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Keratolysis exfoliativa (dyshidrosis lamellosa sicca): a distinct peeling entity

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Summary

Background Keratolysis exfoliativa (KE), also known as dyshidrosis lamellosa sicca, is a palmoplantar dermatosis characterized by air-filled blisters and collarette desquamation. It has been regarded as a subtype of dyshidrotic eczema, a fungal infection or a dermatophytid reaction. KE may also resemble acral peeling skin syndrome and localized epidermolysis bullosa simplex. Although KE is a common disorder, it is a rarely reported and is an under-recognized dermatosis.

Objectives To delineate the characteristic features of KE.

Methods We investigated the clinical, immunohistopathological, ultrastructural and molecular features of KE. Patients were included from the clinical records. Additional diagnostic research consisted of mutation analysis of the candidate genes TGM5, KRT5, KRT14, FLG, SPINK6 and SPINK9.

Results A total of 24 patients with KE were identified, six with familial and 18 with sporadic KE. Lesions consisted of air-filled blisters only on palmoplantar skin, followed by collarette and lamellar peeling. Both light microscopy and electron microscopy showed cleavage and partially degraded corneodesmosomes within the stratum corneum, whereas immunofluorescence microscopy showed normal expression of corneodesmosomal components. No mutations were found in TGM5, KRT5, KRT14, FLG, SPINK6 and SPINK9. There was no clear link with atopy or with FLG mutations.

Conclusions Our study suggests premature corneodesmolysis as the main pathological mechanism of this palmoplantar skin disorder. We conclude that KE appears to be a distinct peeling entity.
Materials and methods

Patients

Patients were enrolled from the specialized expertise centres for blistering diseases and eczema of the academic dermatology department in Groningen between 1988 and 2011. Eligible patients satisfied the criteria of recurrent, palmoplantar air-filled blistering and peeling. These patients were approached by letter or were referred to our clinic and all completed a standardized questionnaire.

Clinical examination

The following clinical data were recorded in each patient: age, age at onset, familial occurrence, morphology and localization of the lesions, subjective symptoms, aggravating factors, presence of palmoplantar hyperhidrosis, history of atopy, history of tinea pedis and response to treatments.

Additional diagnostic examinations

Serum levels of IgE specific to inhaled allergens were determined with the ImmunoCap method (Phadia/Thermo Scientific, Uppsala, Sweden). Also, potassium hydroxide (KOH) preparation along with fungal and yeast culture of palmoplantar scales were performed.

Molecular analyses

Genomic DNA was extracted from blood using the QIAamp DNA Blood Maxi Kit (Qiagen, Venlo, the Netherlands). All exons and their flanking intronic regions of TGM5 and KRT5/14 were analysed as described by Cassidy et al.\textsuperscript{13} and Bolling et al.\textsuperscript{14} respectively. The four most prevalent FLG mutations, i.e. R501X, 2282del4, S3247X and R2447X, were screened as described by Sandilands et al.\textsuperscript{15} Polymerase chain reaction (PCR) amplification of exons 1–4 of SPINK6 and exons 1–4 of SPINK9 and their flanking intronic regions was performed. The following primers (synthesized by Biologio, Nijmegen, the Netherlands) were used: SPINK6 exon 1, forward GAACTTTA GAAAGAGACCG and reverse TTACCTAAACATTGTGTC, SPINK6 exon 2, forward TTGAGATGCAAAGTACCAGGAG and reverse GTGAAAGTCAAGCCAAGC; SPINK6 exon 3, forward CACTGATGCAAGTCGAC and reverse TTGGTTTCTC AGTCTCTATGG; SPINK6 exon 4, forward TGTTGAGTACTT ACATATTGC and reverse AGTAAGAAACAGTCAATGC; SPINK9 exon 1, forward TATAAGGCGATCAAGTGGAG and reverse TATCCCAATTACATAGGCA; SPINK9 exon 2, forward GTAAGATTGGTCCTCGAGAG and reverse AAAGTAG GATGCGTGTACTG; SPINK9 exon 3, forward TGGTGGAAA GAGTTGAAG and reverse CTGGAAGTCTGTTGTAAGAG; SPINK9 exon 4, forward TGGATGCTAATGAAATGCCT and reverse TATCTATTGACAGCAACCA. PCR products were electrophoresed on a 1% agarose gel, and the bands were excised and extracted from the agarose gel with the MinElute Gel Extraction kit (Qiagen) and subsequently sequenced.

