

CONCISE COMMUNICATION

Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome caused by de novo mutation in the *DSP* gene misdiagnosed as generalized pustular psoriasis and treatment of acitretin with gabapentin

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ABSTRACT

Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome is a recently recognized syndrome caused by mutations in the desmoglein 1 (*DSG1*) and desmoplakin (*DSP*) genes. Only two cases of SAM-*DSP* have been reported. We report on a 2-year-old girl presenting with pustular lakes within areas of erythema and large accumulations of intraepidermal neutrophils, which initially led to our misdiagnosis of generalized pustular psoriasis. No mutation was found in either the *IL36RN* or *CARD14* genes by Sanger sequencing. The distinctive manifestations of erythroderma with severe itching, hypotrichosis, enamel defects, onychodystrophy, palmoplantar keratoderma and the crucial result of de novo missense mutation in exon 14 of the *DSP* gene (c.1828T>C, p.S610P) discovered by next-generation sequencing finally confirmed the diagnosis of SAM syndrome. The eruptions significantly improved after a 4-week treatment with oral acitretin and topical pimecrolimus. Oral gabapentin was prescribed simultaneously for 4 months, relieving her skin pruritus and suggesting that early treatment with pimecrolimus, acitretin and gabapentin for SAM-*DSP* syndrome is effective. It may even inhibit multiple allergies induced by skin barrier injury. In this work we also review the clinical features, differential diagnoses and pathological manifestations of SAM-*DSP* syndrome.

Key words: *DSP* gene, hypotrichosis, palmoplantar keratoderma, pustular psoriasis, severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome.

INTRODUCTION

Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome is a rare genetic disorder first identified in 2013.¹ Two responsible genes, desmoglein 1 (*DSG1*) and desmoplakin (*DSP*),² have been identified, both of which are the obligate component of desmosomes that play an important role in the adherence and communication between cells.² To date, only two families of SAM-*DSP*^{3,4} and seven families of SAM-*DSG1*^{1,5–8} have been reported. In the present study, we report the third case of SAM-*DSP* syndrome, describe the currently effective treatment with topical pimecrolimus, oral acitretin and gabapentin, and review the published work of SAM-*DSP* syndrome.

CASE REPORT

We report on a 2-year-old Chinese girl who presented with repeated episodes of erythema, erythroderma and pustules,

accompanied by acute pruritus in the first 2 years of life. At birth, the patient was noted to be normal with no manifestations of collodion membrane or erythroderma. At the age of 10 days, however, scattered erythemas and papules on the face and trunk were first recorded. At 3 months, lesions developing over the entire body accompanied by acute pruritus led to a misdiagnosis of atopic dermatitis (AD). Her eruptions and pruritus repeated and were unresponsive to either topical steroids or oral antihistamines. At the age of 17 months, the baby developed erythroderma with widespread pustulosis and a severe and intractable itch without high fever. She was referred to our department at the age of 22 months because of the deterioration of the skin lesions and a high fever for 5 days.

The patient was born to healthy non-related parents by full-term natural labor and her 8-year-old older brother did not have a similar condition. No familial history of skin disorders had been recorded. Her birthweight was 3.18 kg and her Apgar score was 10.

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Received 2 March 2019; accepted 22 April 2019.

Physical examination showed marked erythroderma with pustulosis and pustular lakes, which are similar to generalized pustular psoriasis (GPP). However, distinctive features including diffuse palmoplantar keratoderma (PPK), onychodystrophy of all nails, hypotrichosis, agomphosis, enamel defects and no sign of geographic tongue differentiated it from GPP (Fig. 1a–h). At 22 months of age, she was 75 cm in height (first percentile) and 9 kg in weight (fifth percentile), which revealed the failure to thrive.

Histopathological examination of the skin showed psoriasiform acanthosis and hyperkeratosis with subcorneal neutrophil accumulations, which were similar to GPP (Fig. 2).

Laboratory evaluations showed elevated serum total immunoglobulin (Ig)E (895 IU/mL; normal, 0–100), C-reactive protein (8–27 mg/L; normal, <8) and white blood cells ($11.85\text{--}16.76 \times 10^9/\text{L}$; normal, 4–10), while the eosinophil count, biochemical and metabolic profiles, T-lymphocyte subsets and Ig and vitamin levels were within normal limits. Repeated blood cultures ($>38.5^\circ\text{C}$), pus bacteria cultures and fungal cultures were all negative. The results of procalcitonin (0.29 ng/mL; normal, <0.5), bacterial endotoxin ($<5.00 \text{ pg/mL}$; normal, <10) and fungal β -(1,3)-D-glucan ($<31.25 \text{ pg/mL}$; normal, <60) did not support the diagnosis of infectious diseases. Moreover, empirical antibiotic therapy with i.v. ceftriaxone sodium for 5 days was ineffective, and her temperature returned to normal and pustules recovered after a 2-week treatment with oral acitretin. Cardiac examination was normal at 2 years of age. After the first diagnosis of GPP was made, Sanger sequencing of

