM patients are susceptible to opportunistic infections in addition to PJP, such as Cryptococcus, Candida, Histoplasma, Leishmania, and Cryptosporidium, which may lead to sclerosing cholangitis [4,7]. Other complications include neutropenia, autoimmunity, liver disease, and malignancy [6]. The immunology evaluation of XHIGM patients typically reveals normal to elevated levels of IgM with reduced or absent serum concentrations of IgG and IgA due to the class switch defect [2]. Here we report a case of XHIGM in a young body with oral ulcers, failure to thrive, recurrent fever, neutropenia, and normal serum IgA level. Although hyper-IgM syndromes classically present with absent serum IgA and IgG, the diagnosis should not be excluded in a patient with normal serum IgA level when suspicion for the diagnosis is high.

Case Presentation

A 20 months old boy with a history of congenital subglottic stenosis was admitted to the hospital for assessment of multiple symptoms, including failure to thrive, recurrent fever, rash, developmental delay, and oral ulcers. His parents reported low-grade fever (100.4-101 F) without documented infection almost

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every two weeks for the last few months with recurrent mouth ulcers. Imaging during admission revealed right middle lobe pneumonia, and he was transferred to the pediatric intensive care unit due to difficulty with extubation after a sedated MRI. Eventually, he was extubated after giving decadron. Pneumatosis intestinalis involving the ascending colon was also observed during admission.

Over the past six months, the patient had four bilateral ear infections but no previous cases of pneumonia or sinus infections. He experienced intermittent watery, non-bloody diarrhea lasting 2-3 days per episode, with normal stooling in between, for several months. A stool study ruled out cryptosporidium infection. The patient also had a history of delayed motor function (sitting at the age of 9 months, not yet walking at 20 months) and speech delay. He was exclusively formula-fed until six months of age when solids were introduced without issues. However, his interest in food decreased in the months leading up to the presentation, resulting in poor weight gain. At presentation, his weight and height were below the 3rd percentile. Dilation for subglottic stenosis was performed at 16 months of age without complications. He was not on daily medications at the time of admission, and his vaccines were up to date. The patient lived at home with his parents and two healthy sisters. There was no family history of consanguinity, immunodeficiency, infant or childhood death, autoimmunity, or Gastrointestinal (GI) disease.

The patient's laboratory evaluation was notable for intermittent elevated CRP (0.3-21mg/dl), intermittent neutropenia (ANC 190/uL) and microcytic anemia. His Immunoglobulin levels showed elevated IgM (397mg/dl), normal IgA (78mg/dl) and low IgG (51mg/dl). Antibody response to Hib, tetanus, measles, and all streptococcus pneumoniae serotypes were undetectable. Given his hypogammaglobulinemia and ongoing infection, 0.5g/kg of IVIG was given during admission. T and B cell flow cytometry with subsets were completed and showed normal CD4+T cell quantitation with CD8+T cell lymphopenia (390/mm3, reference range for age 750-3749/mm3) and normal quantitation of CD19+B cells and Natural Killer (NK) cells. B cell subsets showed decreased memory B cells, specifically with low isotype-switched memory B cells. For additional immune evaluation, given the clinical picture with recurrent infections, hypogammaglobulinemia and elevated IgM, CD40L expression was pursued and was markedly decreased on stimulated CD4+T cells (5%, reference range more than 85%) with intact ICOS expression. Whole exome sequencing showed a likely pathologic hemizygote variant in CD40LG (c.674 T>C, p.L225S) inherited from the patient's mother. The variant had not been observed in large cohorts such as Gnomad or ExAC at the time of this publication.

The patient started immune globulin replacement for hypogammaglobulinemia and received antibiotic prophylaxis with oral trimethoprim/sulfamethoxazole to reduce the risk of PJP infection, commonly seen in patients with Hyper IgM Syndrome due to cellular defects. There was initial improvement in infection frequency and energy level, and stem cell transplant was deferred based on the parents' preference. However, despite the dilation of subglottic stenosis in infancy, recurrent episodes of croup persisted. The patient experienced mild and intermittent neutropenia, and the mouth ulcers returned, occurring up to every other week and limiting oral intake. The Hematology team is currently discussing the benefits and risks of G-CSF therapy with the parents due to these ongoing complications.

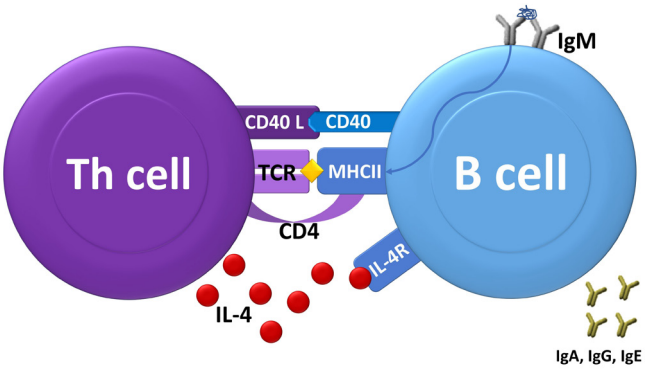

Figure 1: Diagram of T and B cell interaction. CD40-CD40 Ligand is required for T cell-dependent B cell activation and class switching from IgM to IgA, IgG, and IgE.

