QUIZ SECTION

MJS PUBLISHING

Juvenile-onset Skin Fragility with Acral Blistering: A Quiz

Kaan YILMAZ, Miriam LINKE and Marthe-Lisa SCHAARSCHMIDT*
*Department of Dermatology, Heidelberg University, Medical Faculty Mannheim, Theodor-Kutzer-Ufer 1-3, DE-68167 Mannheim, Germany. *E-mail: marthe-lisa.schaarschmidt@umm.de*

A 23-year-old Caucasian woman presented with recurrent palmoplantar exfoliation and blisters, commencing at the age of 2 years. The lesions were prone to exacerbation by friction, heat, and humidity, and accompanied by severe burning sensation (numerical rating scale: 8/10). Notably, the disease activity tapered off slightly with age, with palmar lesions ceasing in the adulthood. Medical history was rather unremarkable, revealing, except for allergic rhinoconjunctivitis, no further atopic diathesis or exposure to irritant agents. No other family members, including her non-consanguineous parents and only sibling, had skin disease. On clinical examination, flaccid blisters, shallow erosions, and residual erythema overlying non-inflamed skin strictly located on the soles and heels were observed, in the absence of atrophy or scarring (Fig. 1). No involvement of mucosal surfaces and cutaneous appendages was identified. Nikolsky's sign was negative.

What is your diagnosis?

Differential diagnosis 1: Localized epidermolysis bullosa simplex

Differential diagnosis 2: Keratolysis exfoliativa (lamellar dyshidrosis)

Differential diagnosis 3: Acral peeling skin disease

Differential diagnosis 4: Exfoliative ichthyosis

See next page for answer.

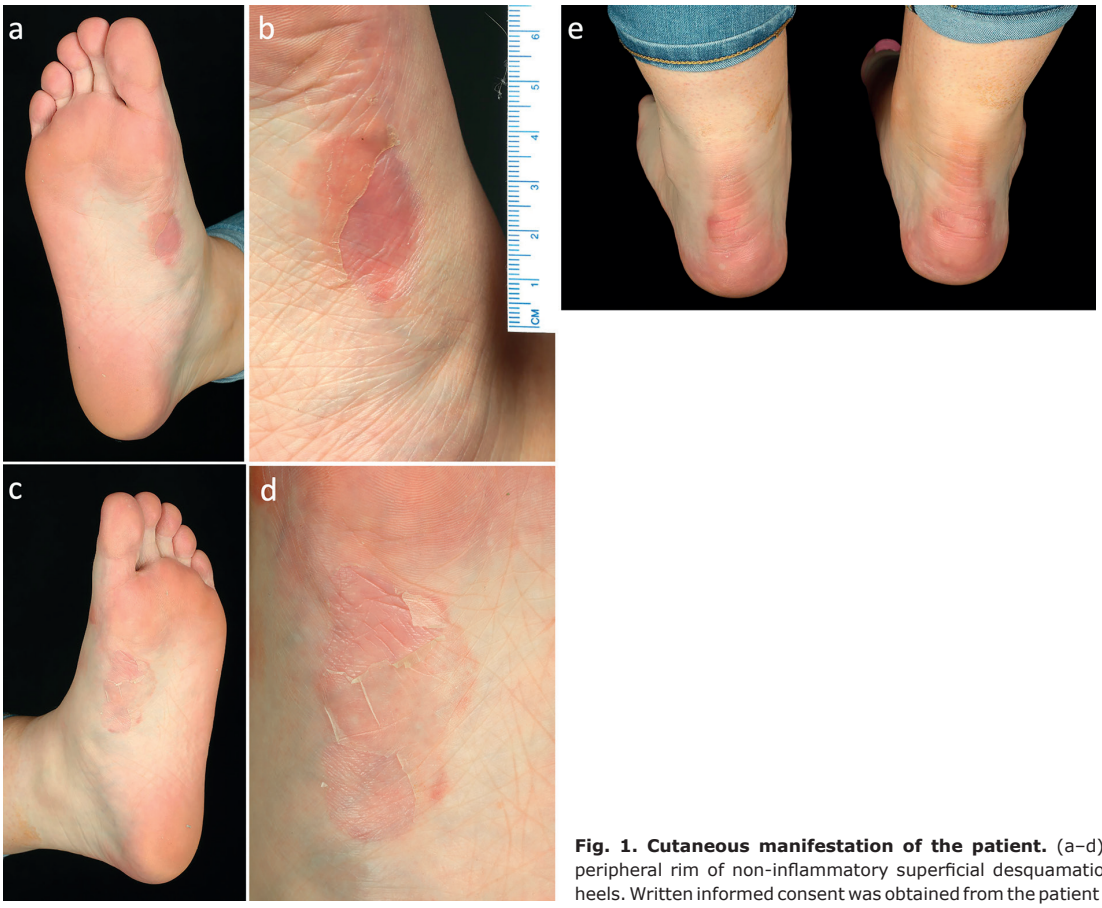

Fig. 1. Cutaneous manifestation of the patient. (a–d) Residual erythema with peripheral rim of non-inflammatory superficial desquamation plantar and (e) on the heels. Written informed consent was obtained from the patient to publish her case details.