IL36RN and *CARD14* was conducted, but no mutation was detected. Whole-exome sequencing was then carried out. The de novo mutation in exon 14 of *DSP* (c.1828T>C, p.S610P) was identified and confirmed by Sanger sequencing, which was not found in her parents or brother (Fig. 3). The variant was predicted to be “disease causing” by Mutation Taster and “destabilizing” by mCSM ($\Delta \Delta \text{G}$ -0.185 kcal/mol) and DUET ($\Delta \Delta \text{G}$ -0.138 kcal/mol). The mutation was found in neither ExAC nor 1000 Genomes Project databases. Conservation analysis of the mutation site using the University of California Santa Cruz Genome Browser database showed amino acid conservation among different species. Finally, the patient was diagnosed with SAM syndrome. Besides, no mutation in *DSG1* was detected by whole-exome sequencing.

After a 4-week experimental treatment with oral acitretin (0.4 mg/kg per day) and topical pimecrolimus, the eruptions were significantly improved. Because the itching was still intolerable, oral gabapentin (20 mg/kg per day) was prescribed simultaneously for 4 months, and her skin pruritus was obviously relieved (Fig. 1i–l).

DISCUSSION

In the present study, we report a rare case of SAM syndrome caused by a de novo missense mutation in the *DSP* gene (c.1828T>C, p.S610P) characterized by pustules and pustular pooling within areas of erythema clinically and the features of accumulated neutrophils in the epidermis, which at first led to

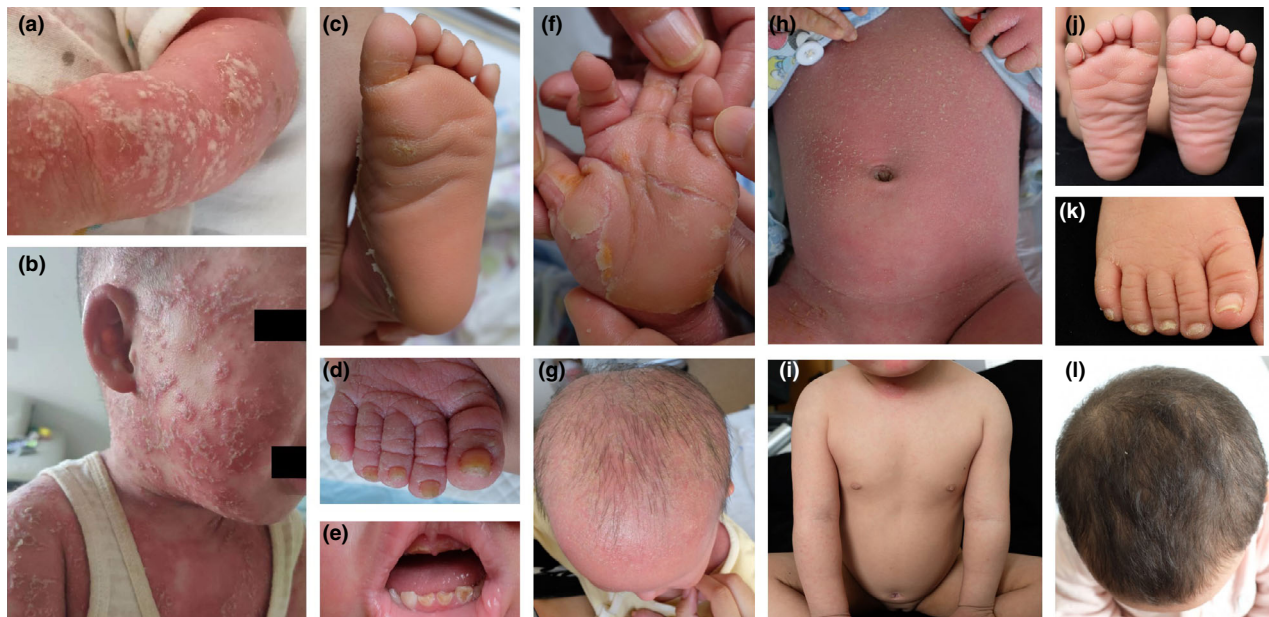


Figure 1. Clinical manifestations of the proband at 22 months of age at the first visit to our department showed (a,b) pustulosis and pustular lake within the background of erythema mimicking generalized pustular psoriasis, (c,f) palmoplantar keratoderma, (d) onychodystrophy, (e) enamel defects (g) hypotrichosis and (h) erythroderma. After 4-months of treatment with oral acitretin, topical pimecrolimus and oral gabapentin, (i) extensive ichthyosis and (j,k) palmoplantar keratoderma were significantly improved, and (l) her woolly hair grew out.

