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Case Report

A Novel Nonsense Homozygous Mutation in *SMARCD2* Gene Causing Specific Granulocyte Deficiency Type 2: Case Report

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Abstract

Background: Specific granulocyte deficiency type 2(SGD2) is a rare disorder of neutrophil defect caused by mutation in *SMARCD2* gene characterized by neutropenia, recurrent infections, skin and mucosal ulceration. *Objective:* We aim to describe a symptomatic patient with a novel homozygous nonsense variant in *SMARCD2* to help expand the phenotypic description of this rare disease. *Methods:* A retrospective chart review was conducted on our patient. Data collection included information on demographic, clinical and laboratory data. *Results:* We report a 4 years old boy with history of delayed separation of cord, recurrent sepsis, skin infections as well as mucocutaneous ulceration, gastrointestinal bleeding and Epstein Barr virus induced lymphoproliferation. He had variable neutropenia, bone marrow biopsy revealed hypogranular neutrophils and no blast excess. Whole genome analysis detected a novel homozygous variant in *SMARCD2* gene c.208C > T p.(Gln70*). *Conclusion:* This case report aims to provide insight on additional clinical and molecular features of SGD2. It also sheds light on potential role of *SMARCD2* gene in other immune cells.

Keywords

Inborn Errors of Immunity, Neutropenia, SMARCD2, Specific Granulocyte Deficiency

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1. Introduction

Specific granulocyte deficiency type 2 (SGD2) is a rare inborn error of immunity (IEI) caused by homozygous/double heterozygous mutations in *SMARCD2* gene (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily D, member 2) on chromosome 17q23. *SMARCD2* gene plays a critical role in granulocyte development and differentiation. Disruption in *SMARCD2* causes absence of neutrophil granules and manifests as recurrent infections and delayed umbilical cord separation [1]. The disorder is apparent from infancy, and patients may die in early childhood unless they undergo hematopoietic stem cell transplantation (HSCT). Most patients have additional findings, including development delay, mild dysmorphic features, tooth abnormalities, and distal skeletal defects. There are only a few cases reported worldwide [1-5]. Here, we are reporting a patient with unique features and a novel homozygous variant causing SGD2.

2. Methods

2.1. Patient Recruitment, Data Collection and Ethical Consideration

At the time of the study, this patient was under the care of the pediatric allergy and immunology division in Tawam Hospital, Al-Ain, United Arab Emirates (UAE). A retrospective chart review was conducted, the data collection process involved gathering demographic, clinical, laboratory, and genetic information.

The patient was recruited for genetic analysis (whole genome sequencing) as part of a research study "Elucidating the Molecular and Cellular Basis of Mendelian Diseases, Cardiovascular Diseases and Cancer in UAE". Prior to their participation, informed written consent was obtained from his parents. Ethical approval for this study was granted by the Ministry of Health and Prevention Research Ethics Committee, with reference number MOHAP/DXB-REC/JJJ/No.71/2020, in accordance with national regulations.

2.2. Case Presentation

This is a 4-year-old Syrian boy born at term to consanguineous parents. At 2 weeks of age, he developed necrotic ulcerative lesions extending to the fasciae of both thighs and left heal, diagnosed with necrotizing fasciitis. This was associated with *Pseudomonas* sepsis. He was managed with surgical debridement, intravenous antibiotics, and intravenous immunoglobulin (IVIG) therapy despite normal immunoglobulin levels. During his hospital stay he developed omphalitis that required surgical removal of the umbilical cord at day 40 of life.

Following that, he had multiple hospitalizations due to bacterial sepsis including *Pseudomonas aeruginosa and Acinetobacter lwoffi*. He also suffered from recurrent episodes of prolonged fever, profuse watery diarrhea with electrolyte imbalance and hemodynamic instability necessitating admissions to the intensive care unit. Stool microscopic evaluation was repeatedly negative except on one occasion when *Rota*virus was detected although he did not receive *Rota*virus vaccine. He only received BCG and hepatitis B vaccines at birth, followed by hexavalent vaccine (Hep B, Hib, IPV and DTap) and pneumococcal 13 at 19 months of age.

Stool elastase level was reduced, suggesting pancreatic insufficiency. The diarrhoea was non-responsive to Creon therapy so it was eventually discontinued.

