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CASE REPORT PEER REVIEWED | OPEN ACCESS

Rare encounter of Hirschsprung's disease and *CARD11* mutation: A diagnostic challenge

Jareatha Abdul-Raheem, Lauren Gabreski, Meredith Schuldt, Karla Adams

ABSTRACT

Introduction: Hirschsprung's disease (HD), a congenital condition characterized by aganglionosis, is associated with enterocolitis, which requires repeated antibiotic exposure to drugs associated with drug-induced lupus (DIL). Drug-induced lupus mimics systemic lupus erythematosus (SLE) but typically resolves upon discontinuation of the triggering medication. *CARD11* is essential for lymphocyte signaling and immune regulation, and its mutations are associated with immune disorders.

Case Report: A five-year-old male with HD and Hirschsprung-associated enterocolitis (HAEC) developed symptoms of DIL, including malar rash, fatigue, while taking cephalexin. During the evaluation, the patient tested positive for SLE-associated autoantibodies and a *CARD11* mutation, making it difficult to determine the origin of the symptoms. Resolution of symptoms and laboratory abnormalities after stopping cephalexin administration made DIL the probable cause.

Conclusion: Through this case, we hope to further elucidate the connections between HD, DIL, and *CARD11* mutation and demonstrate the diagnostic challenge with genetic mutations in the context of autoimmune dysfunction.

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INTRODUCTION

Hirschsprung's disease (HD) is a congenital disorder characterized by the absence of the Meissner and Auerbach autonomic plexus in the intestinal wall [1]. In children, HD increases the risk of Hirschsprung-associated enterocolitis (HAEC), a severe intestinal infection [2]. Hirschsprung-associated enterocolitis typically requires prolonged and repeated antibiotic interventions to manage severe infections [2], setting the stage for potential autoimmune reactions, such as drug-induced lupus (DIL). Drug-induced lupus mimics systemic lupus erythematosus (SLE) with symptoms such as rash, joint pain, and systemic inflammation, which usually resolve upon discontinuation of the triggering medication [3].

CARD11, also known as caspase recruitment domain-containing protein 11, acts as an essential signal transducer from the cell surface antigen receptor on B or T cells to the IκB kinase (IKK) [4–6], which is important for lymphocyte activation during the adaptive immune response. Mutations in the *CARD11* gene can predispose individuals to a variety of immune disorders, such as immunodeficiency 11A, common variable immunodeficiency, hypogammaglobulinemia,

immunoregulatory poly-endocrinopathy enteropathy X-linked (IPEX)-like syndrome, and severe atopic diseases, such as atopic dermatitis, asthma, and eosinophilic esophagitis [7, 8].

This patient presented with clinical features suggestive of HD, DIL, and a *CARD11* phenotype and explored the diagnostic challenges that can occur when genetic variants such as *CARD11* and concomitant autoimmune complications are involved. Through this study, we aim to increase our understanding and guide more targeted approaches to manage such complex medical scenarios.

CASE REPORT

A 5-year-old male patient of Hmong ancestry was born via uncomplicated spontaneous vaginal delivery. On the second day of life, he experienced delayed passage of meconium. He was diagnosed with total colonic HD via biopsy (suction method), which necessitated a stay in the neonatal intensive care unit for the first six weeks of life for abdominal distension. At eight months of age, the patient underwent colonic resection with ileorectal pull-through without covering stoma and anastomosis (the Duhamel procedure). He had a medical history of multiple recurrent enterocolitis infections, approximately 3–4 per year since birth. He received all the recommended childhood immunizations. At four years of age, the patient underwent pouch revision and end-ileostomy with a mucous fistula. The stoma was not reversed. The pouch revision was complicated by enterocolitis, requiring hospital admission for intravenous antibiotics. After discharge, the patient was prescribed trimethoprim-sulbactam, which was shortly discontinued, and cephalexin treatment was started. Three weeks after admission, while still taking cephalexin, the patient developed persistent fever, lethargy, and rash on the face (malar distribution) and arms, raising concerns regarding possible DIL (Figure 1).

