Oxford Medical Case Reports, 2023, **2**, 55–59
https://doi.org/10.1093/omcr/omad005
Case Report

Hyper-IgM and acquired C1q complement deficiency in a patient with *de novo ATM* mutation

Adrian Y. S. Lee[1,2,3,*], Pei Dai[4,5,6], Leslie Burnett[4,5,6,7,8], Xiumei Wei[9], Fakhria Kakar[2,3], Thomas Ohnesorg[7] and Ming-Wei Lin[1,2,3,6]

[1]Department of Clinical Immunology & Allergy, Westmead Hospital, Westmead, NSW 2150, Australia
[2]Immunopathology, ICPMR, NSW Health Pathology, Westmead, NSW 2150, Australia
[3]Westmead Clinical School, University of Sydney, Westmead, NSW 2150, Australia
[4]Immunology Division, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia
[5]St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Darlinghurst, NSW 2010, Australia
[6]Clinical Immunogenomics Research Consortium Australasia, Garvan Institute of Medical Research, University of New South Wales, Darlinghurst, NSW 2010, Australia
[7]The Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia
[8]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, St Leonards, NSW 2065, Australia
[9]Sutherland Centre of Immunology, South Eastern Area Laboratory Services, NSW Health Pathology, Caringbah, NSW 2228, Australia
*Correspondence address. Department of Clinical Immunology & Allergy, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia. Tel: +61 2 8890 6933; Fax: +61 2 9891 3889; E-mail: Adrian.lee1@sydney.edu.au

Abstract

Hyper-IgM syndrome (HIGM) is a rare immunodeficiency phenotype that is usually accompanied by serious infections. We present a curious case of the incidental detection of HIGM in a 45-year-old male with complement C1q deficiency. He had relatively mild sinopulmonary infections, recurrent skin infections and lipomas in his adulthood. Investigations revealed normal enumeration of total peripheral blood B cells and reduced expression of CD40L on his $CD4^+$ T cells. C1q was noted to be absent, due to a peripheral inhibitor such as an autoantibody. Genomic sequencing of the patient and his parents revealed a novel, *de novo* heterozygous mutation in the *ATM* (ataxia telangiectasia mutated) gene although he displayed no clinical evidence of ataxia telangiectasia. This is a rare case of HIGM and acquired C1q deficiency. We present full phenotyping data that contributes to the growing understanding to these interesting immunodeficiencies.

INTRODUCTION

Hyper-IgM syndromes (HIGM) are a group of genetically defined syndromes characterized by recurrent and opportunistic infections and raised or normal IgM with low IgG and IgA. They are caused by the failure of B cells to undergo class switch recombination and/or somatic hypermutation [1]. We present a case of a man with an incidental HIGM phenotype and acquired complement C1q deficiency, on a background of congenital rubella. He presented with mild sinopulmonary infections, recurrent skin cancers and lipomas. Genetic testing revealed a novel pathogenic mutation in the *ATM* (ataxia telangiectasia mutated) gene.

CASE REPORT

A 45-year-old Caucasian male was referred to the Immunology clinic with an incidental laboratory finding of HIGM phenotype after being worked up for causes of abnormal liver function tests and a serum electrophoresis/immunofixation was performed. The patient was born term to non-consanguineous parents. As a neonate, he was admitted to neonatal intensive care unit for respiratory failure due to congenital rubella.

He had suffered from at least two hospitalizations for childhood pneumonias, slow-healing skin wounds and abscesses and unusually frequent growths of biopsy-proven lipomas. These were previously located at his right neck (>10 cm), left axilla (7.5 cm) and numerous small lipomas on his upper limbs and back measuring < 2 cm. In his adulthood, he reported at least three respiratory tract infections a year and recurrent non-melanomatous skin cancers.

His family history (Fig. 1) was remarkable for Mollaret's meningitis in his mother and sister. There was no other overt immunodeficiency or immune dysregulation history. Examination revealed preserved dentition and no focal neurological defects. He was overweight (body mass index 30.1 kg/m^2). Imaging studies showed no significant lymphadenopathy, hepatosplenomegaly or evidence of bronchiectasis.

