Case Report

A PARTICULAR CASE OF AUTOSOMAL RECESSIVE PROGRESSIVE SYMMETRICAL ERYTHROKERATODERMA (PSEK) AND A REVIEW OF THE LITERATURE

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Abstract: ***Case report*** A A 10-year-old female patient born from non-consanguineous healthy parents after a regular pregnancy developed, at the age of 3 months, diffuse hyperkeratotic, pruritic plaques on her face, forearms, wrists, perineal and sacral regions in a mosaic pattern distribution, growing progressively. Laboratory and instrumental investigations, and a skin biopsy were performed, and both the patient and her parents underwent genetic testing. Histology described acanthosis and orthokeratotyc hyperkeratosis in a basket-weave pattern. Genetic investigations revealed, in our patient, a pathogenic paternal variant and the deletion of the corresponding maternal allele associated with the autosomal recessive form of Progressive Symmetrical Erythrokeratodermia (PSEK).

Discussion A review of the literature showed similarities and differences with this case. Diagnosis of autosomal recessive PSEK was made, uniquely associated in our patient with another genetic mutation of the KRT2 gene. Systemic retinoids and topical emollients were started, leading to a significant reduction of hyperkeratosis and a progressive resolution of the lesions. The most interesting feature was their further evolution, with the onset of sparing areas, suggestive of revertant mosaicism, although not confirmed by histology.

Conclusion This is the first case of Progressive Symmetrical Erythrokeratodermia associated with both the c.879G>A genomic variant in the KDSR gene and the p.Ala517Gly genetic variant of the KRT2 gene. A clinical picture was suggestive of revertant mosaicism observed in the patient, which, to date, has never been described in the literature. Systemic therapy with oral retinoids in association with topical keratolytics.

Keywords: Progressive Symmetrical Erythrokeratodermia, rare disease, pediatrics, genetics.

CASE PRESENTATION A 10-year-old female patient born from non-consanguineous healthy parents after a regular pregnancy developed, at the age of 3 months, cutaneous lesions initially described as “eczematous” on her face and scalp.

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At the time of her first dermatological evaluation, four months after, lesions had evolved into diffuse hyperkeratotic and pruritic plaques particularly affecting her face, forearms, wrists, perineal and sacral regions in a mosaic pattern distribution (Figures 1a; 2a; 3a; 4a; 5a). Progressive growth of the lesions was observed until the age of 4 years, when lesions became stable (Figures 1b, c: 2b-d; 3b, c; 4c; 5c).

Considering the positive family history for atopy (mother), the suggested diagnostic hypotheses were atopic dermatitis and Netherton syndrome. According to the

clinical picture, Chanarin Dorfman syndrome and Progressive Symmetrical Erythrokeratodermia (PSEK) were also considered.

Once the parents' informed consent was obtained, several diagnostic investigations were performed, including genetic testing of the patient and both her parents, a skin