At 24 months of age, he had episodes of lower GI bleeding that required blood transfusions. Mesalamine commenced with limited response. Upper and lower gastrointestinal endoscopies were performed at different intervals, the latest examination was done at 39 months of age. Endoscopic examination revealed an area of ulcerated, friable mucosa with cobble stoning appearance extending for almost 20 cm in the ascending colon (Figure 1). Histological examination showed mixed acute and chronic inflammatory changes including scattered plasma cells and occasional multinucleate giant cells and cryptitis. Epstein Barr Virus (EBV) was detected on colonic biopsy.

At the same time (39 months of age), he had prolonged fever associated with high inflammatory markers, high levels of serum ferritin and interleukin-6 with positive SARS-CoV2 antibodies. He was managed as multisystem inflammatory syndrome in children (MIS-C) with IVIG and steroids that resulted in dramatic improvement of diarrhoea and fever resolution. After four days of stopping steroids, the fever recurred with notable cervical and mediastinal lymphadenopathy, hepatosplenomegaly, Epstein Barr (EBV) viraemia (32,975 Copies/ml), elevated soluble interleukin-2 receptor, high ferritin, hypertriglyceridemia, and cytopenia. This was treated as EBV induced lymphoproliferative disease/Hemophagocytic Lymphohistocytosis (HLH) with Rituximab, IVIG and steroids. He achieved remission with 1 dose of Rituximab therapy that lead to consecutive negative EBV PCR results.

Other clinical features included failure to thrive (FTT), developmental delay (motor and speech delay), gingival hypertrophy, as well as recurrent aphthous ulcers. He also had compression fractures of several vertebrae.

Table1 briefly delineates the clinical features and isolated microorganisms during his illness.

Investigations showed mild to severe neutropenia with the range of (0.25 x 10^9/L -1.2 x 10^9/L) at different intervals. Bone marrow biopsy was performed at 6 months of age; reported as markedly hypercellular bone marrow (100%) with granulocytic dysplasia and grade 2 reticulin fibrosis. The study was repeated at 40 months of age and revealed that myeloid maturation was decreased but maturation to the neutrophil stage was seen. Neutrophil precursors showed variable hypogranular cytoplasm. Eosinophils and basophils were normal and there was no blast excess (Figure 2).

Immune work up revealed normal immunoglobulins, normal lymphocyte subset analysis (CD3, CD8, CD4, CD19 and CD16/CD56) and normal expression of the CD11/CD18 integrins. Dihydrorhodamine test was conducted several times but was technically difficult due to low neutrophil count.

Whole exome sequencing (WES) was performed at 5 months of age and was reported as negative.

Given the clinical and paraclinical findings despite negative WES, a neutrophil defect in number and function was highly suspected. He was therefore commenced on trimethoprim/sulfamethoxazole and itraconazole prophylaxis at 8 months of age. Following EBV viraemia and Rituximab therapy, immunoglobulin replacement therapy (IVIG) was recommended.

For the gastrointestinal manifestations, he was treated with elemental diet and Mesalamine as well as steroids during flare ups.

HSCT was recommended. HLA typing did not detect a matched family member so he was considered for haploidentical HSCT.

Whole Genome sequencing was performed at a later stage, at the age of 26 months.

2.3. Family Pedigree

Parents are second degree cousins, he has 2 siblings, one has speech delay (figure 3).

A maternal cousin was diagnosed with immunodeficiency and was receiving monthly injections abroad; however, a clear diagnosis was not established.

3. Genetic Analysis and Results

3.1. DNA Extraction and Whole-genome Sequencing (WGS)

Genomic DNA extraction from peripheral blood was performed using the QIAamp DNA Blood Mini Kit (Qiagen, Germany) on the QIAcube instrument. The DNA's quality was assessed using a Nanodrop One Spectrophotometer (Thermo Fisher Scientific, USA) and an Agilent 4200 TapeStation system (Genomic DNA ScreenTape Assay; Agilent Technologies, USA), while the quantity was measured using a Qubit 4.0 Fluorometer (Qubit dsDNA BR Assay kit; Invitrogen, USA).

WGS was conducted at the United Arab Emirates University (UAEU) Genomics Laboratory, UAE [6]. WGS library preparation was carried out using TruSeq DNA PCR-Free kit (Illumina, USA) in accordance with the manufacturer's protocol. Briefly, genomic DNA was fragmented using LE220-plus Focused-ultrasonicator (Covaris, USA) to generate 350 bp insert libraries. The DNA fragments of each sample were end-repaired and ligated to single-index adaptors. A Qubit 4.0 Fluorometer (Qubit dsDNA HS Assay kit; Invitrogen, USA) and an Agilent 4200 TapeStation system (D1000 and HS D1000 ScreenTape Assays; Agilent Technologies, USA) were used to determine the libraries' concentrations and fragment size, respectively. Prior sequencing, the libraries were accurately quantified using the KAPA Library Quantification kit (Roche, Germany) through qPCR on the QuantStudio 7 Flex system (Applied Biosystems, USA). The final quantified libraries were pooled, normalized, and then sequenced with paired-end reads (2 x 150 bp) on the NovaSeq 6000 System (Illumina, USA) employing S2 flow cell.

