***no patient handout*

Palmoplantar keratoderma

Synopsis

Palmoplantar keratoderma (PPK) is thickening of the palms and/or soles that cannot be attributed to friction alone. Cases are either inherited or acquired. Heritable PPKs are identified by the presence of a family history and childhood onset; they may manifest in isolation, as the defining feature of a syndrome, or as a minor aspect of a syndrome (eg, congenital ichthyoses, Darier disease).

Hereditary PPKs are approached and classified by the pattern of hyperkeratosis: diffuse, focal (often occurring over weight-bearing areas), or punctate.

Diffuse hereditary PPK:

- Vorner (epidermolytic) PPK and Unna-Thost (nonepidermolytic) PPK are the result of keratin mutations and show waxy or verrucous, white-yellow, symmetric hyperkeratosis.
- **Mal de Meleda** is a rare diffuse hereditary PPK associated with *SLURP1* mutations and features stocking-glove distribution of hyperkeratosis with malodor and nail changes.
- **Vohwinkel syndrome** (mutilating PPK) has 2 variants: the classic form associated with deafness and mutations of the connexin gene *GJB2* and the loricrin variant associated with loricrin mutations and ichthyosis. The PPK shows a diffuse honeycomb pattern. Additional features include starfish-shaped keratotic plaques on dorsal hands, feet, elbows, and knees as well as constricting digital bands termed "pseudo-ainhum," which may progress to autoamputation.
- **Papillon-Lefèvre syndrome** is associated with mutations in the gene that encodes cathepsin C and demonstrates diffuse PPK, periodontal disease with loss of teeth, and frequent cutaneous and systemic pyogenic infections.
- Olmsted syndrome is a hereditary disorder of mutilating PPK with periorificial plaques. Affected patients may also experience palmoplantar pruritus, diffuse alopecia, and keratosis pilaris. Onychodystrophy and digital autoamputation can be features of the disease. Autosomal dominant Olmsted syndrome has been associated with a defect of *TRPV3* that may lead to erythromelalgia in some patients.
- Other diffuse hereditary PPKs include Greither syndrome, Bart-Pumphrey syndrome (PPK with knuckle pads, leukonychia, and deafness), Huriez syndrome (PPK with scleroatrophy), Clouston syndrome (hidrotic ectodermal dysplasia), diffuse nonepidermolytic PPK with sensorineural deafness, and Naxos disease (diffuse nonepidermolytic PPK with woolly hair and cardiomyopathy).

Focal hereditary PPK:

- Isolated focal PPKs (striate PPKs) are due to autosomal dominant mutations in genes encoding desmosomal proteins. Lesions favor pressure points on feet and may present as linear plaques on hands.
- **Howel-Evans syndrome** is associated with mutations in the TOC gene, focal weight-bearing area plantar hyperkeratosis, milder palm involvement, and development of esophageal carcinoma.
- **Richner-Hanhart syndrome** is associated with mutations in the gene that encodes tyrosine aminotransferase. Accumulation of tyrosine leads to focal (or diffuse) hyperkeratotic plaques on the hands, feet, elbows, and knees, corneal inflammation / ulceration, and mental retardation in some cases. Diets low in phenylalanine and tyrosine may prevent complications.
- Focal PPK may also be seen in **pachyonychia congenita** type I and type II (syndromes with nail, skin, teeth, and eye anomalies) as well as Carvajal syndrome (striate focal epidermolytic PPK with woolly hair and dilated cardiomyopathy).

Punctate hereditary PPK or keratosis punctata (may not appear until adolescence or after):

- Punctate PPKs are characterized by autosomal dominant inheritance and multiple firm 2-8 mm papules on the palms and soles. A pattern with lesions favoring palmar creases has been identified in patients of African descent.
- **Focal acral hyperkeratosis** and **acrokeratoelastoidosis** present as 2-4 mm papules (some umbilicated) at the marginal borders of hands and feet.
- Spiny keratoderma is a rare entity characterized by multiple asymptomatic "spiny" projections of the palms and/or soles. These keratotic plugs have been likened to the spines of a music box. Both hereditary and acquired variants have been described. The hereditary form usually presents in childhood and is benign. The acquired form presents later in life and may be associated with an internal malignancy or other systemic disease.