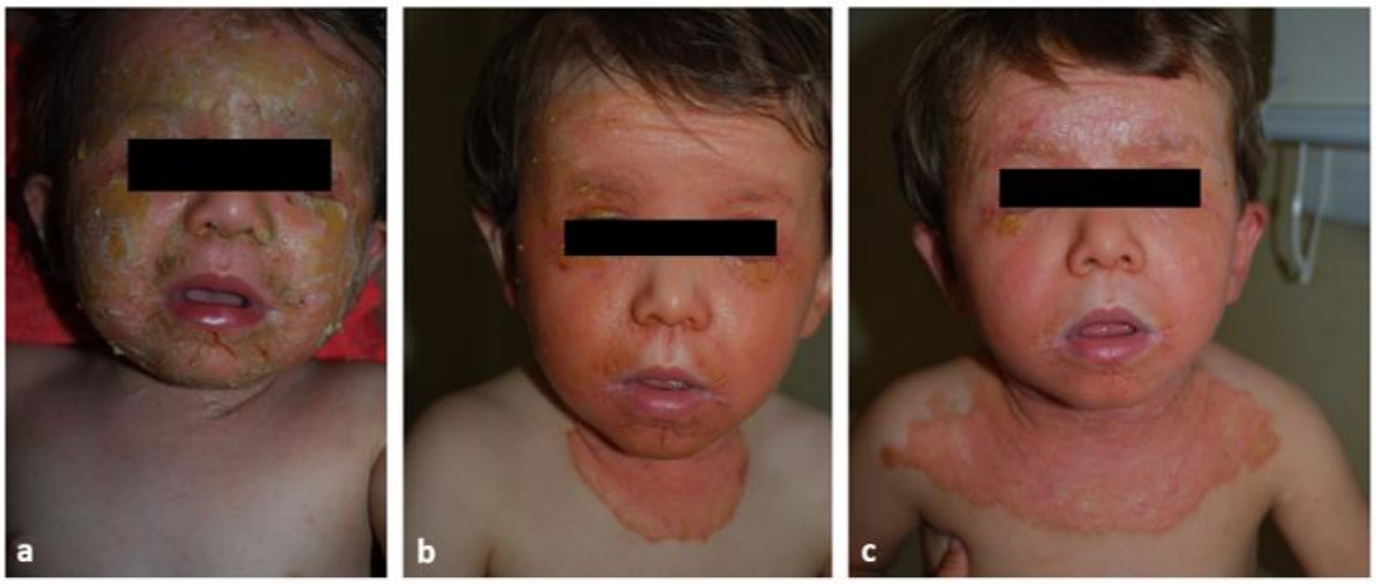

Figure 1: a. Hyperkeratotic confluent plaques of the face on an erythematous base; b-c. Progressive growth of the lesions with neck involvement and reduction of the hyperkeratosis.

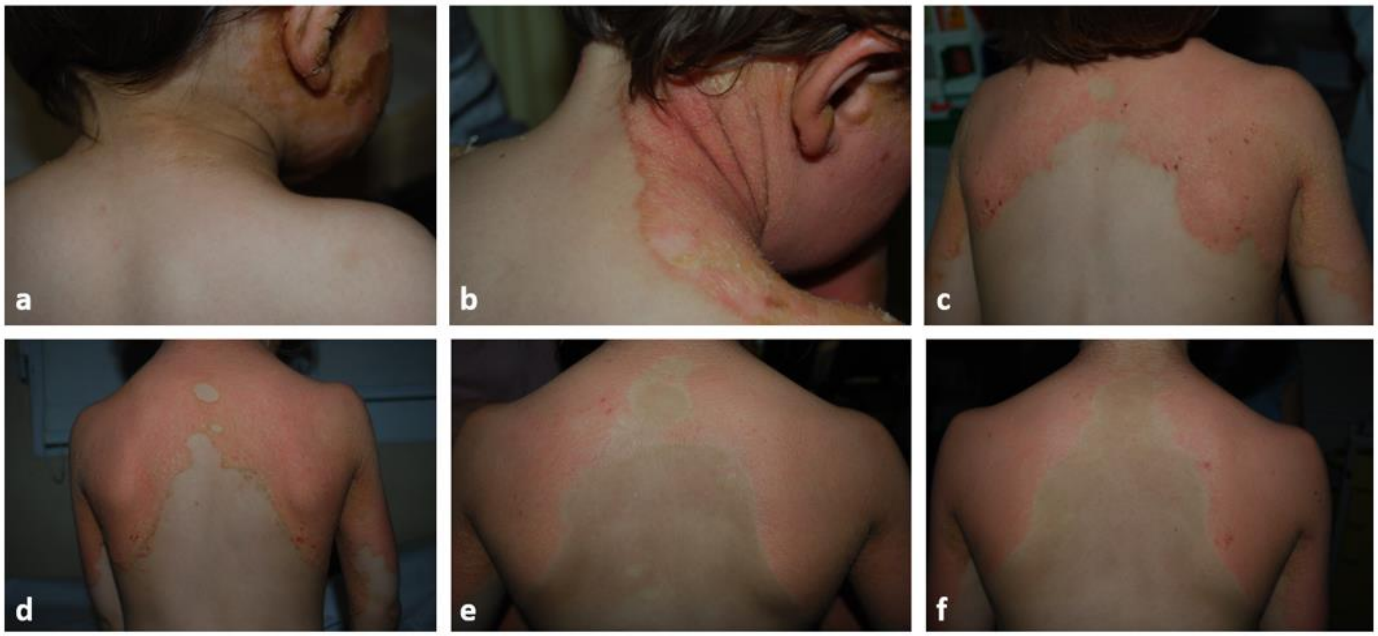

Figure 2: a. Hyperkeratotic confluent plaques of the face on an erythematous base; b-d. Progressive growth of the lesions with neck and upper back involvement and reduction of hyperkeratosis; e-f. Clinical revertant mosaicism on the upper back.