Laboratory evaluation was significant for antinuclear antibody (ANA), double-stranded DNA (dsDNA), ribonucleoprotein, Smith, and antichromatin antibodies, raising concerns for SLE (Table 1). Notably, his immunodeficiency workup was significant for an initially low total complement activity (CH50), but otherwise a normal complete blood count, complement component 3 (C3), complement component 4 (C4), quantitative immunoglobulins (IgA, IgG, and IgM), and quantitative lymphocytes. Further analysis via whole-exome sequencing identified mutations in *CARD11*, *ATAD3A*, *TBCE*, and *RYRI* genes (Table 2). Therefore, cephalexin was discontinued as a precaution. Because of concerns about SLE, the patient was briefly started on prednisone, methotrexate, and hydroxychloroquine, and his symptoms significantly improved after two months of therapy. Consequently, the patient was gradually weaned off these medications. At follow-up one year later, the patient remained symptom free despite stopping therapy for more than one year. Follow-up laboratory tests one year after cephalexin administration showed normalization of the prior abnormal CH50, ANA, and autoantibody levels (Table 1). To evaluate primary immunodeficiency, flow cytometry was performed to access lymphocyte subsets (B cells, T cells, and natural killer cells). Lymphocyte subset analysis was within the standard reference range for all cell lines (Table 1). Ultimately, the patient's symptoms were attributed to DIL, and his infectious history was attributed to his HD diagnosis. However, the effect of his *CARD11* mutation remains unknown.

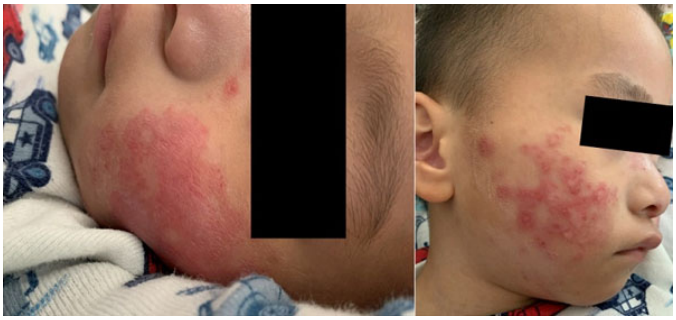

Figure 1: Malar rash distribution observed in the patient during active symptoms of drug-induced lupus.

DISCUSSION

This case demonstrates the diagnostic challenges that occur when a congenital disorder such as HD intersects with genetic predispositions to immune dysregulation, such as a paternally inherited *CARD11* mutation, and environmental exposures like medications that can trigger autoimmune reactions. The overlapping clinical features and laboratory findings makes it difficult to differentiate between primary autoimmune diseases and medication-induced conditions necessitating a nuanced and comprehensive approach.

Interplay between Hirschsprung disease, *CARD11* mutation, and autoimmunity

Hirschsprung's disease is characterized by the absence of ganglion cells in segments of the intestine, leading to functional bowel obstruction and an increased risk of Hirschsprung-associated enterocolitis (HAEC) [1]. Our patient, diagnosed with total colonic HD, experienced recurrent episodes of HAEC requiring multiple hospitalizations and prolonged antibiotic therapy, including cephalexin. The use of antibiotics, while essential for managing infections, introduces the risk of adverse drug reactions, including drug-induced lupus (DIL) [3].

Simultaneously, genetic testing revealed a duplication of exons 2–17 in the *CARD11* gene, affecting the caspase activation and recruitment domain (CARD) and coiled-coil (CC) domains critical for lymphocyte activation and immune signaling [4, 5]. *CARD11* mutations have been

Table 1: Summary of routine blood tests and immunological investigations

Laboratory test	Onset of symptoms	One year off cephalexin	Reference values
ANA	Positive	Negative	Negative
dsDNA	24 IU/mL	2 IU/mL	0–9 IU/mL
Ribonucleoprotein	3.9 AI	0.5 AI	0.0–0.9 AI
Anti-Smith Ab	>8.0 AI	0.2 AI	0.0–0.9 AI
Antichromatin	>8.0 AI	0.2 AI	0.0–0.9 AI
Anti-SCL-70 nuclear Ab	<0.2 AI	<0.2 AI	0.0–0.9 AI
Anti-SS-A Ab	<0.2 AI	<0.2 AI	0.0–0.9 AI
Anti-SS-B Ab	<0.2 AI	<0.2 AI	0.0–0.9 AI
Anti-Jo 1 Ab	<0.2 AI	<0.2 AI	0.0–0.9 AI
Anti-Centromere	<0.2 AI	<0.2 AI	0.0–0.9 AI
IgG	1510 mg/dL	946 mg/dL	504–1464 mg/dL
IgA	84.0 mg/dL	99 mg/dL	27–195 mg/dL
IgM	107 mg/dL	52 mg/dL	24–210 mg/dL
C3	120 mg/dL	NA	90–180 mg/dL
C4	20 mg/dL	NA	10–40 mg/dL
CH50	17 U/mL	>60 U/mL	>41 U/mL
CD3/CD8	NA	19.054%	16.000–44.000%
CD3+	NA	69.510%	56.000–88.000%
CD3–/CD56	NA	16.331%	3.000–27.000%
CD4/(CD8&CD3)	NA	2.320	0.600–4.400
CD3–/CD19	NA	13.223%	6.000–27.000%
CD3/CD4	NA	44.197%	28.000%–62.000%