3.2. Bioinformatics Analysis and Variant Prioritization

A combination of in-house developed pipelines and Illumina DRAGEN Bio-IT Platform (Illumina, USA) were used for reads mapping, alignment and variant calling. VarSeq 2.2.4 software (Golden Helix, USA) was used for variants' annotation and filtration. The output data was filtered against all disease-causing variants in ClinVar (http://ncbi.nlm.nih.gov/clinvar), Human Genome Mutation Database (HGMD; http://hgmd.cg.ac.uk) [7] and variants with minor allele frequency (MAF) of less than 1% in the gnomAD database (http://gnomad.broadinstitute.org) [8]. Variants in homozygous, compound heterozygous, heterozygous and hemizygous states were all examined. Relevant pattern of inheritance based on clinical information and family history provided were taken into consideration to clinically correlate the identified variant/s. Filtered variant/s were interpreted using the American College of Medical Genetics and Genomics (ACMG) guidelines [9] and patient phenotype.

3.3. Variant Confirmation by Sanger Sequencing

The positive disease-causing variant was confirmed through Sanger sequencing. A primer pair, designed to flank the variant on exon 1 of the *SMARCD2* gene, was utilized with the Taq PCR Master Mix kit (Qiagen, Germany) for PCR amplification of the genomic DNA region of interest. The primer sequences were as follows: Forward: 5'-GAC GGG ACG GAG CGA TGT CG -3', Reverse: 5'-CCG GAG TTC CTC ATG CAT TCC-3', resulting in an amplicon size of 342 bp. The PCR amplification was performed according to the manufacturer's protocol. Following amplification, the ABI 3130xl Genetic Analyzer (Applied Biosystems, USA) was used for fluorescent automated sequencing employing the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, USA).

3.4. Genetic Analysis

Whole genome sequence analysis detected a novel homozygous stop-gained variant in *SMARCD2* c.208C>T (p.Gln70*), which is located on exon 1. The variant was observed in heterozygous state in both parents. Sanger se-

quencing confirmed the presence and zygosity of the variant in the patient and his parents. The p.Gln70Ter variant is a rare variant absent from large population studies such as gnomAD. The gene *SMARCD2* has multiple transcript variants and some of them have an alternative exon 1. However, *SMARCD2* isoform expression data from the GTEx (Genotype-Tissue Expression) Project [10] revealed that the stop-gained variant overlaps the most ubiquitously and abundantly expressed protein coding transcripts. The variant is predicted to result in loss-of-function of the encoded protein through protein truncation and/or nonsense mediated mRNA decay and null variants in *SMARCD2* have been established to be disease-causing. Considering all the available information, the variant was interpreted to be a likely pathogenic variant.

4. Discussion

SMARCD2 plays a crucial role in chromatin remodelling and through its interaction with transcription factor CCAAT/enhancer binding protein epsilon (CEBPε) facilitates recruitment of promoter gene for neutrophil granulocyte [1, 11]. *SMARCD2* is highly expressed in hemopoietic stem cells and immune cells including NK cells and CD8 T cells [11-12].

We report a novel homozygous variant in *SMARCD2* in a patient who shares clinical features with the previously described patients in the literature as shown in table 2 [1-5]. The shared features include FTT, GI bleeding, recurrent infections as well as skin ulceration. Our patient lacks other features previously described such as facial dysmorphism and skeletal dysplasia but had compression factures of several vertebrae. *EBV* induced HLH, is a unique presentation in our patient which is not typical of neutrophil defects. This presentation suggests impaired anti-viral immunity and an important role of *SMARCD2* in NK cell/CD8 granule development and function. Further testing/research is needed to investigate the role of *SMARCD2* in NK cell and CD8 cell function. Complications secondary to EBV infection such as HLH, lymphoma and lymphoproliferative disease are increasingly recognized in patients with IEI [13]. Rituximab therapy for EBV viremia is widely used in posttransplant lymphoproliferative (PTLD) disease [14] and is increasingly used in EBV induced lymphoproliferative disease in IEI. Histological findings of PLTD mirror that of EBV induced lymphoproliferative disease in IEI [15]. Our patient responded well to Rituximab as he achieved remission after 1 dose of therapy.