Skin biopsies

Four biopsies (IIIA, VIA, VII and VIIIA) solely for light microscopy, seven biopsies (IA, IIA, IIIB, IV, V, IX and X) for both electron microscopy and light microscopy, and four biopsies (IB, IIB, VIIIB and VIIIIB) for immunofluorescence microscopy were included in this study (Table 1). Biopsies IA, IIA, IV, VIA, VII, VIIIA, IX and X were taken at the edge of an air-filled blister and biopsies IB, IIB, V, VIIIB and VIIIIB were taken from perilesional skin.

For light microscopy, the biopsies were fixed in 4% formaldehyde and embedded in paraffin. Then, semithin sections were cut, stained with hematoxylin–eosin and examined with

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LM, light microscopy; EM, electron microscopy; IF, immunofluorescent microscopy.
For light microscopy, the semithin sections were stained with toluidine blue–basic fuchsin. The ultrathin sections were stained with uranyl acetate and lead citrate, and examined with a Philips CM100 transmission electron microscope (Philips, Eindhoven, the Netherlands).

Four biopsies (IA, IIA, IIIB and V) and control skin were fixed by an adjusted protocol to gain optimal preservation and visualization of lipids and membranes in the stratum corneum. These biopsies were fixed in 2% paraformaldehyde and 2% glutaraldehyde in 0.1 mol L \(^{-1}\) cacodylate buffer. Then, the biopsies were fixed with 1% osmium tetroxide in 0.1 mol L \(^{-1}\) cacodylate buffer and post-fixed with 0.5% ruthenium tetroxide with 0.25% potassium ferrocyanide. The biopsies were dehydrated in ethanol and embedded in Epon. Semithin and ultrathin sections were cut. The semithin sections were stained with toluidine blue and examined with a light microscope. The ultrathin sections were stained and examined as described in the standard protocol.

For immunofluorescence microscopy, four unfixed snap-frozen biopsies of KE skin and a control skin sample were cut in a cryostat into 6-μm sections. The sections were incubated in a humidified chamber in the dark for 30 min at room temperature with primary antibodies for corneodesmosin (Santa Cruz, Heidelberg, Germany), desmocollin-1 (Progen Biotechnik, Heidelberg, Germany) and desmoglein-1 endodomain and ectodomain (Santa Cruz and Progen Biotechnik, respectively). After rinsing with PBS, the sections were incubated for 30 min with the secondary antibodies fluorescein-isothiocyanate-labelled rabbit antigoat IgG antibody (Invitrogen, Paisley, U.K.) or Alexa568-labelled goat antimouse IgG antibody (Dako, Enschede, the Netherlands). Images were recorded using a Leica DMRA immunofluorescence microscope (Leica, Heidelberg, Germany) with the same setting of contrast and brightness in the control and patient sections.

**Results**

**Patients and clinical assessment**

A total of 24 patients were included. Patients 1–11, 17, 22 and 24 revisited our outpatient clinic and were clinically reassessed. Data of patients 12–16, 18–21 and 23 were derived from patient files. The clinical features of the patients with KE are summarized in Table 2. Thirteen patients were male and 11 female, and the age ranged between 5 and 69 years with a median of 32 years. The age at onset ranged between 0 and 64 years with a median of 19 years. Familiar occurrence was present in patients 1–6. Patients 1 and 2 were father and daughter, patients 3 and 4 were siblings, patient 5 reported that his mother had similar lesions and patient 6 had a sister with similar lesions.

KE started with an erythematous ring (Fig. 1a), which was observed at the time of consultation in 13 patients. Subsequently, a pale air-filled blister (Fig. 1b) developed within the boundaries of the ring, of which the roof opened in the centre, followed by superficial centrifugal, collarette peeling on the palm and voral aspects of the fingers (c).