ANSWERS TO QUIZ

Juvenile-onset Skin Fragility with Acral Blistering: A Commentary

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Diagnosis: **Acral peeling skin disease**

For molecular testing, EDTA blood from the patient was subjected to next-generation sequencing-based multigene profiling, encompassing a panel of 28 genes, and mutations were confirmed by Sanger sequencing. Here, a pathogenic variant in the transglutaminase 5 gene (*TGM5*) c.337G>T, p.Gly113Cys was detected in a homozygous state, which is the causative mutation of acral peeling skin disease (APSD).

APSD (MIM 609796), also referred to as acral peeling skin syndrome (APSS), is a rare, autosomal recessively inherited disorder characterized by superficial peeling and blisters on the hands and feet (1). Although dorsal aspects of the acra are by far predominantly affected, an additional or exclusive involvement of volar surfaces, as in the current patient, was also occasionally described (2, 3). The severe burning sensation was another uncommon manifestation, as most patients with APSD exhibit painless lesions (3).

The underlying genetic impairment usually abolishes the activity of epidermal TGM5 protein that significantly contributes to crosslinking of cornified envelope proteins and the consequent differentiation of the epidermis (2, 4). The microscopic correlate is a superficial intraepidermal cleavage between the stratum corneum and granulosum, which clinically translates into flaccid blisters (3). In the present case, a lesional skin biopsy was waived to avert further mechanical stress, since the diagnosis was already facilitated by genetic analysis. Overall, more than 20 different *TGM5* mutations have hitherto been identified in patients with APSD, while the common p.Gly113Cys variant is considered an ancestral founder mutation in the European population (2, 4, 5). The genetic heterogeneity of APSD is further buttressed by the fact that sole mutations in the *CSTA* gene encoding cystatin A were also rarely disclosed (MIM 607936) (6, 7). Even though the term APSS is still widely used, Has instead proposed the designation APSD based on the lack of evidence for syndromic involvement (8).

The prevalence of APSD remains to be defined. To date, just over 100 cases have been reported. However, recent evidence suggests that, due to mild symptoms and a clinical picture potentially mimicking localized epidermolysis bullosa simplex (EBS-loc), it might represent an underdiagnosed and misrecognized entity (3, 5). The differentiation between APSD and EBS-loc has further clinical implications for affected patients and their families, as EBS-loc follows, in contrast to APSD, an autosomal dominant inheritance pattern. Clinically, blisters in EBS-loc tend to be larger, more tense and persistent than in APSD, and predominantly occur on volar aspects of hands and feet (3, 5). On the other hand, no genotype-phenotype correlations in APSD have been established yet. Of note, p.Gly113Cys was reported in 3 of 100 control individuals in heterozygosity, implicating that APSD might be more frequent than previously assumed (2). In this regard, APSD was noted to account for up to 50% of patients with inherited acral desquamation disorders referred to specialized centres in Europe (3, 5). Thus, screening for *TGM5* mutations was recommended in patients suspected of having EBS-loc, but devoid of mutations in the *KRT5* and *KRT14* genes, which were excluded in the current patient (3, 5).

A highly remarkable observation in the current patient was the progressive improvement with increasing age, which parallels the course of disease in 2 siblings with generalized ichthyotic peeling skin syndrome due to mutations in the *FLG2* gene encoding filaggrin-2 (9). Intriguingly, a longitudinal immunofluorescence study of 1 of these patients revealed an almost complete normalization of immunostaining patterns for components of the cornified envelope and corneodesmosomes over time (9). Similarly, amelioration of skin disease with age was also reported in different subtypes of EBS, including the severe form, EBS with mottled pigmentation, as well as intermediate EBS with *KLHL24* mutations (10). The pathogenesis underlying this phenomenon remains elusive. However, it is tempting to speculate that compensatory mechanisms maintaining the stabilization of the epidermal barrier in APSD, as thoroughly characterized by Pigors et al. (2), might be subject to age-dependent structural plasticity, which should be addressed by future research. Another possible explanation may be the fact that sweat gland function deteriorates with ageing (11). This results in a reduced amount of sweating, which, in turn, might alleviate the disease severity in affected individuals.

In conclusion, we describe here a rare case of molecularly confirmed APSD, and highlight this entity as a genetically and clinically heterogeneous and potentially underrecognized condition.

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