Investigations (Table 1) revealed a mild hepatitis with preserved synthetic function. A liver biopsy revealed moderate lobular chronic inflammation and mild portal inflammation. He had raised polyclonal serum IgM and IgD, with undetectable IgG, IgG subclasses, IgA and IgE. CD40L expression was reduced on T cells relative to healthy controls. He had normal total memory B cells ($CD19^+CD27^+$) [28% (>11% of B cells)] with low class-switched memory B cells (Table 1). On flow cytometry, his B cells had detectable IgG and IgA on the surface—albeit slightly reduced compared to a control—indicating that our patient had a problem of immunoglobulin secretion and perhaps production (Fig. 2A).

Received: August 24, 2022. **Revised:** January 2, 2023. **Accepted:** January 6, 2023

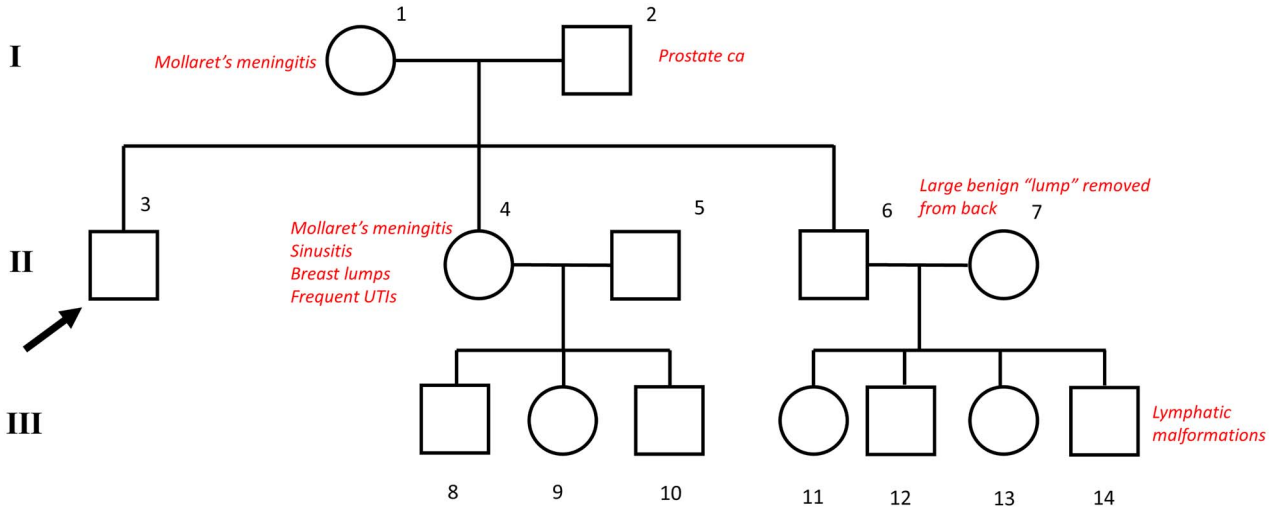

Figure 1. Family tree of the patient (II.3, arrow) and significant medical diagnoses. UTIs, urinary tract infections. Ca, cancer.

The patient had an absent CH50 but preserved AH50, suggesting an early classic pathway (C1q, C2 and C4) deficiency. Individual component testing revealed undetectable serum C1q but the presence of C1q on his monocytes (Fig. 2B). Anti-C1q IgG was not detected; therefore, a mixing study was undertaken. This was achieved by incubating 25 μl of patient sera or bovine serum albumin with 25 μl of C1q-replete control sera for 30 min at room temperature and assaying the levels of C1q by radial immunodiffusion assay. These data revealed reduced C1q complement 96 mg/l (expected 124–200 mg/l based on assay coefficient of variations) consistent with an acquired loss of C1q complement (e.g. an inhibitor in the patient's serum).

Parents–proband trio genomes were sequenced on the Illumina NovaSeq platform with 150 bp paired-end sequencing using DNA isolated from whole blood. Our patient demonstrated a *de novo* heterozygous frameshift variant in *ATM* [Chr11(GRCh37): g.108155193_108155200del; NM_001351834.2 (ATM):c.3986_3993del; p.(Gly1329Aspfs*2)], which is not known to gnomAD (v2.1.1). There were no pathogenic variations noted in key genes such as *C1QA, C1QB, C1QC, CD40, CD40LG* and *AICDA*.

