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Acquired Palmoplantar Keratoderma in Childhood

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Abstract

Palmoplantar keratodermas (PPK) constitute a diverse group of disorders characterized by thickening of the skin of palms and soles. They are often hereditary, but acquired non-familial forms are also common. Acquired PPK are relatively less common in children compared to adults. There is paucity of published literature on this subject with no review article at present. In this systematic review, we discuss the epidemiology and different kinds of acquired PPK in children. An approach towards treatment appropriate for the pediatric age group is also detailed. There is an urgent need for other investigators, especially Pediatric Dermatologists to document and generate more evidence on the epidemiology and clinical presentation of acquired variants of PPK in children.

Keywords: Palmoplantar; Keratoderma; Hyperkeratosis; Children; Pediatric; Acquired; Childhood psoriasis; Childhood eczema Aquagenic PPK; Keratolytics; Retinoids.

Introduction

Palmoplantar keratodermas (PPK's) are a diverse group of disorders characterized by thickening of the skin of palms and soles [1]. Although phenotypically homogenous, the entity displays great deal of etiological diversity. Traditionally PPKs are classified into hereditary and acquired forms [2]. Morphologically they may also be classified as diffuse, focal or punctuate depending upon the epidermal involvement [2].

Hereditary PPKs have been extensively reviewed in literature, however description of the acquired variety is relatively much scarce; literature being far more scantyin children than adults. Acquired PPKs has been defined as non-hereditary, non-frictional, hyperkeratosis (thickening) of the skin of palms and soles, with involvement of > 50% of surface area. It may or may not be associated with clinical and/or histological inflammation [3].

Three morphological patterns have been described for acquired PPK based upon the epidermal involvement. Diffuse PPK refers to uniform involvement of the palmoplantar surface, focal PPK is localized to pressure points (e.g. thenar and hypothenar eminence of palms, and

the forefoot, ball of big toe and heel in the soles), and punctate variety that presents with multiple, discrete, keratotic papules over palms and soles. In addition, disease severity in terms of debility, course (persistent/remitting-relapsing, frequency of flare-ups), involvement of areas other than the palms or soles (transgradient PPK), presence of extracutaneous symptoms, and response to treatment constitute important factors determining management goals and prognosis.

There are no specific histopathological features of acquired PPKs in children separate from those described in adults. Compact hyperkeratosis, i.e. increased thickness of stratum corneum is the most consistent feature. Other common features include parakeratosis, acanthosis, hypergranulosis and superficial upper dermal, perivascular infiltrate [4-9].

Although acquired PPKs associated with a systemic disorder or resulting from an external agent have been extensively reported in adults, such phenomena, although much less common in children, should always be suspected, especially with an atypical morphology and/or clinical suggestion of the underlying disorder or association.

In this semi-analytical review, we focus on acquired PPKs in pediatric population, an issue which has to the best of our knowledge not been reviewed at length. The term hyperkeratosis has been used both clinically and histopathologically, even though most reviews have used the term synonymously with keratoderma. However in this current review we shall conform to the use of this term in histopathological pretext only [4].

Methodology

For the purpose of this review we searched the databases of PubMed, Cochrane, Medline and Scopus with time filter of 1951 to 2018. The following keywords were included - 'palmoplantar keratoderma', 'keratoderma', 'hyperkeratosis', 'keratoderma Palmaris et plantaris', with each of these terms double searched with the addendum of both words – 'children' and 'pediatric'. Only English-based articles were considered. While emphasis on review articles, meta-analysis, clinical trials was more, we also included case series, case reports, letters and image-based items in primary analysis. Articles were filtered out of primary inclusion if their full text was not available, were not in English, or were grey literature. Then articles were also excluded if they predominantly addressed genetic/hereditary PPKs and/or the cohort was majorly (>90%) constituted by adults (age more than 16 years). After this, the remaining manuscripts were analyzed and records generated with respect to the morphology, etiological association (if any), age of onset, morbidity, and non-etiological associations. The following results and discussion symbolize a narrative review after the aforementioned semi-analytical evaluation.