Two years after the patient's diagnosis, despite receiving IVIG and antibiotic prophylaxis with Bactrim, the patient continues to experience non-infectious complications such as intermittent neutropenia and oral ulcers, leading to pain, weight loss, and poor nutrition. The patient remains under close monitoring by Hematology for neutropenia and by Immunology for care management. Chest imaging has remained normal without bronchiectasis, and the patient has avoided opportunistic infections while on therapy.

Discussion

XHIGM is a rare primary immunodeficiency disease caused by mutations in the CD40LG gene on the X chromosome. Defects in CD40L (CD154) interfere with T cell activation and B cell class switching from producing IgM to IgA, IgG, or IgE. Although most patients with XHIGM have low to absent IgG and IgA, this is not a universal finding, as highlighted in this case. There are a few possible explanations for the normal serum IgA level on presentation. 1) IgA production could be a transient reaction to the active infection, as was documented in a case of hyper IgM syndrome with COVID-19 infection [8]. 2) IgA production could be due to the hypomorphic nature of the mutation; however, these patients usually have a milder phenotype and present later in life [9,10]. Of note, markedly low IgG in our patient may argue against this explanation. 3) As documented in a mouse model, plasmacytoid dendritic cells in the gut mucosa can induce IgA production independent of T cells by producing BAFF and APRIL [11,12]. Regardless of the mechanism of IgA production, it is important for the clinician not to rule out XHIGM prematurely just because the IgA level is normal.

Most XHIGM cases develop symptoms during infancy, and 90% are diagnosed by four years of age [4]. The diagnosis is typically made due to family history of XHIGM or when the patient suffers from an opportunistic infection such as PJP, which affects more than 50% of patients [4,13,14]. Other opportunistic infections such as Cryptococcus, Candida, Histoplasma, Leishmania, and Cryptosporidium have been reported [4,15-17]. Cryptosporidium is particularly problematic because it is linked with protracted diarrhea and sclerosing cholangitis, a leading cause of liver transplant and mortality in XHIGM [4,6,18]. Neutropenia affects around 60% of the XHIGM patients [4] and can lead to oral ulcers, as seen in our patient. G-CSF can be used for the treatment of neutropenia. Other complications include an increased risk of malignancy, particularly neuroendocrine tumor and cholangiocarcinoma [6]. There has been increased recognition of autoimmune complications in recent years. For example, Barbouche et al. documented the presence of anti-MIY3 antibody in 50% of XHIGM [19]. They speculated that this antibody

might play a role in the increased risk of sclerosing cholangitis [19]. Other reported autoimmune disease includes arthritis, thrombocytopenia, antiphospholipid syndrome, and inflammatory bowel disease [3,20-22]. In summary, XHIGM is a disease associated with significant infectious and non-infectious complications, which is associated with a mortality rate of 2.2% per year, according to a large international study [6].

There are three main approaches for XHIGM management: 1) conservative approach, 2) Hematopoietic Stem Cell Transplantation (HSCT) 3) gene therapy. The first approach is conservative therapy which consists of IgG replacement therapy, antibiotic prophylaxis, and G-CSF if needed for neutropenia. Oral trimethoprim/sulfamethoxazole is the antibiotic of choice in XHIGM, given patients are at increased risk of PJP infections [22]. This approach is typically used in milder cases of XHIGM or if there is no suitable match for HSCT. HSCT is a more curative approach that leads to a better quality of life, but there is no clear survival advantage [6]. The outcome of HSCT is getting better with time, especially if completed in younger patients with less infection; however, graft vs. host disease remains a major challenge [6,23]. Lastly, gene therapy and gene editing hold great promise for the treatment of XHIGM, with the potential of having a curative therapy without the risk of graft vs. host disease. There are many successful mouse models of CD40LG gene editing [24-26], but the use of CRISPR-Cas gene editing in human patients is still in the early stages.

Conclusion

Although hyper-IgM syndromes classically present with absent serum IgA and IgG due to class switch defect, the diagnosis should not be excluded just because the patient has a normal serum IgA level. Neutropenia, hypogammaglobulinemia, and chronic diarrhea should raise suspicion for hyper IgM syndrome.

Author Statements

Declaration of Interest

There is no potential conflict of interest, real or perceived, by any of the authors.

Consent for Participation and Publication

Verbal consent was obtained from the patient and parent.

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