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Contents

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The two limbs of Dermatologic Drug Development: Seredipity and Systematic Drug Repurposing

Sidharth Sonthalia[1], Nripen Kachhawa[2], Mahima Agrawal[3]

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The term drug repurposing has recently soared up the popularity charts of medical academia. Veritably drug repurposing has, for decades served as the source of majority of drugs being used in cutaneous medicine whether inspired serendipitously [1] or effectuated through plausibility-backed systematic trials. Perfection of serendipitous discovery of a drug's positive side-effect on a skin abnormality when administered for a completely unrelated co-morbidity also called the Renbok phenomenon [2] constitutes the first limb of dermatologic drug development. This concept dates back to Kligman's chance discovery of anti-aging effects of topical tretinoin when given for facial acne [3] and is illustrated with the following examples: minoxidil and finasteride for alopecias stemming from their hair growth 'side effect' observed in patients who were administered the drugs for hypertension and benign prostate hyperplasia respectively [4,5]; vitamin D analogues for psoriasis following dramatic improvement in an old patient who was actually given oral vitamin D for osteoporosis [6]; low-dose tranexamic acid for melasma extrapolated from reduced hyperpigmentation discovered in a patient with chronic urticaria for which the plasmin inhibitor was given [7,8]; tofacitinib for alopecia areata whilst the janus kinase inhibitor was primarily tried to control the patient's refractory psoriasis [9,10]; and the legendary discovery of aesthetic indications of botulinum toxin (BoNT) by the medico-marital sorority of the Carruthers, when the forehead lines disappeared in a patient suffering from blepharospasm treated with BoNT by Dr. Jean, an ophthalmologist, whose dermatologist husband Dr. Alistair Carruther later explored the science underlying this observation [11]. Planned repurposing based on thorough research constitutes the other, albeit less appreciated and addressed limb of pharmaceutical development in dermatology: Immunomodulatory effects of DMARDs like methotrexate, cyclosporine, sulphasalazine and anti-TNF-α biologics used in rheumatoid arthritis for pathogenetically related skin conditions especially psoriasis; antimycotic ciclopirox olamine for multi-drug-resistant bacterial infections of the skin [12-14]; NK-1 inhibitor aprepitant typically used for prevention of chemotherapy-induced and postoperative nausea and vomiting in cancer patients repurposed for chronic refractory pruritus of diverse origins [15,16]; ornithine decarboxylase inhibitor (ODCI) anti-trypanosomal oral drug eflornithine hydrochloride repurposed topically for reducing unwanted hair growth, e.g. in hirsutism, and for prophylaxis against development of non-melanoma skin cancers (NMSCs) [17,18]; translating the repigmenting effect of UV light via induction of PGE2 production into clinical repurposing of PGE2 gel for treatment of vitiligo [19]; and cosmeceutical repurposing of melatonin in AGA using nanostructured lipid carriers [20] exemplify this approach.

However, the biggest concern in this area is the relative lack of evidence in favour of many seredipitiously discovered drugs. Thus, Dermatology colleagues across the globe should indulge in exploration, generation and documentation of evidence by conducting ethical research studies with large cohort size for the drugs that are being used off-label, that too based on limited evidence.

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Premature Graying of Hair: An Ayurvedic Perspective

Reena Rawat

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About Our Guest Editor

Dr Reena Rawat, a world-renowned Healer and Nutrition Expert is currently serving as Deputy Manager (Service and Research) at Dr. Shikha's **Dr Shikha's Nutri Health**, a platform offering comprehensive health and diet management programs to thousands of patients across India. Dr Rawat completed her B.A.M.S. from the coveted A & U Tibbia College-cum-Hospital, University of Delhi and tuned her healing and advanced nutritive skills during her double post-doctoral diplomas in Yoga and Naturopathy obtained from the Morarji Desai National Institute of Yoga, and the International Foundation of Natural Health & Yoga. Following her Internship as Ayurvedic Physician undertaken at the coveted University College of Medical Sciences & GTB Hospital, New Delhi, she eventually joined **Dr Shikha's Nutri Health** in 2007, and continues to contribute to the betterment of people's health through this globally famous platform till date.

Dr. Reena is quoted frequently by many leading publications. A well-known face on television channels, she is also frequently invited to give talks at professional platforms and for patient awareness. Dr Reena practices a unique amalgamation of the ancient Ayurvedic knowledge and skills and contemporary evidence-based nutritional therapeutics.

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Keywords: Ayurveda; Skin health; Graying of Hair Premature; Pitta; Vata; Kapha; Alternative Complimentary medicine; Nutrition Hair.