biopsy of one of the lesions, blood tests, and instrumental examinations.

In the suspicion of Chanarin Dorfman Syndrome and keratinopathic ichthyoses, a gene panel was performed, including ABHD5, KRT1, KRT2, KRT9, and KRT10 genes. Only the maternal variant p.Ala517Gly of uncertain significance in *KRT2*gene was found but not considered causative of the lesions. Molecular analysis of GJB2 and GJB4 genes did not show any alteration. Genetic

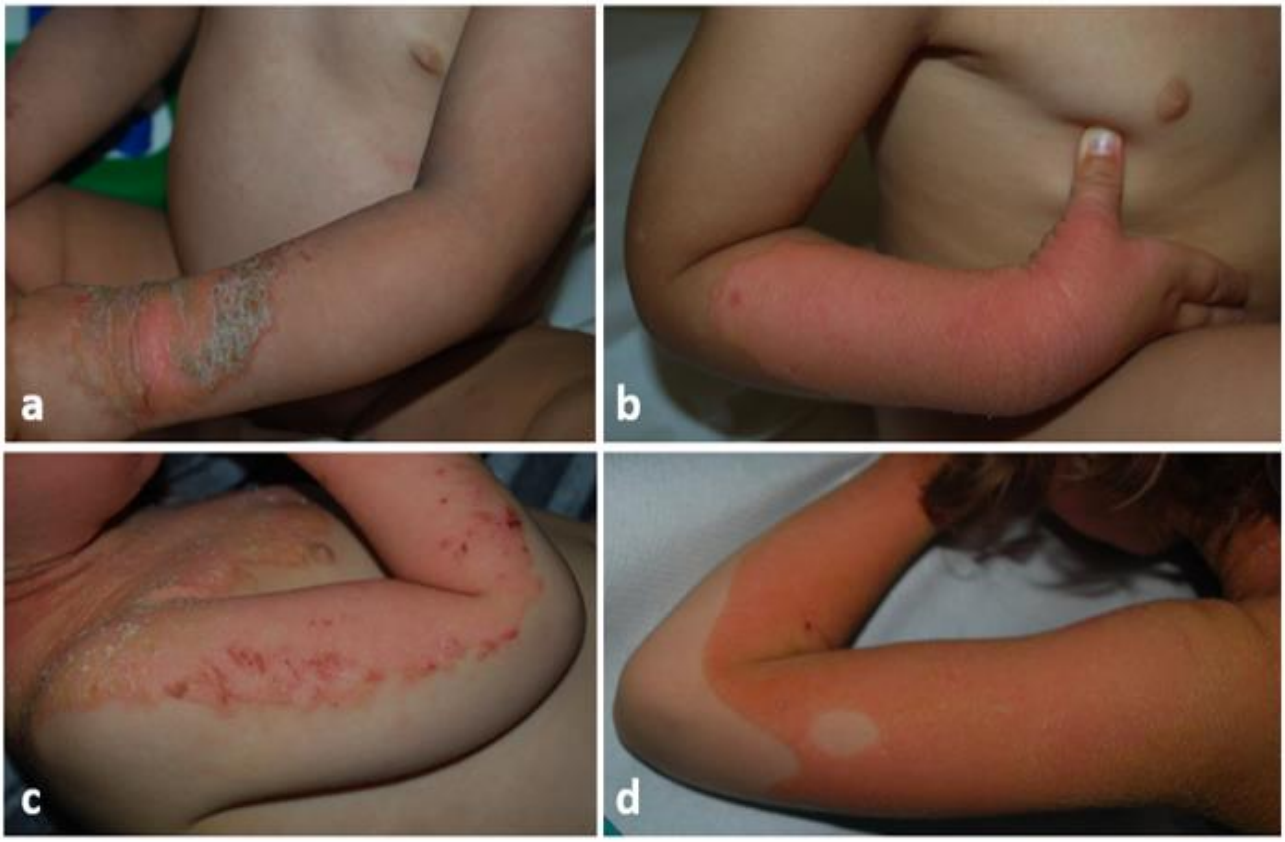

Figure 3: a. Hyperkeratotic plaque of the forearm on an erythematous base; b-c. Progressive growth of the lesion over the arm and reduction of hyperkeratosis; d. Clinical revertant mosaicism on the arm**.**

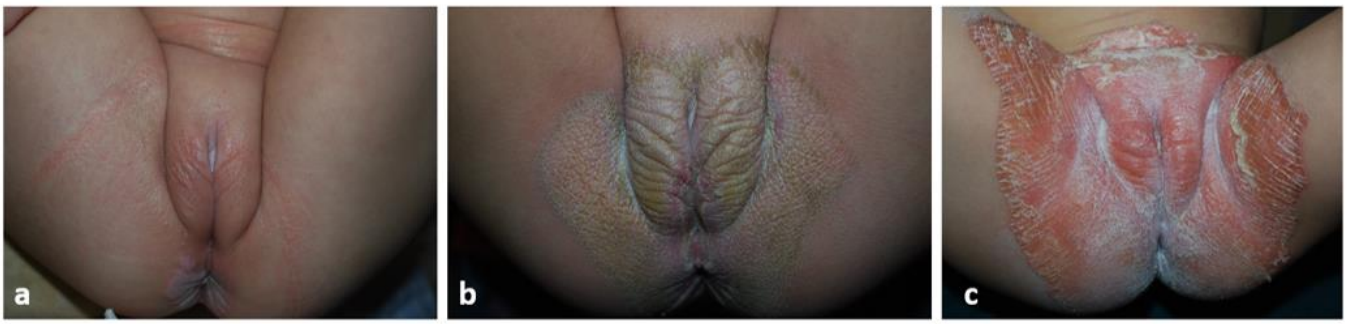

Figure 4: a. Initial hyperkeratotic plaques of the perineal region; b-c. Progressive growth of the lesions over labia majora and inner thighs.