Results & Discussion

Epidemiology

As a general principle, early onset and positive family history favour the possibility of a hereditary/ genetic rather than acquired type. Otherwise, the age and gender predilection of acquired PPKs in children cannot be generalized. The range and mean age of presentation, as well as the predominant gender involved vary across a wide spectrum and shall be discussed in individual subcategories that follow. We have segregated pediatric acquired PPKsinto – Inflammatory and reactive dermatoses-associated, Infective, chemical exposure and drug-related, paraneoplastic, those associated with specific systemic disease, miscellaneous and idiopathic **(Table 1)**.

Table 1: Broad classification of causes of acquired palmoplantar keratoderma (PPK) in children and adolesecents

- **PPK associated with inflammatory and reactive Dermatoses:**
  - Psoriasis
  - Pityriasis rubra pilaris (PRP)
  - Contact allergic eczemas of hand and/or feet, especially in atopic children
  - Reiter's disease
  - Lichen Planus
  - Lichen Nitidus
  - Juvenile Dermatomyositis
  - Aquagenic PPK
- **Cutaneous Infections & Infestations**
  - Extensive and mosaic warts
  - Dermatophytosis – tinea manuum/pedis (dry moccasin variant)
  - Norwegian Scabies
  - Leprosy
  - Miliary tuberculosis

- **Chemical and Intoxicants-induced**
  - Arsenic – contaminated water
  - Chloracnegens like dioxin
- **Drug-induced**
  - 5-Flurouracil
  - Hydroxyurea
  - Bleomycin
- **Systemic disorder-associated**
  - Hypothyroidism & myxedema
  - Growth Hormone deficiency
  - Sarcoidosis
  - Chronic lymphedema – e.g. due to filiriasis
- **Malignancy-associated – not reported in children till date, but reported in adults**
- **Miscellaneous**
  - Spiny keratoderma,
  - Transient reactive papulo translucent acrokeratoderma
  - Acrokeratoelastoidosis, sporadic variant

Inflammatory & Reactive Dermatoses associated

Chronic hand eczemais a common cause of PPK in children **(Fig. 1A)**. Although allergic contact dermatitis to fragrances, nickel and other allergens may be seen in children, atopic dermatitis (AD) tops this list [10-11]. A history of pruritus, seasonal worsening, generalized dry skin, personal and/or family history of hyperreactive airways or frank asthma and other features of atopic dermatitis are important diagnostic clues and must be looked for.

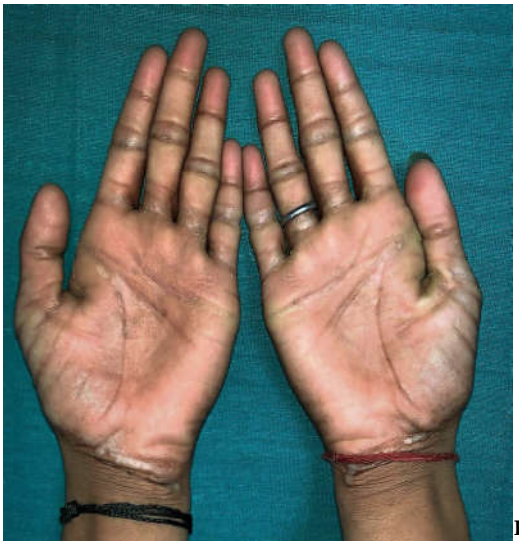

Fig. 1A:

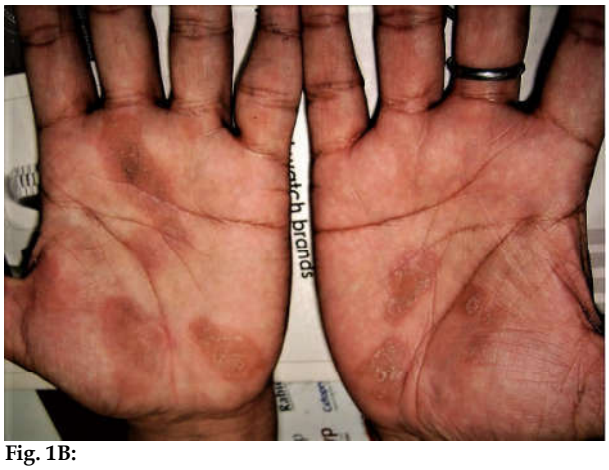

Fig. 1B:

Fig. 1: (A) Palmoplantar keratoderma (PPK) due to recurring hand eczema in a 11-year old boy with atopic dermatitis withboth palms showing diffuse thickening and erythema with fine dirty-white colored scaling with accentuation over the palmar and inter-phalangeal creases; **(B)** Psoriasis-associated PPK in a 15-year old adolescent with multiple well defined dusky red-colored scaly hyperkeratotic plaques over the palms. The scaling is less pronounced on gross examination owing to recent application of mometasone ointment by the patient.