Abbreviations: ANA, antinuclear antibody; dsDNA, double-stranded deoxyribonucleic acid; Ab, antibody; Anti-SCL-70, anti-topoisomerase I; Anti-SS-A, anti–Sjögren's-syndrome-related antigen A; Anti-SS-B, anti-Sjögren's-syndrome-related antigen B; Anti-Jo 1, anti-histidyl-tRNA synthetase; IgG, Immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement component 3; C4, complement component 4; CH50, total complement activity; CD3, cluster of differentiation 3; CD8, cluster of differentiation 3; CD3+, cluster of differentiation 3 positive; CD3–, cluster of differentiation 3 negative; CD56, neural cell adhesion molecule 1; CD4, cluster of differentiation 4; CD19, cluster of differentiation 19.

Table 2: Whole-exome sequencing results of the patient

Gene	Zygosity	Patient's mutation
CARD11	Not applicable* (paternally inherited)	CARD11 NM_032415.5: Duplication of Exons 2–17
ATAD3A	Homozygous (biparentally inherited)	ATAD3A NM_001170535.3:c. 1699C>A (p.Gln567Lys)
RYR1	Heterozygous (not maternally inherited)	RYR1 NM_00540.3:c.8030A>G (p.Lys2677Arg)
TBCA	Heterozygous (maternally inherited)	TBCE NM_003193.5:c581C>T (p.Pro194Leu)

*The patient underwent chromosomal sequence analysis (CSA), which included genome-wide screening for multi-gene deletions, duplications, and whole-exome sequencing with 2-exon resolution. The CSA detects clinically significant CNVs in ClinGen, UPD via AOH analysis (5 Mb resolution), whole-exome sequences, and Fragile X repeat expansions. However, the genetics report noted limitations in determining the exact nature of the CARD11 variant (e.g., tandem duplication vs. chromosomal insertion), leading to its zygosity being classified as "Not Applicable."

associated with a spectrum of immunological disorders, including combined immunodeficiency, atopy, and autoimmune phenomena [6, 7]. In this context, the patient's *CARD11* mutation may have predisposed him to immune dysregulation, amplifying his susceptibility to autoimmune reactions such as DIL.

Implications of the *CARD11* mutation

CARD11 encodes a scaffolding protein essential for antigen receptor-mediated activation in lymphocytes [4, 5]. The *CARD11* protein contains an N-terminal region with the CARD, LATCH, and coiled-coil (CC) domains and a C-terminal region with the "PSD-95, DlgA, ZO-1" (PDZ), SRC-homology 3 (SH3), and guanylate kinase (GUK) domains [5]. Mutations in *CARD11* can result in either loss-of-function or gain-of-function effects, leading to various immunological phenotypes. Hypomorphic mutations, often dominant-negative, in the CARD and CC domains disrupt normal CARD11 function, leading to combined immunodeficiency with features of atopy and autoimmunity [6, 7].

In our patient, the duplication involving exons 2–17 encompasses both the CARD and CC domains, likely resulting in a significant alteration of the *CARD11* protein structure and function. This mutation aligns with pathogenic variants reported in the literature presenting with immunodeficiency and atopic diseases. Dadi et al. described patients with dominant-negative *CARD11* mutations involving the CARD or CC domains exhibiting recurrent infections, eczema, eosinophilia, and elevated IgE levels [7]. Although our patient did not present with atopy or elevated IgE, the mutation may have contributed to immune dysregulation, manifesting as an exaggerated autoimmune response to cephalexin.

Comparison with similar cases

This case is consistent with other reports highlighting the complex interplay between genetic mutations and immune dysregulation. For example, Martone and Lehman reported a 4-year-old female who was diagnosed with very early-onset inflammatory bowel disease (VEO-IBD) and a heterozygous *CARD11* mutation) [8]. She had chronic history of 3 years and 4 months of recurrent infections including infantile pneumonia, otitis media, Methicillin-resistant *Staphylococcus aureus* (MRSA) skin abscesses, molluscum contagiosum and cutaneous warts, as well as eczema, allergic rhinitis, and asthma [8]. Despite treatment with intravenous immunoglobulin (IVIG) and anti-tumor necrosis factor (TNF) therapy, her symptoms required advanced immunomodulatory treatment with vedolizumab. The same *CARD11* variant was present in her father, who was symptomatic with molluscum contagiosum and aphthous ulcers, underscoring the potential heritability and clinical relevance of such mutations. These findings parallel our patient's history of paternally inherited *CARD11* variant along with history of recurrent infections and immune dysregulation, although the clinical manifestations differ [8]. This case parallels our patient's history of recurrent infections and immune dysregulation, although the clinical presentations differ. Other studies have highlighted the variability in immune phenotypes among individuals with *CARD11* mutations. Ma et al. described patients with germline hypomorphic *CARD11* mutations that presented with severe atopic dermatitis, food allergies, and immunodeficiency [9]. These patients had normal T-cell receptor signaling but impaired B cell function leading to hypogammaglobulinemia. While our patient maintained normal immunoglobulin levels, the underlying *CARD11* mutation may have contributed to his atypical immune response to medication.

