A RARE CASE OF UNNA-THOST PALMOPLANTAR KERATODERMA

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Summary

Palmoplantar keratoderma is an ailment that involves a rather persistent thickening of the stratum corneum of the palms and soles. Palmoplantar keratodermas can be either genetically inherited or, more often, acquired conditions. The damage brought about to the palms and soles can lead to not only local pain and mobility difficulties, but also infections and discomfort caused by hyperhidrosis. We report the case of a 67-year-old female patient known to suffer from a congenital form of isolated diffuse palmoplantar keratoderma.

Key words: *palmoplantar keratoderma, diffuse, hereditary, Unna-Thost disease.*

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Introduction

Palmoplantar keratodermas are a group of various inherited or acquired afflictions whose common denominator is the thickening of the skin of palms and soles.[1] Hereditary palmoplantar keratodermas are a heterogeneous group of genodermatoses defined by a marked thickening of the stratum corneum of the palms and soles caused by a defective epidermal differentiation process.[2]Acquired palmoplantar keratodermas can accompany different dermatoses such as lichen planus, psoriasis and eczema, or can be present as a paraneoplastic phenomenon.[3] Occasionally, they can develop as a result of the use of certain medications, such as beta-blockers, calcium-channel-blockers, venlafaxine, lithium, hydroxyurea or bleomycin.[4]

Diffuse palmoplantar keratodermas are diseases with autosomal dominant inheritance caused by mutations in the KRT1, KRT9 and/ or KRT16 genes. Isolated forms of the disorder associate no other abnormalities. However diffuse palmoplantar keratoderma can also be seen in various syndromes, when it is associated with other defects such as deafness, joint damage, hair, nail and teeth abnormalities or arrythmogenic cardiomyopathy.[3] No predilection for race has been demonstrated for the isolated cases of diffuse palmoplantar keratoderma[1], while the incidence does seem to be somewhat higher among males.[5]

Clinical case

We report the case of a 67-year-old female patient who addressed our dermatology department for a thick, compact, hyperkeratotic layer affecting the whole surface of the palms and soles. While a certain degree of hand mobility impairment was present, the patient had no subjective complaints. The patient informed us that she had been suffering from this condition since she was about one year old. Family history revealed the presence of the same disorder in two other family members: her grandmother and her sister. However, the two children that the patient

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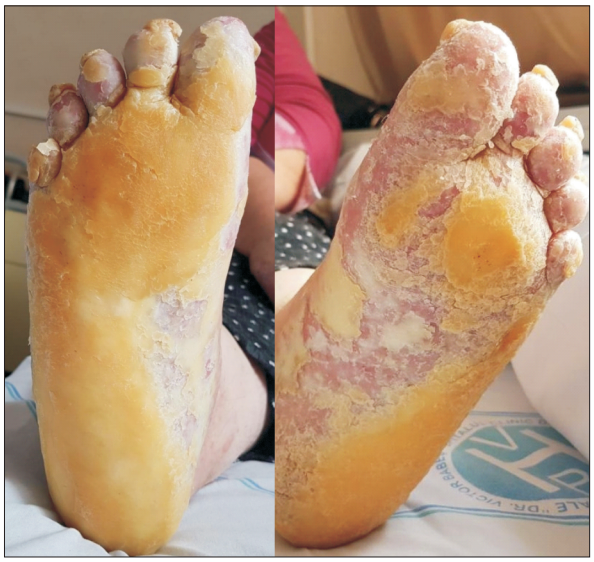