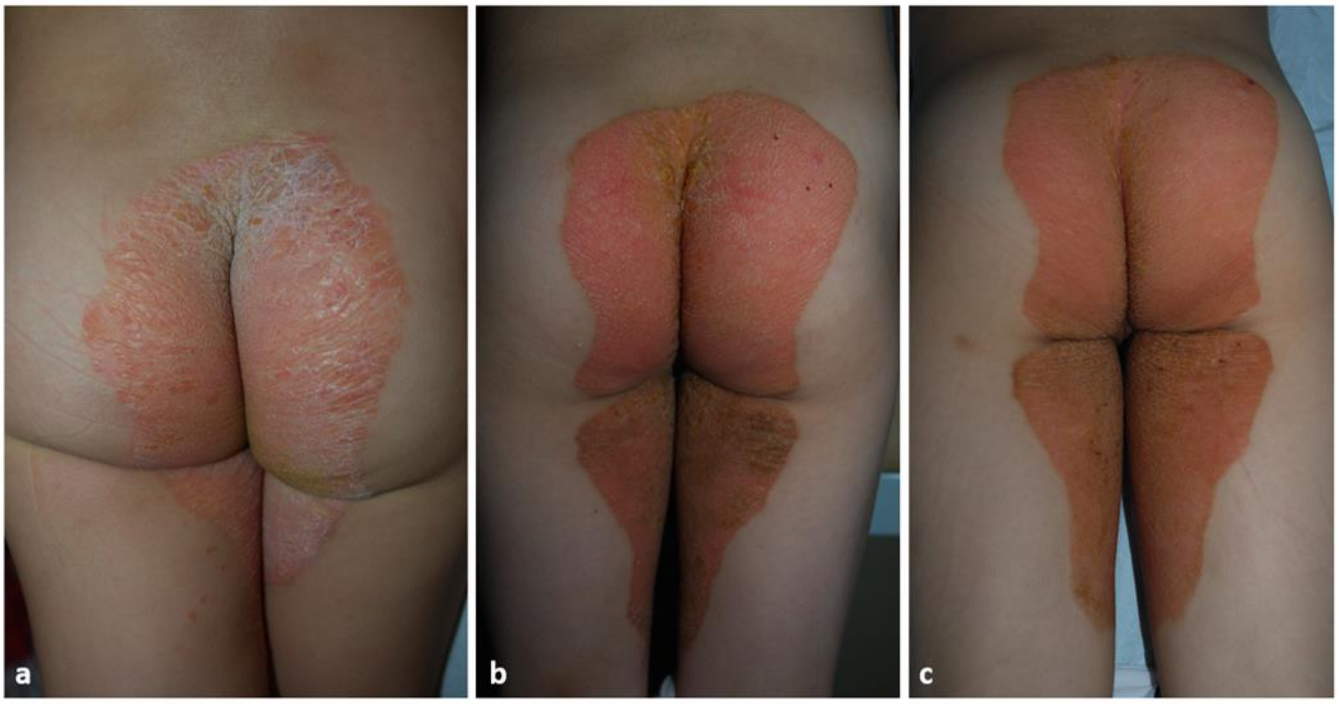

Figure 5: a. Erythematous hyperkeratotic plaque of the sacral and gluteal regions; b-c. Progressive growth of the lesion over the inner thighs and reduction of hyperkeratosis.

investigation revealed the pathogenic hemizygous variant c.879G>A in the paternal allele (heterozygous father), known to be associated with the autosomal recessive form of progressive symmetrical erythrokeratodermia [1].

A deletion on the corresponding maternal allele was also demonstrated. Furthermore, in our patient, molecular analysis of the KRT2 gene detected a genetic variant that causes the replacement of an alanine residue with a glycine residue at the 517 positions of the encoded protein chain, which has been classified as an uncertain significance variant. The latter represents a genetic variant classified by specific informatic predictive tools as benign or uncertain, with a 3/1000 allele frequency in the general population.

Histology of the lesions showed acanthosis and orthokeratotyc hyperkeratosis in a basket-weave pattern.

While laboratory exams were within normal ranges, the peripheral blood smear showed an infiltrate of neutrophils and monocytes presenting intracytoplasmic vacuoles, a "Jordans' anomaly" finding. Abdomen ultrasound and otoacoustic emissions showed no alteration as long as the child's neuropsychiatric and eye examination. The clinical picture, supported by histology and laboratory examinations, led to the clinical diagnosis of autosomal recessive PSEK and was confirmed by genetic analysis of the KDSR gene.