PPK is a common presentation of psoriasis across all ages including children [12-14] (**Fig. 1B**). Although pediatric psoriasis presents differently from its adult counterpart, palmoplantar involvement is often similar. Localized variety of palmoplantar pustular psoriasis may also be seen in children. Presence of plaques of psoriasis at other common locations, nail changes, characteristic dermoscopy, and histopathology help in clinching diagnosis in such cases; they may be required to differentiate between palmar psoriasis from hand eczema (**Fig. 2A-C)**. PPK may be seen in

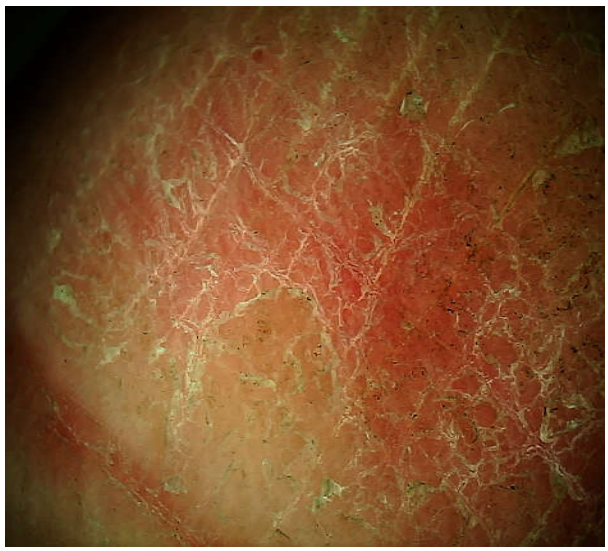

Fig. 2A:

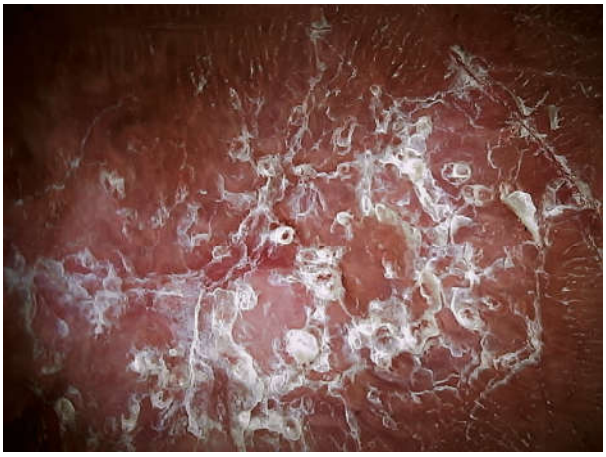

Fig. 2B:

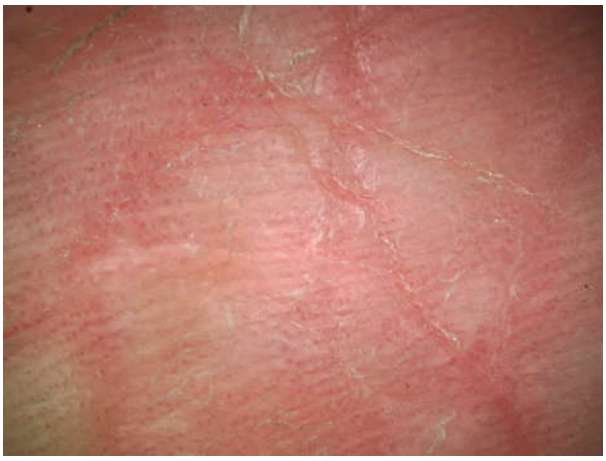

Fig. 2C:

Fig. 2: Polarised video dermoscopic images of the patients demonstrated in Figure 1 demonstrating how the two conditions can be differentiated: **(A)** Reddish-yellow background, dirty white to yellowish scale-crusts, and irregularly arranged red dots characteristic of eczematous affliction; **(B)** Pinkish-red background, visible keratin thickening, loosely adherent silvery white scales highly suggestive of psoriasis. Vessels are not visible due to extensive hyperkeratosis and scaling; and **(C)** Image of the same patient from a palmar region after scraping of the scales demonstrating regularly arranged red dots confirming dermoscopic diagnosis of psoriasis [E-Scope, USB Videodermoscope, 20×, Timpac Healthcare Pvt. Ltd., New Delhi]

pediatric pityriasis rubra pilaris (PRP) especially in circumscribed juvenile-onsetvariant **(Fig. 3)** [15]. PRP is typically associated with red-orange thick scales on the palms and soles with sharp borders. Additionally, follicular papules with surrounding erythema are usually observed over the dorsal proximal phalanges. Lichen planus (LP) also rarely shows florid palmoplantar involvement. However, not only do children contribute to only 4% of all cases of LP [16], palmoplantar involvement in childhood LP is even rarer [17]. Rare cases have been reported from other parts of the globe anecdotally

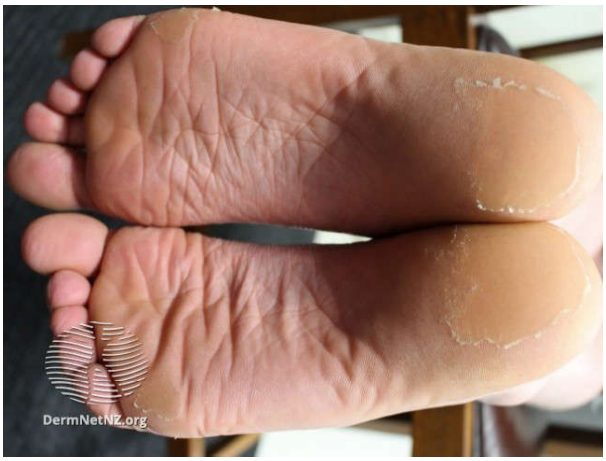

Fig. 3: Clinical image of soles showing yellowish-orange colored mildly hyperkeratotic well circumscribed focal keratoderma over pressure bearing sites in a case of Circumscribed juvenile-onset pityriasis rubra pilaris [Copyrighted watermarked image, unaltered, courtesy image library of www.dermnet.nz; copyright link -https://creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode].

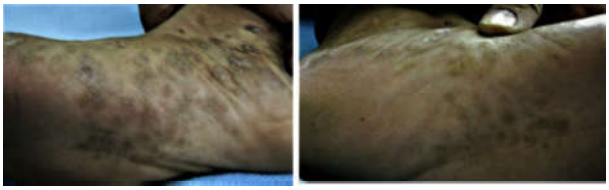

Fig. 4A:

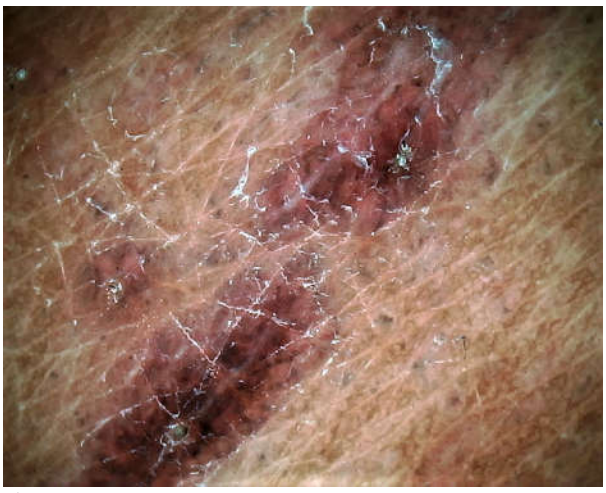

Fig. 4B:

Fig. 4: Lichen planus (LP) with involvement of palms and soles in a 16-year old boy: **(A)** Clinical image showing well defined yellowish to brown punctate hyperkeratotic lesions over both soles with focal scaling. Appreciate the presence of typical violaceous lesions of LP over the lower leg region. **(B)** Polarized Dermoscopic image of the same patient showing dark reddish to reddish-brown background, with prominent Wickham's striae (WS), interspersed with blue-gray and brown dots and globules [E-Scope, USB Videodermoscope, 20×, Timpac Healthcare Pvt. Ltd., New Delhi].

