RESEARCH LETTER

Keratoderma-hypotrichosis-leukonychia Totalis Syndrome: A New Case Report of an Exceptional Entity

Carlos GUTIÉRREZ-CERRAJERO[1,2], Nerea GESTOSO-UZAL[1,2], Nelmar Valentina ORTIZ-CABRERA[3], Rogelio GONZÁLEZ-SARMIENTO[1,2] and Ángela HERNÁNDEZ-MARTÍN[3*]

*[1]Department of Medicine, Faculty of Medicine, University of Salamanca, Salamanca, [2]Biomedical Research Institute of Salamanca (IBSAL), Salamanca, and [3]Department of Dermatology, Hospital Infantil Niño Jesús, Avenida Menendez Pelayo, 65, Madrid, Spain. *E-mail: ahernandez@aedv.es*

Submitted Feb 14, 2025. Accepted after revision May 13, 2025
Published May 27, 2025. DOI: 10.2340/actadv.v105.43168. Acta Derm Venereol 2025; 105: adv43168.

To the Editor,

Keratoderma-hypotrichosis-leukonychia totalis syndrome (KHLS, MIM:104100, ORPHA:1010) is an exceedingly rare disorder of keratinization characterized by hypotrichosis, whitish discoloration of all 20 nails (leukonychia totalis), palmoplantar keratoderma (PPK), and hyperkeratotic lesions on different parts of the body (1). A heterozygous gain of function mutation in *GJA1* has been found to cause KHLS (2). We provide the second report of a molecularly proven case of KHLS displaying this same *GJA1* variant and discuss the clinical overlap of KHLS with other conditions caused by *GJA1* variants.

A 4-year-old Caucasian male showed short sparse hair on the scalp, eyebrows, and eyelashes, keratosis pilaris and erythema (ulerythema ophryogenes) on the eyebrows and cheeks, bilateral auricle erythema, leukonychia totalis and well-defined erythematous hyperkeratotic plaques on the elbows, knees, buttocks, axillae, perineal, and popliteal folds, Achilles heels, as well as bony prominences of the dorsal feet and dorsal aspects of fingers and toes (**Fig. 1**). Palms and soles were spared (**Fig. 2**). Eyes, teeth, and hearing were normal. Histological study showed hyperkeratosis, acanthosis, and mild inflammatory infiltrate within the upper dermis. Electron microscopy revealed trichoschisis, weathering of the cuticle and pits on the hair shaft. He had been born to healthy non-consanguineous parents and had a healthy 7-year-old sister. Family background was unremarkable.

Throughout the 6-year follow-up period, scalp, eyebrow, and eyelash hypotrichosis has remained stable, while cutaneous lesions have experienced waxes and wanes, showing variable degrees of involvement in size, erythema, and hyperkeratosis. Palms and soles continue to be completely spared. Systemic therapy with oral acitretin (doses ranging from 0.5 to 1 mg per kg per