Treatment with oral acitretin at the initial dose of 5 mg daily was then started, associated with topical emollients, which led to a reduction of hyperkeratosis and a progressive resolution of the lesions on the face and scalp (Figures 1b, c; 2b-f; 3b-d; 4c; 5b,c).

The most interesting feature was the further evolution, with the onset of sparing areas within the lesions clinically suggestive of revertant mosaicism (Figures 2d-f; 3d).
The patient is currently followed by our Rare Disease Inpatient, still on oral retinoid treatment with isotretinoin 10mg daily.

DISCUSSION

Progressive Symmetrical Erythrokeratodermia (PSEK), also known as Gottron syndrome, is a rare genetic skin disorder

representing one of the Mendelian forms of erythrokeratoderma, together with erythrokeratoderma variabilis (EKV), Vohwinkel syndrome and a syndrome of erythrokeratoderma, ichthyosis, and cardiomyopathy (EKC syndrome) [1].

PSEK inheritance is usually autosomal dominant and often results from heterozygosity for a de novo mutation [2]. Genetic penetrance can be incomplete, and the clinical expressivity is variable [2]. In 2017, Boyden *et al*. [1] described four patients with biallelic variations in the KDSR gene (3-ketodihydrosphingosine reductase), encoding an enzyme in the ceramide synthesis pathway, which caused a new phenotype included in the progressive symmetric erythrokeratoderma spectrum with autosomal recessive inheritance. The latter mutation corresponds to the one found in our patient who, in addition to that, presented the p.Ala517Gly genetic variant of the KRT2 gene of benign or uncertain significance.