[18]. The PPK in lichen planus is usually of punctate variety **(Fig. 4A)** although diffuse keratoderma has also been reported [7,18]. In presence of isolated palmoplantar lesions, evaluation of oral mucosa may help. Dermoscopy may hint at its possibility **(Fig. 4B)** but a biopsy may become essential for diagnostic confirmation. There have been reports of lichen nitidus presenting with nail dystrophy and palmoplantar hyperkeratosis in children [19-20]. PPK has also been reported as a rare cutaneous finding in juvenile dermatomyositis, pediatric Reiter's disease, and early onset Darier's disease [21,22]. Callosities resulting from heavy mechanical work involving repeated friction over the bony eminences of the palms and soles can result in PPK in adolescents akin to adults.

Aquagenic PPK (APPK) is an acquired condition with a predilection for adolescents and females and involves palms and fingers much more than soles. Patients present with white to translucent papules on palms after immersion of their hands in water **(Fig. 5)** along with variable burning sensation, pain and edema [23]. Apart from rare cases presenting a positive familial history, the rest of the reported cases are sporadic. This condition is often associated with hyperhidrosis and atopy. An aberrant aquaporin 5 expression in the sweat gland has been found in few cases. However, its frequent association with cystic fibrosis (CF) merits mention [24]. In particular, this condition appears to be related to the same mutations found in CF (usually DF508 of the CFTR gene), either homozygous or heterozygous [25].The mutation of the gene, which encodes an ion channel, causes an excessive electrolyte content of sweat. Some pediatric patients <10 years of age with APPK or with the start of the skin disease in childhood have been reported by Garcon-Michel *et al*.[24].

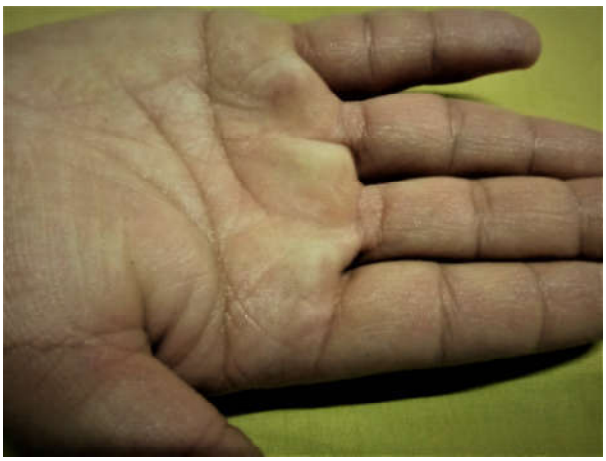

Fig. 5: Aquagenic palmoplantar keratoderma with hyperhidrosis in a 10-year old girl showing wrinkled appearance of the palms and digits and white to translucent papules; the lesions appeared after water immersion test.

Infective Dermatoses

Infections such as human papilloma virus, syphilis, crusted scabies, hyperkeratotic or moccasin variant of dermatophytic infection, and rarely leprosy and military tuberculosis may result in PPK in both adults and children [3]. Exuberant and confluent warts or mosaic warts over the palms and soles often occur in immunocompromised hosts and mimic PPK. Crusted scabies, typically observed in patients suffering from immunosuppression, motor or sensory deficiency, or mental retardation, can occasionally involve children with scabies who have been mistakenly treated with corticosteroids overprolonged duration [26]. Down's syndrome is another predilecting factor for crusted/ Norwegian scabies in children [27]. The epidemic of therapeutically recalcitrant dermatophytic infections has eventuated in more frequent involvement of areas like the face, palms and soles in both adults and kids. Dry moccasin variety of tinea pedis may occasionally be encountered in pediatric population, especially following episodic treatment with steroids and azoles. Secondary syphilis, leprosy and military tuberculosis constitute rare causes of PPK like presentation in pediatric population.

Chemical Exposure-induced PPK

Chemicals, especially arsenic and chloracnegens like dioxin are known causes of inducing PPK-like lesions in adults [3]. Although reports of the latter causing PPK in children are lacking, arsenic is a common contaminant of ground water in many areas of the Indian subcontinent, especially the regions drained by the gangetic-brahmaputra basin; with PPK representing one of the protean manifestations of chronic arsenicosis and is seen in children as well adults [28]. Drinking water from contaminated tube wells was a susbstantial source of this toxicity at one time, presenting with diffuse nodular palmoplantar keratosis. Additional presence of hypo- and hypermelanotic macules increases the possibility of arsenic as a cause of PPK. Arsenic is also used in indigenous medicinal preparations. The case of a 11-year-old girl being treated for epilepsy with multiple ayurvedic preparations high in arsenic content developing punctuate PPK and leucomelanoderma within 6 months is on record [29]. Detection of arsenic in serum and body tissue, e.g. nail, hair etc. confirms the diagnosis.