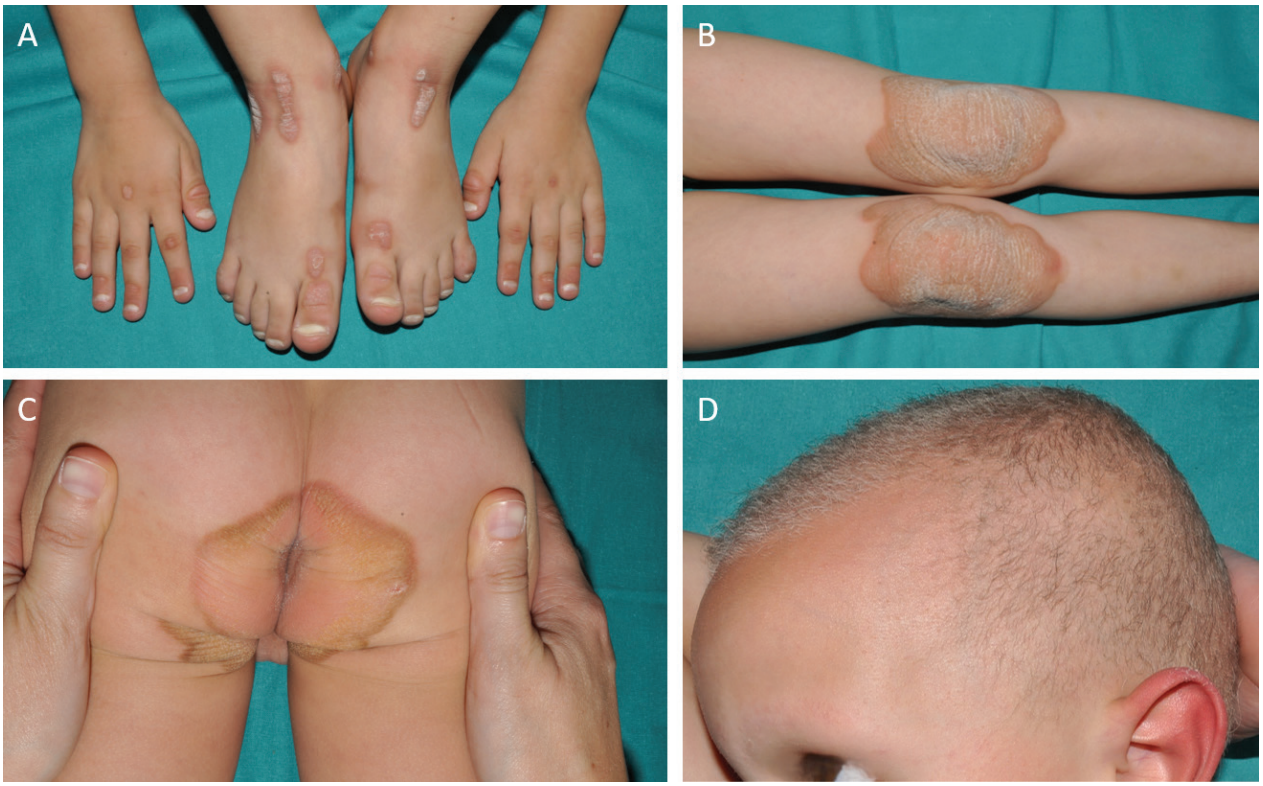

Fig. 1. Clinical presentation of patient with keratoderma-hypotrichosis-leukonychia totalis. (A) Hyperkeratotic lesions on the friccional areas of hands and feet, and leukonychia of all twenty nails; (B) Hyperkeratosis on the knees of reddish-to-brown hue; (C) perineal involvement; (D) Hypotrichosis, keratosis pilaris of the eyebrows and erythema (ulerytherma ophryogenes) and redness of external eaf.