Acquired PPKs occur later in life and have no associated family history. They may be subdivided as follows:

- Keratoderma climactericum – Seen in menopausal women, often associated with obesity or hypertension; pressure points on the soles of the feet are affected first.
- Infectious PPK – Associated with dermatophytosis, leprosy, human immunodeficiency virus (HIV), syphilis, crusted scabies, and human papillomavirus infections.

- Chemical / drug-induced PPK – Associated with exposure to arsenic, halogenated aromatic chemicals such as dioxin, venlafaxine, verapamil, hydroxyurea, etodolac, quinacrine, proguanil, methyldopa, practolol, doxorubicin, bleomycin, imatinib, capecitabine, tegafur, lithium, gold, and mexiletine.

- Dermatosis-related PPK – May be associated with atopic and contact dermatitis, psoriasis, reactive arthritis (keratoderma blennorrhagicum), lichen planus, lichen nitidus, lupus erythematosus, and pityriasis rubra pilaris.

- PPK as a feature of systemic disease – Hypothyroidism, myxedema, diabetes mellitus, and chronic lymphedema.

- Malnutrition-associated PPK

- **Aquagenic keratoderma** – Most often affects palms in patients in the second decade of life. Symptoms develop within 5 minutes of immersion in water.

- Paraneoplastic PPK – **Acrokeratosis paraneoplastica of Bazex** is associated with squamous cell carcinoma of the upper gastrointestinal tract, and "tripe palms" is associated with pulmonary or gastric malignancies. Other malignancies with associated paraneoplastic PPK include breast, bladder, and skin malignancies; myeloma; mycosis fungoides; and Sézary syndrome.

- The acquired form of spiny keratoderma may be associated with an internal malignancy or other systemic disease.

- Idiopathic PPK – a diagnosis of exclusion.

For more information on the epidermolytic form, see **OMIM**.

For more information on striate, focal, or diffuse forms, see **OMIM**.

For more information on the mutilating form, see **OMIM**.

Codes

ICD10CM:
Q82.8 – Other specified congenital malformations of skin

SNOMEDCT:
706885006 – Palmoplantar keratoderma

Look For

Thickening of the palms and/or soles with variable areas affected. Sometimes, there is plate-like scale or confluent, brown-to-yellow thickening. Patterns include diffuse, focal, and punctate. In the focal variants, the areas of hyperkeratosis can be very well defined.

Lesions that extend beyond the plantar or palmar skin may occur. These are referred to as "transgrediens."

In keratosis punctata, look for 2-4 mm keratotic depressions on the palms and soles. A variant favoring the creases of the palms is commonly seen in patients of African descent and can be somewhat painful.

Diagnostic Pearls

Assessment begins by characterizing cases as inherited or acquired.

Hereditary PPK cases are initially evaluated by pattern (diffuse, focal, or punctate), the presence or absence of transgrediens, accompanying symptoms, and of course features of the family history. Refer inherited cases to a dermatologist or geneticist.

Acquired cases should be evaluated with history and physical examination attuned to the list provided in the synopsis section. If no diagnosis is evident, limited diagnostic testing is indicated, including fungal scrapings, chest radiograph, thyroid-stimulating hormone (TSH), CBC, antinuclear antibodies (ANA), rapid plasma reagin (RPR), HIV, and purified protein derivative (PPD). If the cause remains obscure after these tests, an age- and sex-appropriate search for malignancy is indicated, including CT scans of the chest / abdomen / pelvis, upper and lower gastrointestinal tract endoscopy, and cystoscopy. Only if these are negative should the designation of idiopathic PPK be assigned.