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The peeling was preceded by slight pruritus in six patients, and by mild burning sensation in five patients. Fifteen patients reported pain when the skin became thin in the peeled areas, and therefore susceptible to the development of erosions. Six patients did not have any subjective symptoms. Aggravating factors were warm weather (n = 12), friction (n = 11) and water contact (n = 7). Five patients did not experience any aggravating factors. Hyperhidrosis was present in 11 patients (palmoplantar n = 5, palmar n = 3, plantar n = 3). None of the patients experienced improvement of their lesions when treated topically with indifferent compound ointments, keratolytic urea, steroids or antifungals.
Ten of the 24 patients had a history of ‘atopic’ diseases, although only three of 13 had elevated serum levels of allergen-specific IgE (Table 3). Two of the 24 patients had a positive history of tinea pedis, but KOH preparations along with cultures of palmoplantar scales were negative. Moreover, KOH preparations and cultures of palmar and/or plantar scales in 11 other patients were also negative (Table 3).

Histopathological and ultrastructural analysis

Light microscopy of the nine biopsies taken at the edge of an air-filled blister (IA, IIA, IIIA, IV, VIA, VII, VIIIA, IX and X; see Table 1) all showed cleavage within the stratum corneum (Fig. 2a). The level of the cleavage varied between biopsies in the upper, mid or lower part of the stratum corneum. Parakeratosis with a thinned stratum granulosum was found in five of the 11 biopsies (IIIA, IIIB, IV, VIA and VIIIA) (Fig. 2b). None of the 11 studied biopsies demonstrated an inflammatory infiltrate, exocytosis of lymphocytes or acanthosis.

Electron microscopy of control skin and of all seven KE skin biopsies (IA, IIA, IIIB, IV, V, IX and X) showed physiologically partially degraded corneodesmosomes at the stratum corneum surface where the outermost corneocytes begin to desquamate. However, in three (IA, IIA and IIIB) of the seven KE biopsies, degradation of corneodesmosomes with intercellular widening was also observed lower in the stratum corneum just above and below the cleft in biopsies taken at the edge of an air-filled blister (IA and IIA) (Fig. 2c), and in the mid part of the stratum corneum in unclesed perilesional skin (IIIB) (Fig. 2d). None of the samples showed other ultrastructural abnormalities in the basal, spinous or granular epidermal layer.

Immunofluorescence microscopy showed similar expression of corneodesmosin, desmocollin-1 and desmoglein-1, both endodomain and ectodomain, in all four KE skin biopsies, compared with the control skin (Fig. 3).

No mutations in five candidate genes for keratolysis exfoliativa

As the KE phenotype often resembles APSS and EBS, molecular analysis was performed to investigate if KE could also be caused by mutations in TGM5, a gene coding for the transglutaminase 5 protein, or the genes encoding keratin 5 or 14 (KRT5/14). We analysed the TGMS5 gene in nine patients, and the KRT5/14 genes in two doubtful patients. We also screened for FLG mutations and found in one (no. 6) of 16 tested patients the prevalent R501X mutation heterozygously present, thus confirming that an association with atopy is unlikely. Furthermore, we analysed the genes SPINK6 and SPINK9, which both code for epidermal protease inhibitors, in 15 patients. No mutations were found in the exons and flanking intronic regions of these genes (Table 3).

Discussion

This study showed that KE is a separate entity, characterized by superficial collarette-like dry peeling of glabrous palmoplantar skin, which is definitely distinct from dyshidrotic eczema, tinea, APSS and localized EBS. We prefer the term KE rather than dyshidrosis lamellosa sicca, as the latter evokes an association with dyshidrotic eczema, hyperhidrosis or eczema in general, which we demonstrated in this study not to be the case. ‘Keratolysis exfoliativa’ better describes the clinical
phenomenon of exfoliative peeling due to keratolysis of the stratum corneum.