Fig. 1. Hyperkeratosis on the soles

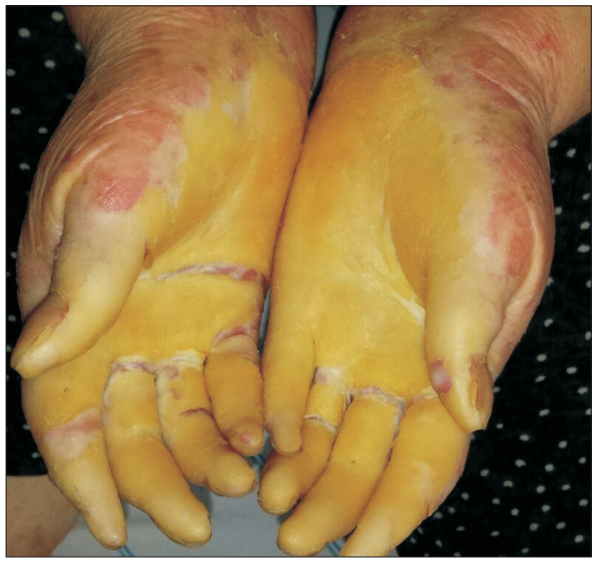

Fig. 2. Hyperkeratosis on the palms

had given birth to did not suffer from this condition. A previous biopsy had established the diagnosis of non-epidermolytic palmoplantar keratoderma, also known as Unna-Thost disease. Medical history also revealed high blood pressure which was treated with a combination of three different antihypertensive drugs. Despite her condition, the patient worked in a textile factory until she retired.

Physical examination showed a dense, hyperkeratotic layer with a wax-like aspect that was occupying the whole area of the palms and soles (*Fig. 1*, *Fig. 2*). On the dorsal sides of the hands and feet,ill-defined, erythematous, scaly patches were easily noticeable, having different sizes and shapes. The excessive keratin production had a damaging effect on the fingers, causing them to remain almost permanently fixed in an adduction position.

Laboratory tests that were performed upon admission only revealed a minor increase in the ESR value. The treatment consisted of topical keratolytic and keratoplastic agents, to which the patient had a favourable response.

Discussions

Genetically inherited palmoplantar keratodermas are very heterogenous medical conditions. Depending on the clinical aspect, they can be divided into three main groups, namely diffuse, punctate and focal palmoplantar keratodermas[1, 6] (*Table 1, 2*). Diffuse palmoplantar keratoderma affects the whole surface of the palms and soles, while focal forms consist of limited, circumscribed, hyperkeratotic lesions. Punctate forms involve hyperkeratotic papules and sometimes nodules scattered on the palms and soles.[7] Palmoplantar keratodermas can show up as isolated clinical conditions or they can be part of various syndromes(*Table 3*).[3]

Diffuse palmoplantar keratoderma was first described in a family in 1880 by Thost. Three years later, Unna reported the same disease in two other families. The disorder was subsequently named Unna-Thost disease or, based on the histopathological findings, non-epidermolytic palmoplantar keratoderma.[2, 8] In 1901, Vörner described the first case of epidermolytic palmoplantar keratoderma, the disease later taking his name.[8] However, further investigation carried out in 1990 by Küster on the family first described by Thost demonstrated that they were, in fact, suffering from the epidermolytic form of the disease.This discovery not only proved that non-epidermolytic forms were not the most common ones as it was previously believed, but it further confirmed the fact that the two forms cannot be

Table 1. Diffuse palmoplantar keratodermas (after Saurat et al., modified)

1. Isolated forms
Unna-Thost Keratoderma
Vörner Keratoderma
Greither Keratoderma
Mal de Meleda
Mal de Nagashima
2. Syndromes associating cutaneous signs
Olmsted Syndrome
Huriez Syndrome
KLICK Syndrome
Naegeli-Franceschetti-Jadassohn Syndrome
Naxos Syndrome
Carvajal Syndrome
CAPK Syndrome
3. Syndromes associating deafness
Vohwinkel Syndrome
KID Syndrome
Bart-Pumphrey Syndrome
4. Syndromes associating dental anomalies
Papillon-Lefèvre Syndrome
Haim-Munk Syndrome

KLICK= Keratosis linearis with ichthyosis congenita and sclerosing keratoderma; CAPK= Cardiomyopathy with alopecia and palmoplantar keratoderma; KID= Keratitis-Ichthyosis-Deafness

Table 2. Non-diffuse palmoplantar keratodermas (after Saurat et al., modified).

1. Punctate keratodermas
Bushke-Fischer-Brauer Syndrome
Acrokeratoelastoidosis
Mal de Cole
PLACK Syndrome
2. Focal keratodermas
a. Isolated forms
DSP Mutations
DSG1 Mutations
b. Associating Cutaneous Signs
Congenital pachyonychia
Carvajal Syndrome
Naxos Syndrome
c. Associating Ocular Signs
Richner-Hanhart Syndrome
d. Associating Digestive Signs
Howel-Ewans Syndrome

PLACK= Peeling skin with leukonychia, acral punctate keratoses, cheilitis, and knuckle pads; DSP= Desmoplakin; DSG1= Desmoglein 1

distinguished from one another only taking into account the clinical aspects.[2, 9]