Clinically, PSEK is characterized by fixed hyperkeratotic plaques on an erythematous base, with a symmetric distribution on extremities, buttocks, and occasionally face and torso. The lesions slowly become progressive in number and size, usually stabilizing after puberty, but without spontaneous remission [2].

Thrombocytopenia is another distinctive feature of the disease. It could be explained by the defective enzyme activity in KDSR, resulting in an impaired biosynthesis of acylceramide and sphingolipids, which represent key cofactors in developing cytoskeleton in keratinocytes and platelets. In literature, four affected patients are described with piastrinopenia [18,19] due to the same share affected pathway in skin and platelets.

Diagnosis of PSEK is based on clinical examination, typical histologic findings, and genetic testing.

Treatment options include topical keratolytics and retinoids in milder cases, while systemic therapy with retinoids is the first-line choice for moderate to severe manifestations [2].

Retinoids have proven to increase sphingosine acylation and upregulate sphingomyelinase, thus stimulating the ceramide salvage pathway and sphingomyelinase pathway, which produce ceramides independent of KDSR. Thus, the effectiveness of the therapy may be due, at least in part, to the compensation for a genetic defect in the ceramide de novo synthesis pathway, via pharmacologic induction of alternative pathways for ceramide generation [1].

Due to its rarity, only case reports of PSEK are described in the literature (Table 1). Of the 21 patients described [2-16,18], in one patient [10] the c.434A>G genomic variant in the KDSR gene, determining the p.Asn145Ser variant at the protein level, was found. Takeichi *et al*. [18] described four patients who carried different mutations of the KDSR gene, with two clinically resembling Harlequin ichthyosis. In all other case reports, the inheritance pattern is reported, but not the genetic variations.

Cutaneous lesions and their progression are comparable to our patient's, as are histologic findings of the biopsied lesions [2,3,5,7-13,15-17]. However, our patient never developed thrombocytopenia.

In literature, 12 patients were treated with oral retinoids, 1 of which with etetrinate [4], 1 patient assumed isotretinoin [9], while 10 patients were treated with acitretin [2,3,5-8,10-13,18], as in our case, and one of them was then switched to isotretinoin [10]. Topical keratolytics were used in monotherapy in one patient[16], while in association with systemic retinoids in 4 patients [2,4,8,13]. Other local treatments associated with systemic therapy were topical 0.025% tretinoin in two cases [2,11] and topical calcipotriol in one patient [9].

When reported, outcomes show a good response to therapy in six patients [2,9-12,16], but with a relapse of the lesions after discontinuation of the treatments in 2 of them [9,16], in one patient on acitretin and topical keratolytics no improvement was observed [8], and 3 patients were treated with acitretin without any benefit. None of the cases reported a revertant behavior of the lesions, as in our patient.

CONCLUSION This is the first case of Progressive Symmetrical Erythrokeratodermia associated with both the c.879G>A genomic variant in the KDSR gene and the p.Ala517Gly genetic variant of the KRT2 gene. It has to be proven whether this genetic association is coincidental or a phenotype- determining factor.Furthermore, a clinical picture suggestive of revertant mosaicism was observed in our patient, which, to date, has never been described in the literature. Based on reported cases, systemic therapy with oral retinoids in association with topical keratolytics was started and is still ongoing, with a progressive improvement of the lesions maintained over time.