Testing for complement components (including C1q) and serum immunoglobulins in his family members were all within normal limits. He declined a trial of intravenous immunoglobulin and was placed on a prophylactic trimethoprim/sulfamethoxazole tablet daily. He was diagnosed with fatty liver disease and remains well to this date with no serious infective complications.

DISCUSSION

In our patient, a novel *de novo* mutation in *ATM* was discovered. ATM is a protein involved in the regulation of DNA repair during the cell cycle and minimizes genetic 'damage'. Dysfunctional ATM causes an increased risk of cancer and the paediatric immunodeficiency, ataxia telangiectasia [2]. ATM is important in isotype switching by enhancing activation-induced cytidine deaminase activity [3], being a probable mechanism for its role in hypogammaglobulinaemia. Although heterozygous *ATM* mutations have been found associated with increased cancer risk [4], its links with lipomas and other skin cancers is less defined.

In addition, congenital rubella has been linked with acquisition of a HIGM phenotype in several patients [5, 6]. Congenital rubella is known to inflict multiple insults onto the developing fetus including cardiac defects, sensorineural hearing loss and immunological perturbations [7]. Patients with congenital rubella-induced HIGM have normal CD40L expression and function, normal *CD40LG*, *AICDA* and *UNG* sequencing, with the purported mechanism being a defect in antibody secretion from B cells [8, 9]. Our patient's CD40L expression was markedly reduced (Table 1), although his *CD40LG* sequencing did not reveal any pathogenic variations.

The acquired C1q deficiency is an interesting finding. One patient presenting with central nervous system systemic lupus erythematosus also had a homozygous *C1Q* mutation resulting in genetic deficiency and concomitant HIGM phenotype with recurrent infections [10]. How these two phenomena may be pathologically linked is unknown. Another report of HIGM and acquired C1q deficiency in activated phosphoinositide 3-kinase delta syndrome (APDS) speculated that increased apoptotic bodies may be a possible mechanism for increased consumption of C1q complement [11].

It is not clear at what point his HIGM arose but, given his congenital rubella and infections as child, it was perhaps present for many years. His serum immunoglobulins have not previously been tested. It is also unclear what relative contributions the congenital rubella and *ATM* mutation play in his phenotype as specific, functional studies of the mutation were not undertaken. It is possible that they both contribute to his disease pathogenesis. Indeed, resolution of congenital rubella-associated immunodeficiency over time has been described as the child clears the virus [9]. In our patient, there was no detectable rubella virus RNA in his peripheral blood by polymerase chain reaction, and no dynamic change in his anti-rubella IgM over 3 months, but we cannot exclude the presence of virus in other reserves.

In summary, we present a unique report of HIGM with C1q deficiency and an incidental *de novo ATM* pathogenic variant. A comprehensive immunological phenotype has been provided. To our knowledge, this is the first report of its kind. Future longitudinal and functional studies in our patient may shed light on his condition and our understanding of the robustness of the immune system.

Table 1. Summary of immunological investigations. L, result lower than normal. H, result higher than normal. ANA, antinuclear antibody. ENA, extractable nuclear antigens