Drugs

Various drugs are known to induce PPK-like features. Chemotherapeutic agents such as 5-FU

(administered as continuous infusion) and its analogues, hydroxyurea, and bleomycin have been reported to cause PPK. Although more commonly reported in adults, pediatric cases have also been described. In a study that evaluated the efficacy and safety of parenteral bleomycin in patients aged 15-92 years, with advanced squamous cell carcinoma, lymphomas and miscellaneous tumours, skin eruptions were common including moist erythematous lesions, thickening of the skin of the terminal phalanges, distal paresthesia, pigmentation of palmar creases, and pigmented bands involving the nails [30]. The cutaneous adverse effects seemed to be dose-related. Skin and nail changes, including nail hyperpigmentation and longitudinal bands, and hyperkeratotic hyperpigmentation of the palms and other skin surfaces has been reported to develop in 7 children with sickle cell anemia following hydroxyurea therapy ranging from 6 to 16 weeks [31].

Thus, when faced with a child or adolescent with new onset non-familial acquired PPK, history of any new medications, and the duration between starting the drug and onset of PPK must be ascertained to determine the likelihood of drug-induced-PPK. Resolution of cutaneous changes following discontinuation of the suspected medication offers confirmation of the suspicion [3].

Specific Diseases

Palmoplantar keratoderma is known to occur with systemic diseases in children. Endocrinological disorders like hypothyroidism are known to cause PPK. In a study done to evaluate the cutaneous effects of hypothyroidism in Kashmir valley in India where 460 patients were studied in individuals of age ranging from 5-72 years, cutaneous findings like PPK were frequent in addition to xerosis, edema, purpura, urticaria and alopecia [32]. Deficiency of growth hormone has also been reported to be a cause of PPK in pediatric age group [33]. Although myxedema leading to PPK is frequently seen in adults, no specific report in children is available in literature. Chronic lymphedema is a well-known cause of hyperkeratosis of palms and soles. In the Indian sub-continent, filariasis is a common cause of chronic lymphedema in children. Thickening of skin is seen in grade-3 and grade-4 of chronic filariasis [34,35]. Diffuse PPK has been seen with circulatory disorders like acrocyanosis and livedo reticularis [3]. Vitamin A deficiency, although typically described in familial cases of PPK, may be present and causative in an odd case of pediatric PPK as well [36]. Sarcoidosis has been reported to present in a 6-year old boy with extraordinary cutaneous features including erythroderma, exfoliation and PRP-like follicular spiny keratoses, and palmo-plantar pitting [37].

Malignancy associated

PPK associated with malignancy is typically seen in adults in form of specific forms like Bazex syndrome and tripe palms or as paraneoplastic manifestations of internal malignancies mainly of aerodigestive tracts [3]. Similarly, diffuse hyperkeratosis accompanied by subungual hyperkeratosis and nail dystrophy have been reported in adults with cutaneous T-cell lymphoma, especially with Sézary syndrome. However, we couldn't find any literature of such association in children.

Miscellaneous & Idiopathic

Many otherwise typically hereditary PPK-related disorders and syndromes are well-known to also present sporadically without familial traits. At least three of them deserve mention - spiny keratoderma, which manifests with multiple 1-2 mm spiny papules and hyperkeratotic plugs involving the palms & soles & sides of digits [38], transient reactive papulo translucent acrokeratoderma, which is a rare, acquired, reactive, and episodic disorder of the palmar skin in children [39], and sporadic variant of acrokeratoelastoidosis, a marginal keratoderma that present with clusters of keratotic, crateriform papules along the sides of the palms and digits, and sometimes the soles as well **(Fig. 6)** [40]. Idiopathic PPK is a diagnosis of exclusion.