The lesions in KE involved only palmoplantar skin, most frequently the volar aspects of the fingers. The peeling was preceded by air-filled blisters, which were never filled with fluid. Skin lesions in KE began typically with an erythematous ring bordering the imminent lesions. Our findings concerning the clinical presentation of KE are in agreement with the earlier literature.\textsuperscript{3,5}

KE has often been described as essentially asymptomatic,\textsuperscript{5,6,8} although some authors report sensitiveness of the peeled skin.\textsuperscript{9,10} This study demonstrated that slight pruritus or a burning sensation may precede the peeling, as well as pain in peeled areas, although an absence of subjective symptoms was also found.

This study confirmed that friction and water contact may aggravate KE.\textsuperscript{3,11} An explanation for this could be the disruption of the epidermal barrier by mechanical forces or soaking of the skin.\textsuperscript{16} In addition, and similar to APSS and localized EBS,\textsuperscript{13,17} KE worsens in warm weather in about half of the patients. Also, palmar and/or plantar hyperhidrosis has been described as being associated with KE,\textsuperscript{5,11} yet this was seen in only 11 of the 24 patients in this study. Thus, it remains unclear whether palmpoplantar hyperhidrosis and warm weather are associated with KE. However, it seems plausible that palmpoplantar hyperhidrosis could have similar effects on the skin as water contact, which may increase the pH of the stratum corneum (loss of ‘acid mantle’) and therefore push the balance towards desquamation, as an alkaline pH increases serine protease activity enforcing premature corneodesmolysis and thus impairing the stratum corneum cohesion.\textsuperscript{18}

It has been suggested that KE is a subtype of dyshidrotic eczema.\textsuperscript{11,12} However, dyshidrotic eczema is characterized by pruritic fluid-filled vesicles mainly on the lateral aspects of the fingers, the palms and occasionally on the soles.\textsuperscript{19} Based on our data and previous reports,\textsuperscript{3,9} it appears that KE differs from dyshidrotic eczema, as it is not pruritic nor vesicular. In our patients, atopic diathesis does not appear to be associated with KE, nor was the disease associated with filaggrin mutations. In addition, none of the studied biopsies showed an inflammatory infiltrate, exocytosis of lymphocytes or acanthosis. Therefore, this study also demonstrates that KE differs histopathologically from dyshidrotic eczema and atopic dermatitis.\textsuperscript{20}

Table 3  Additional diagnostic research in series of patients with keratolysis exfoliativa

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+, Positive; –, negative; NP, not performed.
It has been proposed that KE is a fungal infection\(^3\) or a dermatophytid reaction caused by interdigital dermatomycosis of the feet.\(^8\) Our findings demonstrated that KE is neither a fungal infection nor a dermatophytid reaction (eczematid).

The histopathological hallmark of KE is clean cleavage within the stratum corneum without a cellular infiltrate. Also, parakeratosis with a thinned stratum granulosum was observed possibly arising from enhanced keratinocyte proliferation. Furthermore, the stratum corneum cleavage easily distinguishes KE histopathologically from localized EBS, which is characterized by cytolysis in the basal layer.\(^14\) Histopathological differentiation of KE from APSS may be more difficult, as the level of blistering in APSS is located at the junction of the stratum granulosum and the stratum corneum or within the stratum corneum.\(^13,17,21\)

In contrast to KE, fluid-filled blisters characterize localized EBS and some cases of APSS, and both involve the dorsal aspects in addition to the volar or plantar aspects of hands and feet.\(^14,21,22\) In this study, molecular analysis of TGM5 and KRT5/14 in doubtful cases excluded APSS and localized EBS, respectively. In addition, KE appeared to be familial in a minority of cases (six of 24, 25%), which keeps the possibility of a genetic cause open.

Degradation of corneodesmosomes at the upper stratum corneum is a normal physiological process of desquamation to maintain a constant thickness of the corneal layer by shedding the outermost corneocytes at the skin surface.\(^23\) More interesting is our observation that corneodesmosomes also degraded in the middle part of the corneal layer. This finding suggests premature corneodesmolysis, which may play a pivotal role in the pathogenesis of KE.