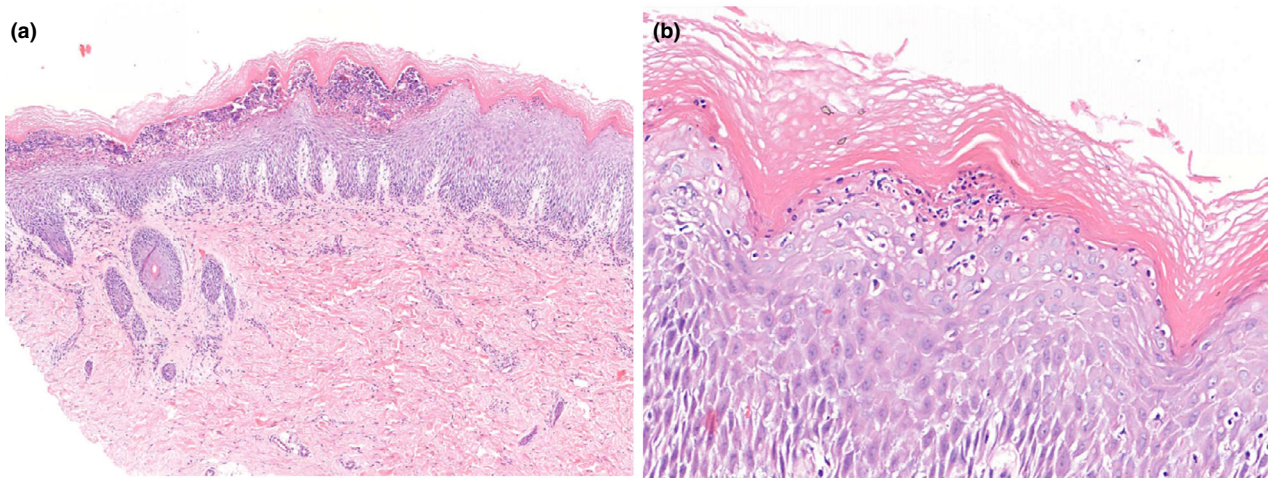


Figure 2. Skin biopsy obtained from the trunk showing (a) psoriasiform hyperplasia and hyperkeratosis with large subcorneal neutrophil accumulations and (b) Kogoj's spongiform pustule (hematoxylin–eosin, original magnifications: [a] $\times 40$, [b] $\times 100$).

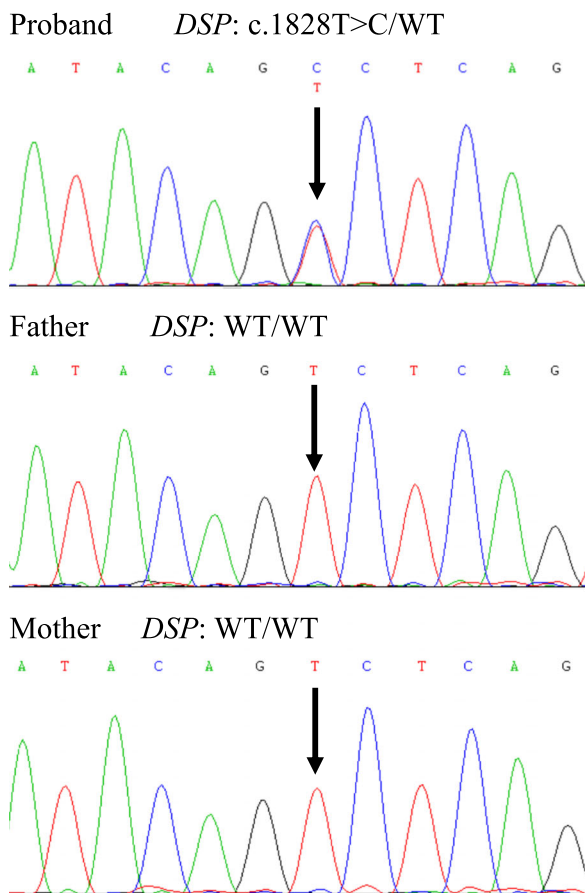


Figure 3. Sanger sequencing of the *DSP* gene for the proband showed de novo mutation of c.T1828C in the spectrin 6 (SR6) domain (exon 14) in a heterozygote state resulted in the substitution of a serine residue for a proline residue (p.S610P). The mutation was not found in her parents.