Approach to management of pediatric acquired palmoplantar keratoderma

Management of childhood acquired PPK should be approached sequentially. It is vital to

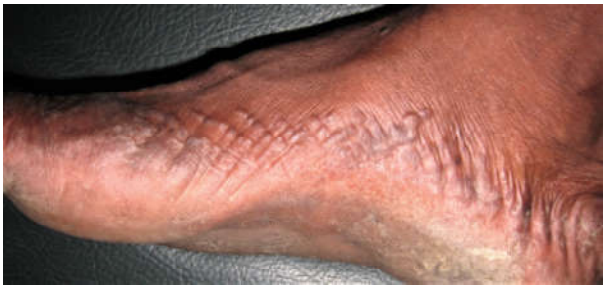

Fig. 6: Acrokeratoelastoidosis of Costa (AKC) in a 16-year old patient with the inner margin of the sole showing well defined round keratotic papules with some showing central crater. In contrast to the common autosomal dominant inheritance of AKC, this adolescent had negative family history and represents sporadic occurrence.

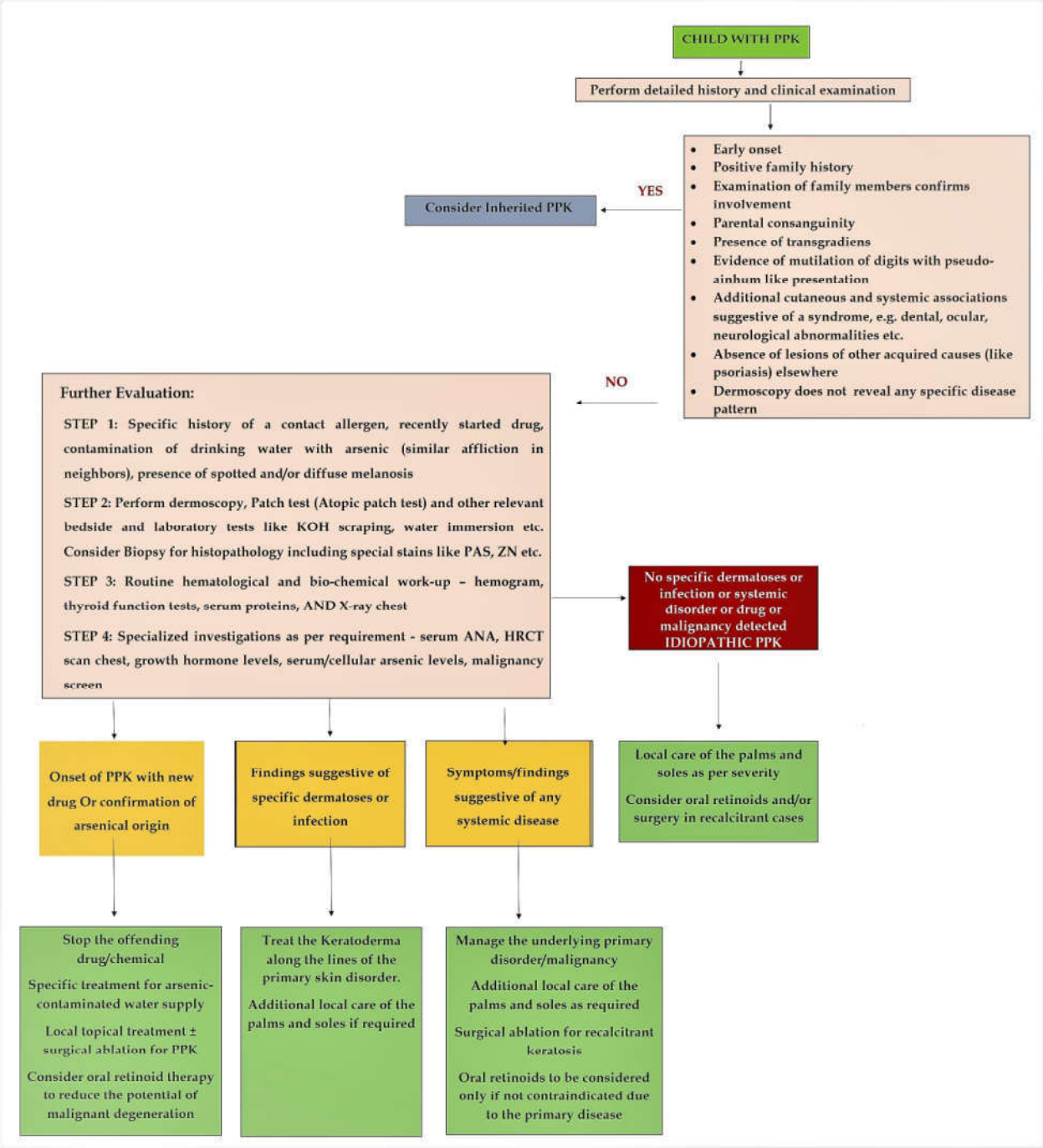

Fig. 7: Schematic flow chart outlining general approach to a child with palmoplantar keratoderma