Author, Year	n pts	Sex, age	Mutation	Clinical picture	Histology	Treatment
Agrawal US et al., 1987	1	M, 6	NA, positive family history	Progressive, well-defined, erythematous hyperkeratotic plaques on the dorsum of hands, feet, shins, popliteal fossae, axillae, neck, anterior abdomen	Marked hyperkeratosis, acanthosis, patchy parakeratosis	NA
Ghorpade A et al., 1995	1	M, 10	NA, sporadic	Symmetrical, well-defined, erythematous raised plaques with fine scales on knees, dorsa of the hands, upper arms, elbows and ankles.	Hyperkeratosis, focal parakeratosis, intact granular layer, acanthosis. Mild dermal chronic inflammatory infiltrate	Topical keratolytics but recurrence after discontinuation
Sunil G et al., 1999	1	M, 13	NA sporadic	Erythematous, scaly, bilaterally symmetrical, gradually progressive plaques on knees and elbows, hyperkeratotic plaques on fingers and toes. Keratoderma of palms and soles. Arched palate, fissured tongue, pectus excavatum.	Hyperkeratosis, focal acanthosis, papillomatosis. Dermal focal aspecific inflammatory infiltrate	NA
Arroyo MP., 2002	1	M	Other family members affected	symmetric and progressive hyperpigmented, hyperkeratotic plaques	NA	NA
Chu DH et al., 2003	1	M, 9	NA, 2 brothers similar lesions	Multiple, hyperpigmented, hyperkeratotic plaques in geographic shapes on the face, neck, chest, back, abdomen, and arms, including the axillae and antecubital fossae. No nail changes. Normal digits, palms, and soles.	papillated epidermal hyperplasia with hypergranulosis, parakeratosis, and compact orthokeratosis.	NA
Raza N et al., 2006	1	M, 9		Fixed hyperpigmented, keratotic plaques, perioral involvement	NA	Oral etetrinate and topical keratolytics
Akman A et al., 2008	1	M, 3,5	No mutation. Similar findings in uncle (father's brother)	Hyperkeratotic skin lesions on the flexural regions and the trunk. pruritic erythematous, brownish patches on the axillae at 3 months of age. Similar lesions gradually developed in other flexural areas and on the trunk	hyperkeratosis, irregular acanthosis, focal papillomatosis and perivascular lymphocytic infiltration	NA
Prabhu S et al., 2010	1	M, 28	NA	Dry, scaly, well-demarcated plaques with fissures over dorsa of the hands, elbows, knees, ankle, and shin,palmoplantar keratoderma. Less demarcated and less scaly plaques over both axillae and scapular regions with diffuse scaling over scalp, waist, and buttocks	hyperkeratosis, parakeratosis and acanthosis with mild spongiosis and a patchy lymphohistiocytic infiltrate in the upper dermis	Acitretin 25 mg/day perorally with improvement
Bilgin I et al., 2011	1	F, 20	NA	Symmetrically distributed erythematous and hyperkeratotic reddish-brown plaques in axillae, groins and submammary regions. palmoplantar hyperkeratosis	orthohyperkeratosis , irregular acanthosis and focal papillomatosis	oral isotretinoin (0,5 mg/kg) with no improvement after two months. topical calcipotriol ointment was applied twice a day with