The risk of hypogammaglobulinemia post-rituximab therapy is determined by several factors including the number of doses, age at administration and concomitant use of high dose steroids. Therefore, close monitoring of immunoglobulin levels is recommended [16, 17]. Rituximab also affects the efficacy of prior vaccination [16, 17].

We recommended immunoglobulin replacement therapy as our patient received Rituximab at an early age and was not fully vaccinated in order to provide passive immunity as we could not fully understand his risk of acquiring viral infections.

SMARCD2 deficient neutrophils demonstrate impaired chemotaxis, impaired in-vitro killing of bacterial pathogen [2, 12] and defective neutrophil burst response to N-formylmethionyl-leucyl-phenylalanine. For our patient, the Dihydrorhodamine test evaluation of neutrophil burst, was technically difficult due to neutropenia.

In the intestines, neutrophils are involved in maintaining intestinal hemostasis through multiple mechanisms, one of which is facilitating mucosal healing [18, 19], therefore disruption in this function can result in mucosal inflammation and ulceration as seen in our patient.

Six of the reported patients with SMARCD2 deficiency underwent successful HSCT, which is being considered for our patient. He is currently on prophylactic Bactrim, Itraconazole, Immunoglobulin replacement and TPN for FTT.

5. Conclusions

In summary we report a novel variant in *SMARCD2* causing SGD2 deficiency. We hope that this description will aid in expanding the clinical and molecular characteristics of this disorder. Further research is needed to better understand SGD2 deficiency and elucidate the role of *SMARCD2* in other immune cells**.**

Abbreviations

SGD2	Specific Granulocyte Deficiency Type 2
IEI	Inborn Error of Immunity
HSCT	Hematopoietic Stem Cell Transplantation
IVIG	Intravenous Immunoglobulin
EBV	Epstein Barr Virus
FTT	Failure to Thrive
PTLD	Posttransplant Lymphoproliferative Disease

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Author Contributions

Amna Ali Al Kuwaiti: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing

Haifa Al Awadi: Investigation, Writing – original draft, Writing – review & editing

Praseetha Kizhakkedath: Performed variant annotation, filtration, NGS data analysis and interpretation Whole exome sequencing (DNA extraction, library preparation, and sequencing)

Ibrahim Baydoun: Investigation, Methodology, Validation

Mohammed Tabouni: Investigation, Methodology, Writing – review & editing

Hiba Alblooshi: Funding acquisition, Project administration, Writing – review & editing

Fatma Al-Jasmi: Funding acquisition, Project administration, Writing – review & editing

Aisha Al Shamsi: Conceptualization, Investigation, Writing – original draft, Writing – review & editing

Hiba Mohammed Shendi: Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing

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Data Availability Statement

Data generated for this study are included in the manuscript. Any further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix

Table 1. *Clinical features, isolated microorganism and management in our patient.*

Age	Diagnosis	Isolated organism (site)	Management
2 weeks	Necrotizing fasciitis, sepsis	Pseudomonas aeruginosa (blood)	Surgical debridement, IV antibiotics and IVIG
1.5 months	Omphalitis	-	Surgical removal and IV antibiotics
2.5 months	Sepsis and acute gastroenteritis	*Acinetobacter lwoffi* (blood) *Rota virus* (stool)	IV antibiotics
3 months	Sepsis, perianal ulcerative lesions and acute gastroenteritis, dehydration, electrolyte abnormalities	*Rota virus* (stool), *Klebsiella pneumoniae* (skin)	IV antibiotics
6 months (prolonged admission)	Sepsis, chronic diarrhea, electrolyte abnormality, anemia required transfusion, pericarditis, right ileofemoral thrombosis, Osteomyelitis of the sacroiliac, foot abscess	*Enterobacter species* (foot wound)	Multiple courses of antibiotics, transfusion Ibuprofen for pericarditis Enoxaparin for thrombosis
10 months	Decompensated shock, coagulopathy electrolyte imbalance Acute gastroenteritis, upper respiratory tract infection	*Pseudomonas aeruginosa* (blood) *Rota* (stool) *RSV* (nasopharyngeal)	IV antibiotics, inotropic support, hydrocortisone Vitamin K and FFP
13 & 15.5 months	Acute gastroenteritis sepsis	Negative	IV antibiotics
16 months	Perianal abscess	Negative	IV antibiotics
20 &22 months	Febrile neutropenia, sepsis	Negative	IV antibiotics
24 months	Enteritis, colitis, ulcers in the ulcers seen the rectosigmoid	Negative	IV antibiotics, blood transfusion
29 months	Colitis	Negative	IV Antibiotics and blood transfusion
30 months	Chronic/ fungal sinusitis, mild chronic hepatitis Suspected IBD/ Chron's, sepsis	*Pseudomonas aeruginosa* (sputum) *Enterobacter aerogenes* (blood)	IV antibiotics, IV anti-fungal, G-CSF Mesalamine
38 months	Septic shock, EBV induced lymphoproliferative disease / HLH, MIS-C, bloody diarrhea	EBV PCR (blood), Pseudomonas aeruginosa (blood) *Influenza A* (nasopharyngeal aspirate)	steroids, rituximab, IVIG, blood transfusion