distinguish if the presenting patient has acquired PPK or hereditary PPK. Although such distinction can be confusing, early onset and progression, positive family history, presence of transgradience and other associated and/or specific features of inherited PPK's help to rule them out. A diagnosis of idiopathic acquired PPK can only be made when no cause can be identified.

Once a diagnosis of inherited PPK is ruled out, next step is to identify the cause of acquired PPK through a detailed history, clinical examination especially the morphology of keratoderma, nail involvement, and specific laboratory evaluation. Most acquired PPK's in children are amenable to treatment once the specific etiology has been identified and treated. PPKs due to specific dermatoses can be identified by looking for presence of the signs of the dermatological disease in the patient and confirming the diagnosis with Dermoscopy and/or histopathology. Dermoscopy

is becoming increasing popular for evaluation of cutaneous disorders in children, owing to its non-invasive nature [41]. HPE may be of help in specifically recognizing them. Infections like scabies, dermatophytes could be rules out by simple microbiological tests. HPV infection could be identified by HPE. History becomes very important in identifying culprit drugs and chemicals. Epidemiological data may be become necessary to find out conditions like chronic arsenicosis.

Treatment of acquired PPK revolves around treating the specific etiology and use of emollients and keratolytics to reduce the hyperkeratosis. Physical measures like gentle scraping of scales and hyperkeratosis using pumice stone after wet soaks are helpful. Emollients and moisturizers help by softening and smoothening the skin, preventing loss of moisture by forming a film over the lesions, by their hygroscopic properties, and by restoring the natural moisturizing factors (NMFs) back to the skin. Substances like urea, cetylated esters, sodium pyrrolidonecarboxylic acid (PCA), glycerol and fatty acids are used in combination along with additives like vitamin-E, C and aloe vera to achieve the desired moisturizing effect.

Keratolytics like urea, alpha-hydroxy-acids, salicylic acid, ammonium lactate, expedite skin exfoliation and facilitate better penetration of topical drugs. Although keratolytics and moisturizers may be used 2-3 times per day but caution must be exercised in children, with respect to surface area being exposed to compounds like urea and salicylic acid.

Judicious use of topical corticosteroids (TCS), calcineurin inhibitors (CNIs) like tacrolimus, vitamin-D analogues, palmoplantar phototherapy (narrow-band ultraviolet B – nB-UVB), coal tar extracts etc. is warranted for specific dermatoses like psoriasis, lichen planus, atopic dermatitis, allergic contact eczema and related conditions. Use of systemic retinoids is mainly restricted to treatment of recalcitrant PPK due to psoriasis, PRP, LP and non-remitting hand eczema but should be used in limited doses for limited duration to prevent specific pediatric adverse effects (e.g. premature epiphyseal closure) of retinoids [42]. Growth charting during therapy is equally important. Immunosuppressives like low dose methotrexate, azathioprine should be considered after weighing the risk-to-benefit ratio. In acquired PPK's the goal is to cause a break down in recalcitrant PPK and shift to topical therapy at the earliest.

Biologics are rarely indicated in acquired PPK of children and should be used only when conventional therapies fail. Etanercept and omalizumab may be used for recalcitrant childhood psoriasis and atopic dermatitis respectively, with utmost care [43].

Surgical removal or destruction (eg, excision, curettage, cryosurgery, dermatome shaving may be required for hard/painful keratotic masses, especially in the punctate variants [44]. **Figure 7** depicts a schematic flow-chart to approach a child with PPK.

Conclusion

Acquired palmoplantar keratoderma in children is less commonly documented and understood compared to its adult counterpart as well as hereditary variants. However, in clear absence of any suggestion of inheritance, the child should be carefully approached to clinch the diagnosis. Treatment mainly revolves around treating the specific cause and providing symptomatic and functional relief to the patient with extensive use of emollients and keratolytics and judicious use of oral agents.

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Disclaimer: "We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work"

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