Ayurveda, the ancient healing system of India and one of the oldest healing systems of the world defines the fundamental composition of the human body as a combination of three different *doshas* (types of bio-energies), which are named as -*VATA, PITTA* and *KAPHA*. Each individual is constituted by a varying combination of these three *doshas* – Vata, Pitta and Kapha, in which usually, two types tend to predominate. In non-vitiated form they nourish our system but an imbalance of these doshas whether aggravated or depleted, leads to disease. This concept is in sharp contrast to the conventional western system of medicine.

Another important term is '*prakriti*' referring to 'constitutional tendency'. In broad terms *Vata* is responsible for functions aligned to the movement in the body (such as food movement through the bowels, nervine communication, flow of nutrients, thinking, cognition etc), *Pitta* is responsible for digestion and metabolism (including digestion and assimilation of food) and *Kapha* is responsible for growth and development of the body (in vitiated form this growth can form tumours).

Pitta dosha has qualities like unctuousness, hot, swift, liquid, mobility, sour and pungent taste. It is responsible for regulation of functions like digestion, body temperature, hunger, thirst and vision. Graying of hair, hair fall and general skin disorders are more common in individuals with *Pitta prakriti*. In simple terms, aggravation of *Pitta dosha* leads to graying of hair and skin disorders.

Gray Hairs – Premature canities and Ayurveda

In Ayurveda graying of hair is called as *Palitya* [1]. Graying of hair according to age is a common phenomenon. Conventionally, graying of hair is a marker of progressive chronological age. But drastic changes in today's life style and environmental pollution have led to the increasing trend of premature graying of hair. In Ayurveda premature graying of hair is called "*Akalpalitya*". Premature or early graying of hair is frequently being observed these days due to erratic lifestyle including eating habits, and polluted environment. Melanocytes of the hair follicle are responsible for the color of hairs and depletion of melanocytes leads to graying of hair. In Ayurveda aggravation of ***Pitta*** and ***Ushna Guna*** (also referring to hot/ heat quality) leads to premature graying of hair.

Causes of Palitya

Four main reasons have been cited: (1) Dietary *(Aharaja)*; (2) Life-style*(Viharaja);* (3) Psychological (*mansik*); and (4) Unknown (*adibalapravritta)* [2].

1. **Nutritional (Aharaja):** Excessive use of pungent, sour and salty foods aggravates *Pitta dosha*, e.g. excessive consumption of mustard and curd. Excessive use of salt in diet aggravates *Pitta* (as mentioned in *charaka sutrasthana atreyabhadrakapiyaadhyaya*) [2]. Excess use of other pungent/hot/sour foods such as amla phala (sour fruits), sesame oil (til ka tail), linseed (alasi), goat flesh, fish (matsya), sheep (aavika), in addition to mustard, curd and excess salt cause the vitiation of pitta leading to palitya [3]. In terms of conventional medical opinion, premature graying of hair has been associated with deficiency of Iron, vitamin B12, Calcium & Vitamin D3 and other micronutrients [4-6]. However, correlative study such as the effect of mustard and linseed on the absorption of iron and vitamin B12 do not exist, although merit exploration.
2. **Lifestyle (*Viharaja*):** Overindulgence in physical exercise (*ativyayama*), night-time awakening (*raatrijagarana*), excessive sunlight exposure (*atiatapasevan*), intake of vitiated air (*dushitvayusevan*), smoking (*dhumasevan*), excess fasting (*upvasa*) may cause the *palitya* [7].
3. **Psychological (*Mansik*):** Certain psychological morbidities like anger (*krodha*), fear (*bhaya*), grief (*shoka*), and mental stress (*maansikashrama*) vitiate the *pitta dosha* thereby contributing to *palitya* [7].
4. **Unknown/Genetic (*Adibalapravritta*):** It is well-established that genetic inheritance contributes >90% of premature graying [4,5]. Ayurvedic principles also identify this aspect of this condition.

Summarizing Ayurvedic Pathogenesis of Graying of Hair (Fig. 1)

How to deal with Gray Hairs

1. Avoid Pitta aggravating food, lifestyle and psychological factors.
2. Madhura (Sweet), tikta (Bitter) & Kashaya (Astringent) rasa diminish the *pitta dosha*- like *Moong daal* (whole or split green gram, yellow moong dal), cow's *ghee*, milk, coconut and dates.
3. *Nasyam Therapy* - An Ayurvedic therapy in which medicated oils are administered in the nostrils.
4. Regular use of hair oil, especially Bhringraj oil.