The clinical features that best describe the diffuse form of palmoplantar keratoderma, regardless of whether it is epidermolytic or not, consist of an initially erythematous palmoplantar surface that gradually develops towards a thick, yellow, wax-like hyperkeratotic layer, which extends towards the lateral margins of the hands and feet. Although not necessarily frequent, hyperhidrosis and secondary infections can occur. The disorder usually shows up during the first months of life and becomes more obvious in early childhood.[3]

In the case we are presenting, the patient had dense hyperkeratosis with a wax-like appearance that was occupying the whole area of the palms and soles as well as ill-defined, erythematous, scaly patches of different sizes and shapes on the dorsal sides of the hands and feet. The fingers were almost permanently fixed in an adduction position. The disease had begun during the first year of life (*Fig. 1*, *Fig. 2*). The clinical features were therefore highly suggestive for the diagnosis of diffuse palmoplantar keratoderma.

The genetic defect that causes palmoplantar keratodermas involves the keratin proteins. Keratins are durable fibrous proteins expressed by keratinocytes which are connected to various subcellular structures in order to assemble the epithelial cytoskeleton.[10] There are two families of keratins, namely type I keratins, consisting of keratins 9 to 20 and 31 to 38, which are encoded by genes located on chromosome 17q, and type II keratins, consisting of keratins 1 to 8 and 81 to 86, which are encoded by genes located on chromosome 12q.[2, 11] Autosomal dominant mutations of KRT1 and KRT16 genes encoding keratins 1 (K1) and 16 (K16) respectively have been described in families suffering from diffuse nonepidermolytic palmoplantar keratoderma (NEPPK).[12] The KRT1 mutation seen in Unna-Thost keratoderma seems to affect the supramolecular interactions of the keratin filaments through the damage caused to the amino-terminal end.[13] The epidermolytic form of the diffuse palmoplantar keratoderma was shown to develop as a result of autosomal dominant mutations of KRT1 and KRT9 genes.[12] The mutations observed in Vörner

Table 3. Palmoplantar keratodermas (after Saurat et al and Bolognia et al., modified)

Disorder	Chromosome	Defective Protein	Onset	Clinical Aspects
Unna-Thost PPK	12 or 17	K1 or K16	Birth/ early infancy	Yellowish, waxy hyperkeratosis with an erythematous border
Vörner PPK	12 or 17	K1 or K9		
Greither Keratoderma	12	K1	Infancy	Slowly progresses towards the ankles, knees and elbows
Mal de Meleda	8	SLURP-1	0-3 years	Subjacent joints can be affected; lesions may become infected
Olmsted Syndrome	17 or X	TRPV-3 or MBTPS-2	0-1 years	Can associate hair and nails anomalies and periorificial erythema
Naxos Syndrome	17	Plakoglobin	Infancy	Associates wooly hair, arrhytmias and right ventricular cardiomyopathy
Carvajal Syndrome	6	Desmoplakin	Infancy	Associates wooly hair, arrhytmias and left ventricular cardiomyopathy
Vohwinkel Syndrome	1 or 13	Loricrin or Connexin 26	Infancy	Can associate auto-amputation of digit and sensorineural deafness
Papillon-Lefèvre Syndrome	11	Cathepsin C	Birth/ early infancy	Associates periodontitis and premature loss of dentition
Bushke-Fischer-Brauer Syndrome	15	AAGAB	Early adolescence	Hyperkeratotic papules on the palms and soles
Richner-Hanhart Syndrome	16	Tyrosine amino-transferase	Infancy to adolescence	Associates corneal dystrophy and mental retardation
Howel-Ewans Syndrome	17	RHBDF-2	Middle child-hood	Associates esophageal squamous cell carcinoma

PPK= palmoplantar keratoderma; K=keratin; SLURP-1= Secreted Leukocyte Antigen-6/ Urokinase-type Plasminogen Activator Related Protein-1; TRPV-3= Transient Receptor Potential Vanilloid-3; MBTPS2 = Membrane-Bound Transcription Factor Protease, Site 2; AABAG= Alpha And Gamma Adaptin Binding Protein; RHBDF-2= Rhomboid 5 Homolog 2.

keratoderma appear to affect the assembly and stability of the filaments through the error that occurs in the central part of the proteins.[14] These genetic defects lead to the occurrence of a histologic image consisting of marked non-epidermolytic/ epidermolytic hyperkeratosis, moderate acanthosis and hypergranulosis along with a mild superficial dermal lymphocytic infiltrate.[15] The histological features of NEPPK are non-specific and the absence of epidermolytic hyperkeratosis differentiates Unna-Thost keratoderma from Vörner disease.[2] Electron microscopy shows normal and abnormal keratohyaline granules located in the lower stratum granulosum and in stratum spinosum.[2, 12]

In our case, a previously performed biopsy established the diagnosis of NEPPK.