Investigation	Result	Reference Range
Liver function tests		
ALT	170 U/l (H)	<50 U/l
AST	55 U/l (H)	<35 U/l
GGT	37 U/l	<50 U/l
ALP	84 U/l	<110 U/l
Albumin	49 g/l	35–50 g/l
INR	0.8	
Immunoglobulins		
IgG	<1.1 g/l (l)	6.6–15.6 g/l
IgA	<0.10 g/l (l)	0.80–4.40 g/l
IgM	7.14 g/l (H)	0.30–2.30 g/l
IgE	<2 U/ml (L)	0–113 U/ml
IgD	448 mg/l (H)	0–153 mg/l
Isohaemagglutinins (O+ blood)	Anti-A: 256 titre Anti-B: 512 titre	
23-valent Pneumococcal vaccine challenge	<3.5 ➔ <3.5 μg/ml (L)	>4-fold increase
Serum electrophoresis	No paraprotein	
ANA, anti-ENA, anti-dsDNA	Not detected (IgG)	
Rheumatoid factor	<4 IU/ml	<20 IU/ml
Flow cytometry (blood)		
T cells	58% of lymphocytes (L)	62–88%
$CD4^+$ T cells	14% of lymphocytes (L)	37–63%
$CD8^+$ T cells	34% of lymphocytes	10–39%
$CD19^+$ B cells	19% of lymphocytes	5–24%
Class-switched memory B cells ($CD19^+CD27^+IgM^-IgD^-$)	2.1% of B cells (L)	>8.0%
$CD21^{lo}$ B cells ($CD19^+CD21^{lo}CD38^-$)	23.6% of B cells (H)	<20.0%
NK cells	25% of lymphocytes	4–25%
$CD4^+CD25^+$ regulatory T cells	5.1% of T cells	5–10%
$\gamma\delta$ T cells	14% of T cells (H)	ca. 5%
CD40L expression of $CD4^+$ T cells	Reduced (~50%)	Normal
Lymphocyte proliferation to PHA	Reduced	Normal
Interferon gamma release assay—mitogen control	8.76 IU/ml	>0.5 IU/ml
NK cell function		
Chromium release cytotoxicity	Normal	Normal
CD107a expression	Normal	Normal
Neutrophil function		
Nitroblue tetrazolium test	Normal	Normal
Chemiluminescence assay	Normal	Normal
CD18 expression (on neutrophils)	Normal	Normal
Complement studies		
CH50[a]	1% (L)	>60%
AH50[b]	111%	66–129%
C1 esterase inhibitor quantitation	0.49 g/l (H)	0.22–0.38 g/l
C1 esterase inhibitor function	>130% (H)	70–130%
C1q	<35 mg/l (L)	118–238 mg/l
C2	29.9 mg/l (H)	14.0–25.0 mg/l
C3	1.34 g/l	0.74–1.57 g/l
C4	0.17 g/l	0.13–0.41 g/l
C5	>200.0 mg/l (H)	90.0–172.0 mg/l
C6	117.0 mg/l (H)	45.0–96.0 mg/l
C7	>110.0 mg/l (H)	55.0–85.0 mg/l
C8	146.0 mg/l	112.0–172.0 mg/l
C9	246.0 mg/l	125.0–265.0 mg/l
Mannose binding lectin	2224 ng/ml	>1300 ng/ml
Soluble C5b-C9 fragment	483 ng/ml (H)	<219 ng/ml
Anti-C1q IgG	Not detected	Not detected

[a]Total classical complement pathway activity. The patient's CH50 was measured by an enzyme-linked immunosorbent assay (ELISA)-based method. The patient serum is added into a microtitre plate well coated with complement classical pathway activators, and a neoantigen is detected chromogenically.
[b]Complement alternative pathway activity. Patient serum was loaded into an agarose gel containing chicken red blood cells, and the diameter of lysis ring was measured to determine the activity. The diameter is directly proportional to the activity of the alternate complement system.