Table 2. Clinical and gene mutation described in patients with specific granulocyte deficiency.

Reference	Number of patients	Age of onset	Clinical features	Variant in SMARCD2
1	4	Neonate	Delayed separation of umbilical cord, recurrent bacterial infections (pneumonia, septicemia), chronic diarrhea, anemia, thrombocytopenia, developmental delay, brittle dysplastic nails, mild distal skeletal anomalies, irregularly placed teeth, dysmorphic features	c.118+1G>A c.401+2T>C c.414_438dup
2	1	Infancy	Delayed umbilical cord separation with omphalitis, sublingual ulcer, chronic diarrhea, recurrent respiratory infections, FTT, developmental delay	c.118+1G>A
3	1	Neonate	Neonatal cholestasis, hypotonia, delayed cord separation, recurrent bacterial and fungal infections, dysmorphic features	c.511 C>T
4	1	Infancy	Delayed umbilical cord separation, recurrent infections (pneumonia and diarrhea), aphthous stomatitis, lymphadenopathy, dysmorphic features	c.93delG
5	1	Infancy	Recurrent infections (chronic rhinosinusitis, recurrent otitis media, sepsis, fungal infections, multiple superficial skin abscesses and deep cellulitis), lymphadenopathy, chronic stomatitis, vaginal, rectal ulcers, GI bleeding, post-infectious glomerulonephritis	c.217C>T c.1081del
Our patient	1	Neonate	Delayed separation of umbilical cord, recurrent bacterial infections (sepsis), chronic diarrhea, recurrent ulcerative lesions including the rectum, HLH secondary to EBV infection, Lymphadenopathy, lower GI bleeding	c.208C>T

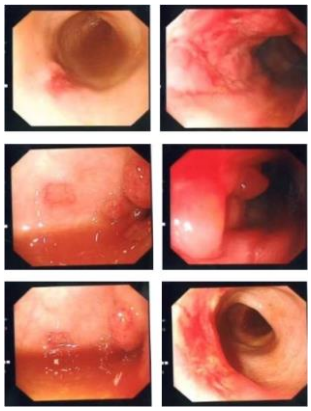

Figure 1. Colonoscopy showing multiple ulcers.

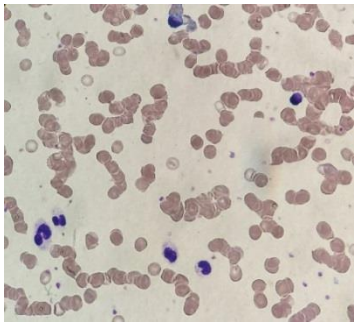

Figure 2. Bone marrow biopsy showing neutrophil precursors with hypo granular cytoplasm.

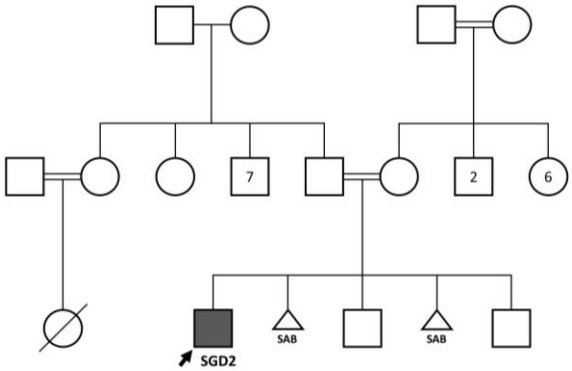

Figure 3. The pedigree chart of the enrolled family.

Male and female are represented with squares and circles, respectively. The proband is denoted by a black arrow. SGD2, specific granulocyte deficiency type 2; SAB, spontaneous miscarriage.

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