Prior research has revealed that *CARD11* somatic mutations are commonly found in a variety of human cancer types, such as triple-negative breast cancer, colorectal cancer, and lymphoma [10]. Furthermore, *CARD11* variants were found in two patients having combined immunodeficiency and atopic skin disease [11]. Meshaal et al. reported novel homozygous *CARD11* variants in these patients, who presented with recurrent infections and severe atopic dermatitis [11]. These cases underscore the role of *CARD11* mutations in immune dysregulation and their potential to manifest as combined immunodeficiency and atopic conditions.

Collectively, these comparisons highlight the variety of presentations of *CARD11* mutations and their role in amplifying immune responses. It demonstrates the need for comprehensive genetic and immunologic evaluations to distinguish between primary immune dysfunction and environmentally induced autoimmunity, as demonstrated in our case.

Differential diagnosis and diagnostic challenges

While receiving cephalexin, the patient developed typical symptoms of DIL, including a malar rash and fatigue accompanied by serological markers such as ANA and dsDNA antibodies [3, 8]. The overlapping presentation of DIL and SLE in this case underscores the diagnostic challenge posed by coexisting genetic mutations and medication exposures. Comparing drug-induced lupus to SLE, the former has a better prognosis with lower morbidity and death. Drug-induced lupus usually goes away a few weeks after stopping the medication, while some individuals may require treatment for several months symptoms that are life-threatening are rare [12]. However, because the diagnosis is ambiguous, early detection is essential to avoiding lengthy hospital stays or repeated outpatient visits. While the presence of ANA and SLE-associated autoantibodies raised concerns for an underlying autoimmune disorder, the resolution of symptoms upon discontinuation of cephalexin strongly supports DIL as the primary diagnosis. The diagnostic complexity was heightened by the patient's *CARD11* mutation, which predisposes to immune dysregulation

and autoimmune phenomena. Careful differentiation between medication-induced and primary autoimmune processes is crucial, as the management and prognosis of these conditions differ significantly.

Long-term management and follow-up

One year after discontinuation of cephalexin, follow-up diagnostics showed normalization of previously detected autoantibodies and ANA levels, consistent with the resolution typically seen in DIL when the triggering medication was stopped. In the setting of normal flow cytometry results, primary immunodeficiency is less likely. However, the possible pathogenic *CARD11* mutation suggests that ongoing immune interactions may have affected the patient's immune reaction and initial clinical presentation.

The long-term management of patients with both congenital conditions and genetic predispositions requires a comprehensive and proactive approach to monitoring and care. Regular follow-up is essential to evaluate immune function and detect any emerging autoimmune or immunodeficiency manifestations. This includes routine laboratory assessments such as immunoglobulin levels, complement activity, and autoimmune serologies. Avoidance of known triggers, particularly medications associated with autoimmune activation, is critical. In this case, cephalexin was permanently discontinued, and alternative antibiotics with lower risk profiles were recommended to minimize the likelihood of recurrence.

Additionally, genetic counseling should be offered to the patient and his family, as *CARD11* mutations can exhibit variable penetrance and expressivity [7]. This allows for early identification and management of potential immunological issues in family members. Education also plays a vital role, with the patient's family being informed about recognizing signs and symptoms of autoimmune or immunodeficiency conditions to facilitate timely medical intervention. Collectively, these measures aim to reduce the risk of recurrence, ensure early detection of complications, and optimize long-term outcomes in patients with complex medical and genetic profiles.

CONCLUSION

This case demonstrates that mutations in *CARD11* are linked to immunodeficiency, atopy, and autoimmune reactions due to signaling dysregulation. The wide range of clinical characteristics associated with hypomorphic *CARD11* mutations emphasizes the necessity of a high index of suspicion and genetic testing to guide clinical practice. Even when recognized as a variant of unknown significance, targeted genetic testing supports clinical decision-making, aiding in accurate diagnosis, management, and long-term care of complex cases where genetic and environmental factors intersect.

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Author Contributions

Jareatha Abdul-Raheem – Conception of the work, Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Lauren Gabreski – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.