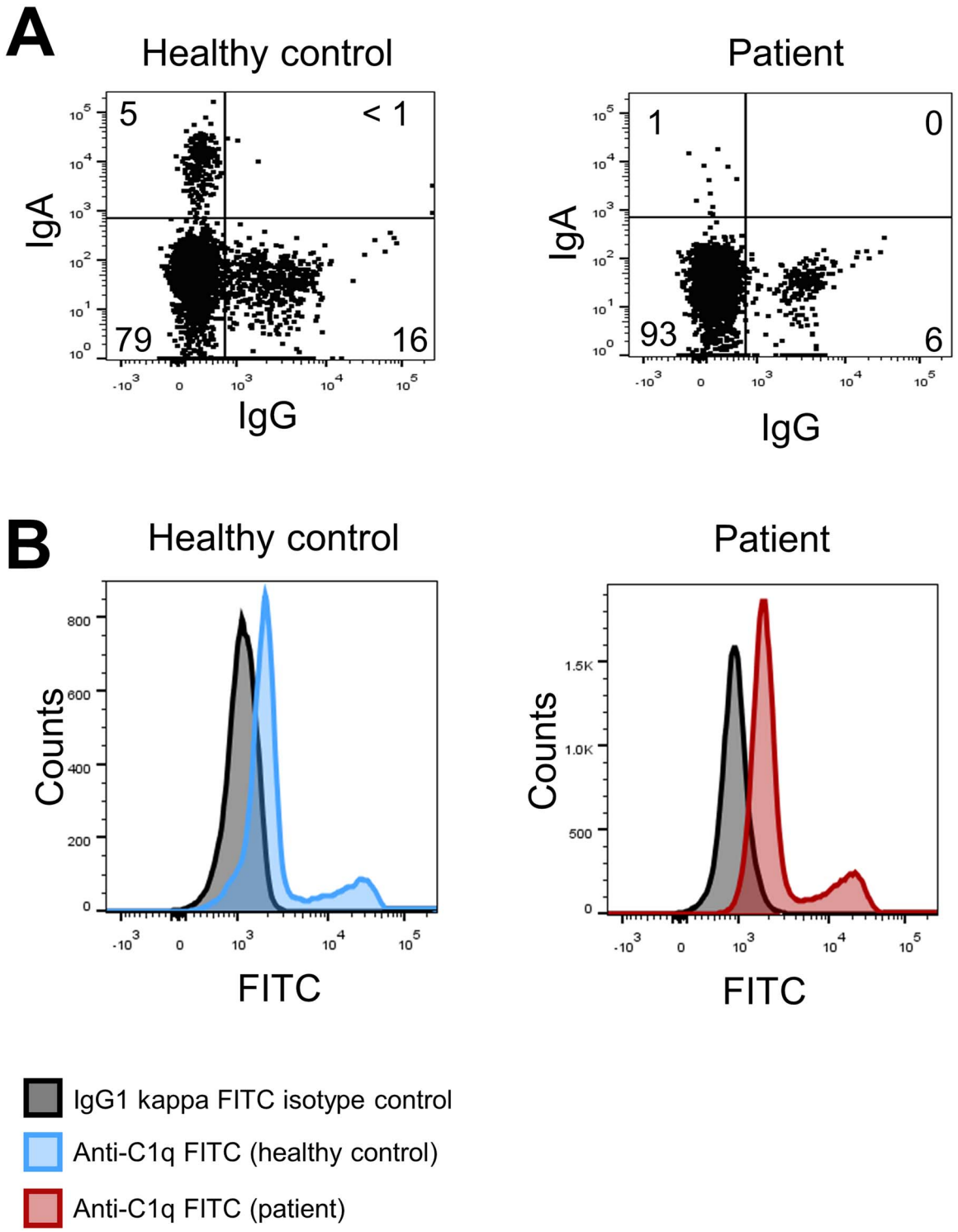

Figure 2. Evaluation of patient's B cell surface immunoglobulins (**A**), and monocyte C1q (**B**) by flow cytometry. (A) Patient and a healthy controls' peripheral blood mononuclear cells (PBMCs) were obtained by Ficoll density gradient centrifugation. PBMCs were then subjected to flow cytometry analyses. Plots are gated on lymphocytes, singlets, live cells and then $CD19^+$ events (B cells). Gates were set using fluorescence-minus-one (FMO) controls. (B) PBMCs were stained with anti-C1q-fluorescein isothiocyanate (FITC) or IgG_1 kappa-FITC isotype control. Histogram plots were gated on live cells and then $CD14^+$ monocytes.

ACKNOWLEDGEMENTS

Dr Logan Gardner (Westmead Hospital) is thanked for his technical contributions to the patient's case report.

CONFLICTS OF INTEREST STATEMENT

None declared.

GUARANTOR

AYSL accepts full responsibility for the work, had access to the data and controlled the decision to publish.

FUNDING

The authors declare that no funds, grants or other support were received during the preparation of this manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to patient privacy and confidentiality reasons. The data (minus patient identities) may be shared on reasonable request to the corresponding author.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No ethics approval required. Written, informed consent was obtained from the patient and his parents to participate.

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