Symmetry is usual, but asymmetric changes should prompt consideration of infectious or dermatosis-related PPK. Unilateral scale should indicate another process such as dermatophyte infection.

Patients of African descent can present with small hyperkeratotic plugs in the large creases of palms and fingers (punctate keratosis of palmar creases), with incidence increasing in patients aged 50 years and older. These lesions may be tender and painful when performing manual labor. Both idiopathic and inherited cases exist.

Differential Diagnosis & Pitfalls

- **Psoriasis**
- **Tinea pedis** / manum
- **Dyshidrotic eczema**
- **Contact dermatitis**
- **Pityriasis rubra pilaris**
- **Reactive arthritis** (Reiter syndrome)
- **Atopic dermatitis**
- **Acrokeratosis paraneoplastica**

- **Arsenical keratosis** (arsenical exposure)
- **Acanthosis nigricans** (tripe palms are associated)
- **Acquired ichthyosis** associated with a malignancy
- **Cutaneous T-cell lymphoma**
- **Lymphedema**
- PPK may occasionally be confused with **corns** and **callosities** or **plantar warts**.

Additional inherited conditions that may have PPK as a feature (see Synopsis for inherited conditions in which PPK predominates):

- Inherited ichthyoses (**ichthyosis vulgaris**, **lamellar ichthyosis**, **epidermolytic hyperkeratosis**, **congenital ichthyosiform erythroderma**, **X-linked ichthyosis**)
- **Erythrokeratodermia**
- **Ectodermal dysplasias**
- **Dyskeratosis congenita**
- **Darier disease**
- **Basal cell nevus syndrome**
- **Incontinentia pigmenti**
- **Epidermolysis bullosa simplex**
- **Kindler syndrome**
- **Franceschetti-Jadassohn syndrome**

Best Tests

Biopsy can usually differentiate warts from PPK but is often not helpful in defining the underlying cause of an acquired keratoderma. In hereditary cases, the presence or absence of epidermolysis on histopathology may narrow the differential diagnosis.

Scrape any scaly lesions and examine under the microscope with potassium hydroxide (KOH) to rule out a fungal infection. Dermatophytosis may be the cause of PPK or a treatable complication of a PPK.

Consider thyroid function testing if the clinical scenario warrants, as cases of PPK associated with myxedema have been reported.

Genetic testing in inherited cases.

Management Pearls

Saline soaks and the paring down of hyperkeratotic areas are important adjunctive treatments.

Therapy

Treat any identifiable underlying condition (eg, infection, malignancy, dermatosis, hypothyroidism) or stop any causative agents such as drugs.

Topical keratolytics are the mainstay of treatment. Examples include 5%-10% salicylic acid, 10% lactic acid, 10%-40% propylene glycol, or a 10%-40% urea cream applied once or twice daily to thickened skin. Overnight occlusion may enhance the results.

Topical retinoids are also efficacious, but their use may be limited by irritation: tretinoin 0.1% gel or 0.1% cream nightly. Systemic retinoids (isotretinoin approx. 1 mg/kg daily, acitretin 25-50 mg daily) should be considered second-line and require careful monitoring for toxicities.

Alternative therapies that have demonstrated some efficacy include:

- Surgical excision and grafting
- Topical calcipotriol
- Topical corticosteroids
- Psoralen plus UVA (PUVA) (sometimes combined with acitretin or isotretinoin)
- Dermabrasion
- Carbon dioxide laser

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
Angiotensin II receptor blocker	1

Medication	Citations
Antimetabolite	4
arsenic	3
BCR-ABL tyrosine kinase inhibitor	3
BRAF kinase inhibitor	3
Calcium channel blocker	1
capecitabine	2
dabrafenib	1
hydroxyurea	2
imatinib	3
lithium	2
losartan	1
Serotonin-norepinephrine reuptake inhibitors	1
sorafenib	1

Medication	Citations
sunitinib	1
tegafur	2
trametinib	1
Tyrosine kinase inhibitor	2
vemurafenib	2
venlafaxine	1
verapamil	1