

A case report of severe dermatitis, allergies, and metabolic wasting (SAM syndrome)

Abstract

The presence of eczema and elevated IgE in pediatric patients does not always indicate atopic dermatitis. Rare genodermatoses may share this clinical presentation and should be considered in the differential diagnosis for patients with congenital immunodeficiency and severe refractory dermatitis. We describe a case of severe dermatitis, allergies, and metabolic wasting syndrome, due to a novel mutation in *DSG1* gene, an additional example of this uncommon genetic disorder of desmosome function.

1 | CASE REPORT

A 5-year-old female presented with extensive erythematous, xerotic, and desquamative skin. The rashes were noted from the second day of life, initially involving the perioral region and flexural surfaces (Figure 1). During the first year, she was diagnosed with failure to thrive and severe atopic dermatitis. She was treated with different systemic immunosuppressive therapies with only limited improvement. Laboratory tests revealed hypogammaglobulinemia with fluctuating elevation of IgE and eosinophils.

At 18 months of age, the patient progressively developed marked striated palmoplantar keratoderma (SPPK). A skin biopsy obtained from an abdominal area with dermatitis revealed subcorneal and intragranular acantholysis associated with parakeratosis and hypergranulosis. Radioallergosorbent (RAST) tests were positive for various food allergens (multiple types of fish and shellfish, eggs, milk, wheat, peanuts, soybeans) and environmental allergens (multiple aeroallergens, including dust mites, different pollens, and cat epithelium).

At 4 years of age, clinical exome sequencing (CES) was conducted, revealing biallelic pathogenic variants in *DSG1*: c.1A>G (p.Met1) and c.2569C>T (p.Arg857). The first variant was predicted to affect the start codon of protein translation and was not described in mutation databases. The second variant was described in dbSNP and deemed likely pathogenic although no clinical correlations have been reported. Due to the possible association with SAM syndrome,

cardiac involvement and eosinophilic esophagitis were subsequently ruled out.

At 5 years of age, nutritional intervention with relevant food avoidance as well as rigorous emollient skin care, improved the patient's quality of life, having a positive impact on appetite and nutritional status. The patient's growth was within the low limit of normal range with overall improvement in the dermatitis. Scant desquamation and slight hypotrichosis were observed on scalp. A worsening of the SPPK, accentuated at pressure points (Figures 2 and 3), prompted the addition of 5 mg oral acitretin every three days to improve symptoms of palmoplantar discomfort.

2 | DISCUSSION

Severe dermatitis, allergies, and metabolic wasting (SAM) syndrome is an autosomal recessive genodermatosis produced by different mutations of the *DSG1* gene (OMIM#125670), which encodes the desmosome cadherin desmoglein 1. There have also been additional reports of SAM syndrome due to mutations in the *DSP* gene (OMIM#125647), which encodes another desmosomal protein, desmoplakin.¹

Patients characteristically develop focal or diffuse palmoplantar keratoderma, which may even be present in healthy progenitors with a monoallelic mutation in *DSG1*.² In some cases, like the one described here, hyperkeratotic plaques follow a striated pattern. This is consistent with the well-documented relationship of heterozygous mutations in *DSG1* gene and SPPK type 1, the most common of the three types of inherited SPPK.^{3,4}

Genetic testing is required for the definitive diagnosis of SAM syndrome. Sequencing tests such as CES (clinical exome sequencing) or an appropriate next generation sequencing panel, should be ordered at an early stage in complex cases.^{1,2,4,5}

Severe dermatitis, allergies, and metabolic wasting syndrome-causing mutations result in lack of *DSG1* expression. This loss of function generates impaired desmosome formation, abnormal differentiation, and acantholysis. The resulting compromised epidermal barrier function in turn may expose the immune system to abnormal stimulation resulting in an increase of Th2 immunologic responses and production of allergy-related cytokines.^{1,5}

Besides severe refractory eczematous dermatitis, SAM syndrome is also characterized by hypotrichosis. Defective epidermal

FIGURE 1 Severe erosive dermatitis with marked perioral involvement



FIGURE 2 Palmar keratoderma with striated accentuation in folds



FIGURE 3 Plantar keratoderma demonstrating accentuation over pressure points

barrier causes significant skin discomfort that may be related to low mood, anorexia, and impaired growth. Additionally, the metabolic wasting in patients with this syndrome may be attributable to the restrictive diets derived from their frequent food allergies and may also be associated with eosinophilic esophagitis, gastroesophageal reflux, and enteropathy. Esophageal involvement seems to be based on the strong *DSG1* expression in esophagus. Moreover, thymic stromal lymphopoietin (TSLP) has been

reported up-regulated in cells of some patients, and TSLP has been shown to induce allergic manifestations in the gastrointestinal tract.⁵

Desmosomes are abundant in myocardium and mutations in many different desmosomal genes have been associated with myocardial dysfunction. Cardiomyopathy screening is required for all patients with skin abnormalities who harbor mutations in *DSP* (which has been related to SAM and SPPK), *PG* or *DSC2* genes, in order to assess the possibility of a cardiocutaneous syndrome.⁶

The prognosis of these patients is mainly influenced by their increased risk of skin and lung infection and sepsis. This can be attributed in part to the critical role of the desmosome in maintaining the integrity of the epithelial barrier. In addition, *DSG1* is known to reduce epithelial inflammation by inhibiting the NF- κ B signaling pathway¹

In the first cases reported, SAM syndrome was described with severe skin involvement (congenital erythroderma and intense dermatitis) and associated with several systemic symptoms, including one instance of early death due to sepsis.⁵ Many cases with a milder presentation have been described since then. SAM syndrome appears to be phenotypically heterogeneous.²

Future treatment of SAM syndrome will be probably based on gene therapy. Recent reports of increased levels of cytokines of the Th1 and Th17/IL-23 pathways suggest that biological drugs targeting these pathways, such as ustekinumab, could be beneficial.⁷

AUTHOR CONTRIBUTIONS

The authors of this publication are physicians working at “Hospital Universitario Virgen de las Nieves” in Granada. All have read the current publication guidelines of the magazine and accept all instructions and conditions. All authors significantly contributed to the manuscript and approved this final version of the document. Each author participated in the conception and design of the work, the literature search, and the drafting of the article.

ETHICAL APPROVAL

This study has been duly approved by the Ethical Committee of “Hospital Universitario Virgen de las Nieves University”.

KEYWORDS

allergic disorder, atopic dermatitis, desmoglein, genetic desmosomal diseases, palmoplantar keratoderma, SAM syndrome

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