a misdiagnosis of GPP. The multiple manifestations including refractory itching, PPK, dental abnormalities and hypotrichosis, which were not seen in GPP, and the genetic result confirmed the diagnosis of SAM syndrome. Because of the clinical and genetic heterogeneity, diagnoses of inherited skin diseases are challenging, especially at early stage. The value of whole-exome sequencing with bioinformatic analysis has been highlighted by Takeichi *et al.*⁹ and proved in our case. In addition, repeated eczematoid lesions with severe itching should be distinguished from AD and AD-like diseases such as Netherton syndrome. The characteristic of intractable itching unresponsive to topical steroids and oral antihistamines differentiates it from AD. Netherton syndrome⁹ is characterized by ichthyosis linearis circumflexa, bamboo hair, severe pruritus and a lake of pus mimicking GPP, which are also present in some patients.¹⁰

Desmoplakin, a member of the plakin family, encoded by the *DSP* gene, is an obligate component of functional desmosomes, providing adherence and communication between cells.² The *DSP* gene is a 2871-amino acid plakin protein on Chr.6p24.3⁴ composed of three domains:¹¹ six spectrin repeats (no. 3–6, 8 and 9) in the N-terminal region, and rod and plakin repeats at the C-terminal.⁴ Mutations scattered throughout the three domains can cause a variety of skin, dental, hair and cardiac abnormalities by the autosomal recessive or autosomal dominant modes. The clinical manifestation spectrum includes congenital ichthyosis, extensive ichthyosis, severe pruritus, PPK, pustules, alopecia and hypotrichosis, woolly hair, onychodystrophy, failure to thrive, recurrent infections, multiple food allergies, a high level of eosinophilia or IgE, conjunctival irritation, photophobia, hepatomegaly, cardiomyopathy, arrhythmia and dental abnormalities.⁴ Remarkably, all reported cases of SAM-DSP, including the present patient, have been caused by mutations in the spectrin 6 (SR6) domain of *DSP* in autosomal dominant conditions.⁴ Besides, mutations within SR6 can cause the other two autosomal dominant disorders

with overlapping clinical features: (i) dilated cardiomyopathy with woolly hair, keratoderma and tooth agenesis (DCWHKTA); and (ii) erythrokeratoderma-cardiomyopathy (EKC) syndrome.⁴

The patient's manifestations are similar to those of the two previous cases. However, unlike reported disorders with *DSP* mutations in the SR6 domain, our patient presented with diffuse hyperkeratosis of the palms and soles, rather than the linear or local type. All of the patients with SAM-*DSP* syndrome presented with pustules within an erythematous base, while no pustules have been reported with other *DSP*-SR6-related diseases or SAM-*DSG1* syndrome. Pustular psoriasis-like lesions may be a characteristic feature of SAM-*DSP* syndrome. The symptom complex that includes pustules with ectodermal dysplasia should suggest the diagnosis of SAM-*DSP* syndrome. Pustules in previous cases of SAM-*DSP* have always been transient, which is different from the long-term recurrent pustules of GPP.

Mutations in the SR6 domain of *DSP* show a high degree of clinical heterogeneity. In SAM syndrome, skin, hair and teeth are involved, while in EKC, DCWHKTA/dominant Carvajal syndrome severe cardiomyopathy is detected. Because cardiomyopathy caused by mutations in *DSP* is asymptomatic in the early stages and sudden cardiac death has been reported,^{12, 13} early and close long-term cardiac follow up is necessary for SAM-*DSP* patients.

The treatment of SAM is still uncertain because of its rarity. It is responsive to retinoids, as reported in the previous published work.² A recent study suggests that ustekinumab therapy is effective on the basis of the discovery of T-helper (Th)1 and Th17/interleukin-23 skewing in the skin and blood of two SAM-*DSP* patients.⁴ In this study, oral acitretin combined with topical pimecrolimus was used. In addition, gabapentin was prescribed to relieve severe itching.¹⁴ The combination of three drugs was obviously effective, which may inhibit multiple allergies induced by skin barrier injury.

ACKNOWLEDGMENTS: We thank the patient, National Nature Science Foundation of China (no. 81703104) and Clinical Research Plan of SHDC (no. 16CR3118B).

CONFLICT OF INTEREST: None declared.

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