We first examined deficiency of structural corneodesmosomal components, such as corneodesmosin, desmocollin-1 and desmoglein-1, which are associated with peeling skin disease, staphylococcal scalded skin syndrome and palmoplantar keratoderma, respectively.\(^24\) However, immunofluorescence microscopy in KE revealed normal staining for these components.

Subsequently, we hypothesized that premature corneodesmolysis could be the result of an imbalance in the activity level of enzymes involved in the desquamation process, specifically in the palmoplantar skin.\(^25\) Furthermore, SPINK6 (serine protease inhibitor Kazal-type), encoding lymphoepithelial Kazal-type inhibitor (LEKTI)-3,\(^26\) and SPINK9, encoding LEKTI-2,\(^27\) are recently discovered serine protease inhibitors of kallikrein-related peptidases (KLK) 5/7/14 and KLK5, respectively. LEKTI-3 immune expression was found within the stratum granulosum and stratum corneum of various anatomical sites of the skin (face, arm, plantar site), sebaceous glands and sweat glands, whereas LEKTI-2 immune expression was found within the stratum granulosum and stratum corneum of palmoplantar skin only. Activated KLK5, 7 and 14 can degrade corneodesmosomal components.\(^24\) We selected SPINK6/9 as candidate genes for KE, because we hypothesized that premature corneodesmolysis could be the result of increased activity of KLK5, 7 and/or 14 caused by dysfunction or absence of

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**Fig 3.** Normal expression of corneodesmosomal components in keratolysis exfoliativa (KE). Analysis of (a) corneodesmosin (CDSN), (b) desmocollin-1 (DSC1), (c) desmoglein-1 endodomain (DSG1-B11) and (d) desmoglein-1 ectodomain (DSG1-P23) in skin sections of patient no. 1. The images show a normal expression of corneodesmosomal components in KE skin, which was similar to control skin (not shown). Bar = 40 μm.
protease inhibitors LEKTI-2/3. For example, in the case of Netherton syndrome, which is characterized by ichthyosiform dermatosis, hair shaft abnormality (trichorrhexis invaginata) and atopic diathesis, mutations in SPINK5, encoding LEKTI, cause unrestricted serine protease activity in the stratum corneum resulting in overdesquamation of corneocytes.\(^{28,29}\) As no mutations were found in SPINK6/9 in our patients with KE, our theory of an imbalance between enzyme activity of serine proteases and their inhibitors in the desquamation process could not be demonstrated. However, it might be possible that other proteases, such as cathepsins, which are also present in human epidermis, are involved in the pathophysiology of KE.

In summary, KE is a distinct entity characterized by cyclic air-filled blisters and centrifugal collarette peeling of glabrous digital, palmar and plantar skin. Both sporadic and familial cases were found. The histopathological and ultrastructural characteristics are cleavage within the stratum corneum and partial degradation of corneodesmosomes in the mid stratum corneum, suggesting premature corneodesmolysis as the main pathological mechanism in KE. However, immunofluorescent staining showed normal expression of corneodesmosomal components and no mutations were found in SPINK6/9.

Further studies in KE cases on other desquamation enzymes and inhibitors, such as secretory leucocyte protease inhibitor (SLPI), alpha-2 macroglobulin-like 1 (A2ML1), cholesterol sulphate and zinc ion may shed more light on the possibly genetic or acquired cause of this succinct dermatological entity.\(^{30}\)

### What’s already known about this topic?

- Keratolysis exfoliativa also known as dyshidrosis lamelllosa sicca was initially described a century ago, but has almost been forgotten.
- This palmoplantar peeling disorder has been confused with dyshidrotic eczema, dermatophytid reaction or acral peeling skin syndrome.

### What does this study add?

- Delineation of this distinct peeling entity, not related to eczema, was carried out by studying the largest cohort of 24 patients using modern laboratory techniques.
- Premature corneodesmolysis was found in the stratum corneum. Mutations in TGM5, KRT5/14 and SPINK6/9 were excluded.

### Acknowledgments

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