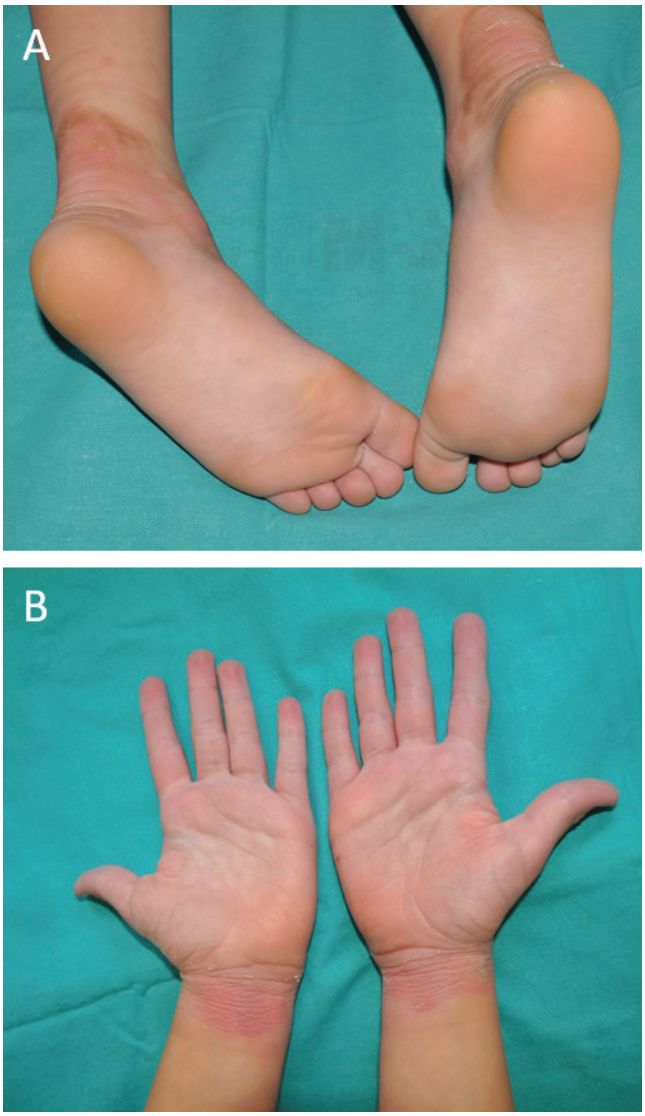

Fig. 2. Palms and soles were spared lacking palmoplantar hyperkeratosis.

day), first introduced when the patient was 5 years old, has achieved only partial improvement in the hyperkeratotic lesions.

After obtaining informed consent, DNA from patient peripheral blood was obtained and exome sequencing was performed using the Illumina Truseq DNA Exome Kit (https://www.illumina.com/documents/products/datasheets/datasheet_truseq_dna_sample_prep_kits.pdf). Mutation NM_000165.5 c.23G>T (NP_000156.1 p.Gly8Val) in *GJA1* was identified in heterozygosis and subsequently validated using Sanger sequencing with the following primers: GJA1-1F: 5'-TGTTTCTTTCAGGTGGTGCCC and GJA1-1R: 5'-TCCCTCCAGCAGTTGAGTAG.

A scarce number of patients characterized by the triad of 20-nail leukonychia, hyperkeratotic lesions, and PPK have been reported to date (1–3). The causative gene was first reported by Wang et al. in 2015, who observed the same *GJA1* variant as seen in our patient and coined the term KHLS (2). Shortly thereafter, Boyden et al. reported 3 additional patients with another 2 *GJA1* variants showing a similar clinical condition that they classified as erythrokeratodermia variabilis et progressiva (EKVP), an umbrella term that describes clinical findings that completely overlap with those of KHLS and has been associated with several gene variants (3, 4). Interestingly, all reported patients showed a variable degree of palmoplantar hyperkeratosis, a clinical finding completely absent in our patient. This finding challenges the current categorization of the disorder as a palmoplantar keratoderma and may have diagnostic relevance, particularly in atypical or mild presentations (5). The striking phenotypic similarities, common genotypic basis and variable palmoplantar involvement suggest that KHLS and EKVP might be the same condition with slight (or underrecognized) clinical differences.

Conflict of interest disclosures: CGC, NGU, NVOC, and RGS have no conflicts of interest to declare. AHM: Researcher: Mayne Pharma, Celgene; Advisory boards: Sanofi, Viatris, Almirall, Galderma, L'Oréal; Speaker/Faculty Education: Sanofi, Viatris, L'Oréal, Leti Pharma, Beiersdorf, Alexion.

REFERENCES

1. Basaran E, Yilmaz E, Alpsoy E, Yilmaz GG. Keratoderma, hypotrichosis and leukonychia totalis: a new syndrome? Br J Dermatol 1995; 133: 636–638. https://doi.org/10.1111/j.1365-2133.1995.tb02720.x
2. Wang H, Cao X, Lin Z, Lee M, Jia X, Ren Y, et al. Exome sequencing reveals mutation in GJA1 as a cause of keratoderma-hypotrichosis-leukonychia totalis syndrome. Hum Mol Genet 2015; 24: 243–250. https://doi.org/10.1093/hmg/ddu442
3. Boyden LM, Craiglow BG, Zhou J, Hu R, Loring EC, Morel KD, et al. Dominant de novo mutations in GJA1 cause erythrokeratodermia variabilis et progressiva, without features of oculodentodigital dysplasia. J Invest Dermatol 2015; 135: 1540–1547. https://doi.org/10.1038/jid.2014.485
4. Ishida-Yamamoto A. Erythrokeratodermia variabilis et progressiva. J Dermatol 2016; 43: 280–285. https://doi.org/10.1111/1346-8138.13220
5. Sprecher E, Ishida-Yamamoto A, Schwartz J, Akiyama M, Aldwin-Easton M, Choate K, et al. Palmoplantar epidermal differentiation disorders: a new classification towards pathogenesis-based therapy. Br J Dermatol 2025 Mar 19 [Online ahead of print]. https://doi.org/10.1093/bjd/ljaf054