The differential diagnosis includes other forms of inherited and acquired palmoplantar keratodermas (*Table 3*). Vörner disease is the most important differential diagnosis. The two disorders are clinically identical and the histopathological examination has a paramount importance in distinguishing the two diseases. Epidermolytic hyperkeratosis occurs in Vörner disease but multiple biopsies are often required to establish the diagnosis.[2, 16] Genetic testing could also help differentiate the two disorders.[2, 12]

Naxos syndrome is a rare autosomal recessively inherited disease characterised by

woolly hair and diffuse palmoplantar keratoderma associated with arrhythmogenic right ventricular cardiomyopathy. The disease is determined by a two base-pair deletion in the gene for plakoglobin which is located at 17q21.[16-18] The woolly hair is present since birth, the palmoplantar keratoderma occurs during the first year of life and the cardiomyopathy usually develops by adolescence.[17, 18]

Palmoplantar keratoderma is also present in Huriez syndrome, a rare disorder with autosomal dominant inheritance. However, patients presenting this disorder also have scleroatrophy of the distal extremities and hypoplastic nail changes.[19]

Olmsted syndrome is a rare genodermatosis characterized by bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques. Many patients however also associate diffuse alopecia, nail abnormalities, leukokeratosis and pseudoainhum. The exact aetiology is not completely understood, both sporadic and inherited cases having been reported. A mutation in the transient receptor potential vanilloid-3 (TRPV-3) on 17p13 was identified in most patients suffering from this disease and a mutation in membrane-bound transcription factor protease, site 2 (MBTPS2) was identified in recessive X-linked Olmsted syndrome.[20, 21]

Mal de Meleda is another autosomal recessive palmoplantar keratoderma that must be differentiated from Unna-Thost syndrome. Mutations in the secreted leukocyte antigen-6/urokinase-type plasminogen activator related protein-1 gene (SLURP1) have been identified in patients suffering from this disorder. The disease onset is shortly after birth or in early infancy. The hyperkeratosis is transgredient, as it progresses to the dorsal surface in a glove and stocking distribution, and progredient, as it worsens with age.[2, 3, 22] Patients suffering from this disorder also present periorificial lesions, hyperhidrosis, nail changes and brachydactyly.[3]

Greither keratoderma is a rare, progredient and transgredient palmoplantar keratoderma with autosomal dominant inheritance characterized by hyperkeratosis of the palms and soles with lateral and dorsal extension in a glove and stocking distribution associated with hyperhidrosis. Hyperkeratotic plaques can also pe observed on the knees and elbows and pseudoainhum has been reported.[2, 3, 23]

The treatment is similar for all keratodermas[16] and should take into account factors like the severity of the disease and the age of the patient.[2] Mechanical debridement, topical treatment, systemic therapy, as well as the treatment of complications and associated disorders should all be considered when dealing with a patient with palmoplantar keratoderma.[3] Mechanical debridement can be performed with a blade or a dental drill and helps reduce keratotic masses in problematic areas.[2, 3] Topical applications of salicylic acid, benzoic acid, lactic acid, creams containing urea, as well as 50% propylene glycol in aqueous cream under occlusion for several nights have been associated with good results.[2, 3] Systemic retinoids have shown some success. However, since patients require a life-long treatment, the adverse events, including epidermal fragility, limit their usefulness.[3, 12] Dermatophyte and bacterial infections can occur and require topical or even systemic treatment.[3]

In the case we are presenting, the patient was treated with topical keratolytic and keratoplastic agents, to which she had a favourable response.

Conclusions

Palmoplantar keratodermas are a group of various inherited or acquired afflictions characterized by thickening of the skin of palms and soles. Unna-Thost disease is a NEPPK inherited in an autosomally dominant manner which occurs during childhood and has a lifelong duration. We report a rare case of NEPPK in a patient who, despite the serious affliction which limited the mobility of the hand, managed to work in a textile factory.

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Conflict of interest
NONE DECLARED

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