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CARMIL2-related immunodeficiency manifesting with photosensitivity

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Abstract

We report a case of a newly recognized primary immunodeficiency due to biallelic mutations in *CARMIL2* manifesting as an actinic prurigo-like photodermatitis, allergic diathesis and recurrent infections in a child. We present this case to highlight a rare phenotype seen in this T-cell immunodeficiency and provide an overview of other dermatologic manifestations among published reports of this condition.

Keywords

eczema; genodermatoses; immunodeficiency

1 | INTRODUCTION

An infant of Mexican descent initially presented at 6 months of age for a pruritic facial rash. Physical examination was notable for an eruption with erythema and scale on her forehead

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

and scalp with symmetric periorbital red patches and yellow crusting, as well as erythematous papules on the dorsal upper extremities.

The patient underwent an extensive evaluation beginning at age 6 months. A skin biopsy, taken from the forehead, at age one showed features of a spongiotic dermatitis. As the patient continued to present with recurrent skin infections, the working differential diagnosis included impetiginized atopic dermatitis, contact dermatitis, porphyria, chronic granulomatous disease, or another immunodeficiency. Immunologic evaluation, including testing for nitroblue tetrazolium, immunoglobulin levels, porphyrins, anti-nuclear antibody, and anti-double-stranded DNA, was initially negative. Metabolic studies were within normal limits. Patch testing at age three revealed contact allergy to ethylenediamine, but elimination of nystatin cream, which contained ethylenediamine, did not improve her dermatitis.

The patient re-presented at age seven with a photodistributed dermatitis on her cheeks, nose, perioral region, scalp, and dorsal arms and hands noted to worsen with sun exposure (Figure 1A,B). A clinical diagnosis of actinic prurigo was made, and the patient improved with topical steroids and strict photoprotection. Additional flares of skin disease were noted during lapses in sun protection (Figure 2A,B). In addition to her cutaneous findings, she was followed for multiple associated symptoms, including poor weight gain and short stature, consistently measuring in the 1st percentile (−2.7 to −3 SDS) for height beginning in childhood with a growth rate of 4–6 cm per year until the age of twelve. DEXA scan at age eleven demonstrated low bone mineral density, and though bone age was normal, she failed a growth hormone stimulation test (peak of 8.27 ng/dL).

She also developed severe asthma requiring ICU admission and intubation as well as food allergies. The patient was diagnosed with Crohn's disease requiring enteral therapy at age eleven, with biopsies demonstrating patchy granulomatous inflammation with mild-moderate active colitis from cecum to rectum as well as esophageal eosinophilia. A combined immunodeficiency was suspected, with a differential diagnosis including *CARD11* mutations, MALT1, Bcl10, or DOCK8 deficiencies, while monogenic lupus or metabolic defects such as erythropoietic protoporphyria were also considered given her photosensitive eruption.

The patient again underwent genetic evaluation at age 13. Despite a family history notable only for asthma in one sibling and no consanguinity, whole-exome sequencing revealed a homozygous *CARMIL2* mutation (c.1942delC, p.H648TfsX20) resulting in a pathogenic stop codon. First described as a gene downregulated in psoriasis lesions,¹ *CARMIL2* codes for a capping protein regulator and myosin 1 linker 2 which organizes T-cell polarity via modulation of microtubules and intermediate filaments.¹ In 2016, certain *CARMIL2* mutations were found to give rise to a novel primary immunodeficiency syndrome characterized by cytoskeletal disorganization, defective T-cell polarity and migration, absent regulatory T cells, and impaired CD28 co-signaling.^{2–7} To date, fewer than 50 cases have been reported worldwide with clinical manifestations including failure to thrive, inflammatory bowel disease (IBD), asthma, skin and airway infections, and smooth muscle tumors^{2–12} (Table S1). Immune phenotyping of our patient demonstrated normal absolute T- and B-cell counts but decreased NK and regulatory T-cell counts, with significantly

decreased B- and T-cell proliferative responses to mitogen stimulation and completely absent T-cell response to candida antigen and tetanus toxoid (Table S2 A–C). Consistent with other reports, our patient did not demonstrate severe autoimmunity despite a lack of regulatory T cells, likely due to impaired activation of effector T cells given defective CD28 co-signaling characteristic of this genetic syndrome.^{2,3,6,12}

Reported dermatologic manifestations include widespread verrucae, mollusca, eczematous and psoriasiform dermatitis, and palmoplantar hyperkeratosis.^{2–12} Widespread verrucae, mollusca, and recurrent superficial bacterial abscesses can be seen in association with T-cell immunodeficiencies^{2–12}; Table S1.

The occurrence of photodermatitis is less readily explained. Although photosensitivity has been reported in four cases, described as atopic dermatitis worsening with sun exposure, sun intolerance with pruritic facial plaques, UVA-sensitive dermatitis, and solar urticaria,^{2,8} actinic prurigo-like lesions have not been specifically described in *CARMIL2*-related immunodeficiency. The predisposition to IBD, recurrent ulcers, and psoriatic-like lesions among patients with *CARMIL2* mutations has been hypothesized to represent a hyperinflammatory response in the setting of low T-reg activity,⁸ and this hyperinflammatory state may extend to photosensitivity.⁸ We hope that our case broadens the known clinical manifestations of this newly recognized immunodeficiency and adds to the differential diagnosis of photosensitivity in the pediatric population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

(A) The patient's nose at age 7 demonstrating erythematous, lichenified skin with superficial fissures and excoriation. (B) The patient's forearm during an admission for an asthma exacerbation at age 7 demonstrating excoriated erythematous papules and post-inflammatory hyper- and hypopigmentation

FIGURE 2.

(A) The patient's facial eruption following a 1-h episode of outdoor exposure without adequate sun protection. (B) The patient's right hand following the same episode of outdoor sun exposure