				and mild desquamative plaques on eyelids. Normal teeth, nails and hair		clearing of lesions but relapse after stop
Yan HB et al., 2011	1 proband	M, 22	NA. 16/45 individuals of his f ive generation family affected (AD inheritance, incomplete penetrance)	Well-demarcated, symmetrically distributed hyperkeratotic erythematous plaques covered with white pityriasiform scales on the extensor surfaces of the extremities (dorsum of hands and feet, wrists, elbows, knees, ankles and lower limbs) Desquamation and keratosis of the palms and soles. thickened yellowish nails of the left hand and feet, transverse ridges in some nail plates.	marked hyperkeratosis, parakeratosis, acanthosis, elongation of rete ridges, extension of dermal papillae and lymphocytic infiltration around the superficial blood vessels	oral acitretin 20 mg/day along with topical tretinoin 0.025% ointment with marked improvement
Guaraldi Bde M et al., 2013	1	F, 55	NA	Fixed, finely scaly, symmetric erythematous keratotic plaques on the dorsum of the hands, interphalangeal pads, wrists, elbows, groin and feet. Thicker plaques on the elbows. Well-defined, brownish-colored hyperpigmentation halo on the inguinal region.	Discrete papillomatosis and acanthosis, orthokeratotic hyperkeratosis in a basket-weave pattern and maintenance of the granular layer	Acitretin 20mg/day, topical 0.025% tretinoin , 20% urea and 3% salicylic acid and moisturizing lotion, with excellent response
Guo BR et al., 2013	2 probands	1) F, 16 2)M, 26	1) 10 affected members in 4 generations 2) 5 affected members in 3 generations AD inheritance in both families, no mutations found	Both pts presented with typical characteristics of PSEK	NA	NA
Gupta LK et al., 2014	1 proband	M, 30	NA. Other 6 family members affected (AD inheritance)	Asymptomatic, multiple, relatively fixed, sharply demarcated, hyperkeratotic, polycyclic, dark brown plaques of varying sizes and shapes simmetrically on the trunk, buttocks, elbows, and dorsal surfaces of the hands, knees, and feet . diffuse thickening and scaling palms and soles.normal hair, nails, teeth, and mucous membranes	thick, laminated, bright pink, orthokeratotic horny layer, moderate irregular epidermal hyperplasia, and a well-formed granular layer with sparse, superficial perivascular lymphocytic infiltrate	emollients, urea and salicylic acid ointment, acitretin at 25 mg/day for three months without any benefit
Asha GS et al., 2016	1	M, 44	NA, family members similar lesions	Well-demarcated, hyperpigmented, scaly plaques symmetrically distributed, palmoplantar keratoderma (PPK) with pseudoainhum, dystrophic nails	marked hyperkeratosis, significant parakeratosis, acanthosis, church spire appearance, moderate mononuclear infiltration in the upper dermis	Acitretin 0.5mg/kg/die→isotretinoin 20mg/die

Takeichi T et al., 2017	4	1)M, 15 2)M,21 3)M, 0 4)M, 6	1)KDSR (c.413T>G: p.Phe138Cys) 2)KDSR (c.413T>G: p.Phe138Cys) 3)KDSR (c.812G>A: p.Gly271Glu) 4)KDSR (c.223_224delGA: p.Glu75Asnfs*2)	1) Palmoplantar and perianal keratoderma, thrombocytopenia 2) Palmoplantar and perianal keratoderma, perianal erythema and hyperkeratosis, thrombocytopenia 3) Harlequin ichthyosis, thrombocytopenia 4) Harlequin ichthyosis, thrombocytopenia	1) psoriasiform acanthosis, hyperkeratosis, focal hypergranulosis and parakeratosis	1) Acitretin 0.5 mg/kg/day, with no improvement 2) Acitretin, with no improvement 3) Acitretin, greasy emollients, lubricating eye drops. Scaling reduction, but fatal pseudomonas septicaemia 4) Neonatal intensive care with gradual desquamation resulting in generalized erythroderma and fine scaling
Tiwary AK et al., 2019	1	F, 10	NA	Well=defined, erythematous, hyperkeratotic, scaly, plaques symmetrically distributed over the dorsa of fingers and knuckles, knees, and dorsa of feet and toes. multiple round, keratotic, punctate lesions on palmar creases and hypothenar skin and plantar surface, predominantly over pressure-prone areas.	orthohyperkeratosis , focal parakeratosis, acanthosis, and superficial perivascular lymphocytic infiltration	Topical keratolytics, emollients, and oral vitamin A but lost at follow-up
Altawil L et al., 2021	1	M, 4	KDSR (NM_002035.4:c.434A[G [p. Asn145Ser])	At birth, thick, platelike hyperkeratotic scales, ectropion, eclabium. thick scales gradually desquamated, resulting in well-demarcated, symmetric, erythematous thick hyperkeratotic plaques on the face, neck, trunk, axillae, groin, buttocks, medial aspect of the extremities, and dorsal and volar aspects of the hands and feet. fixed flexion deformity of the elbows, hands, and feet, mitten hand deformity. a sharply demarcated erythematous scaly plaque on the upper half of the face.	hyperkeratosis, acanthosis, and papillary dermis fibrosis	Acitretin 1 mg/kg/day started at the age of 5 months then isotretinoin 1 mg/kg/day with slow tapering to 0.5 mg/kg/day with good response

Table 1. Number and characteristics of patients, clinical picture, histology, treatments of PSEK cases reported in literature. NA=not applicable, genetic investigations not performed.

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