This short Editorial just gave you a glimpse into the approach to pathogenesis of graying of hair as per Ayurvedic healing system. Trials with correlation/contrast with the conventional system would be fruitful in possibly deriving a

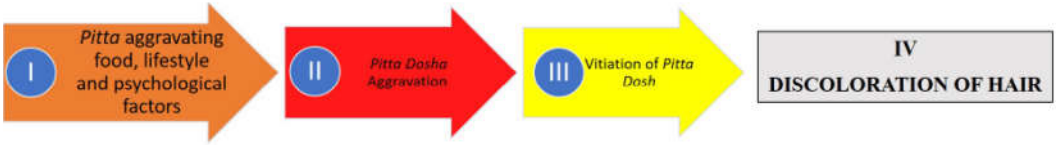

Fig. 1: Schematic diagram depicting the pathogenesis of premature graying of hair as per the Ayurvedic Principles

unified theory of pathogenesis and healing of this increasing menace.

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Original Article

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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.

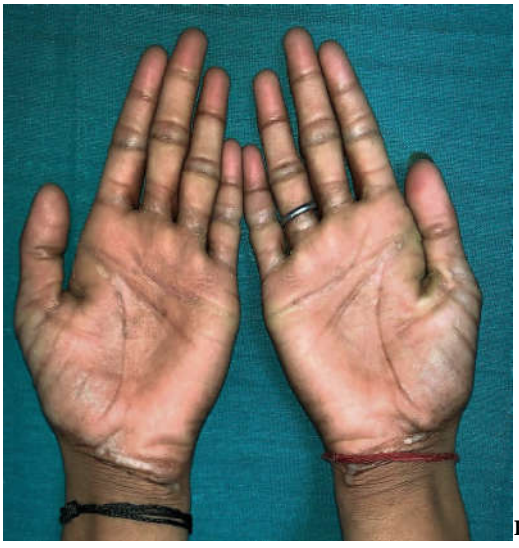

Fig. 1A:

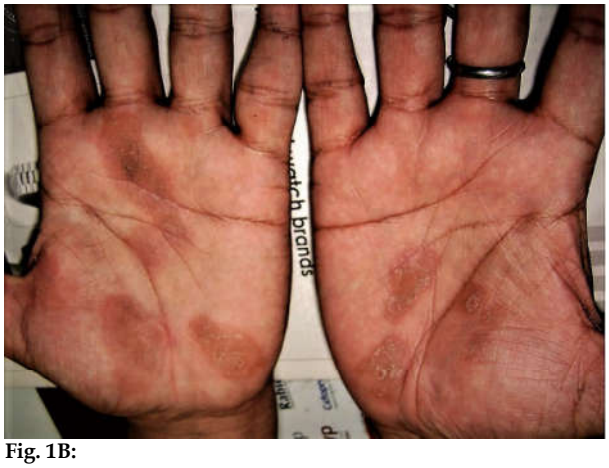

Fig. 1B:

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

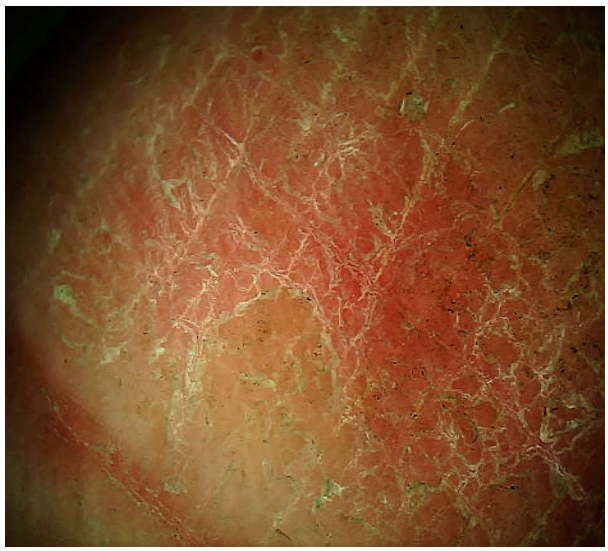

Fig. 2A:

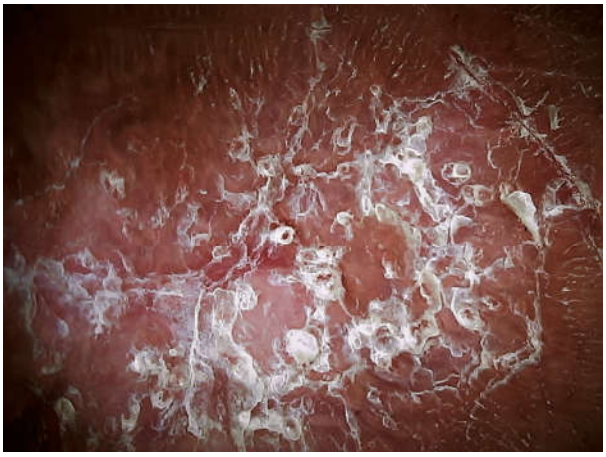

Fig. 2B:

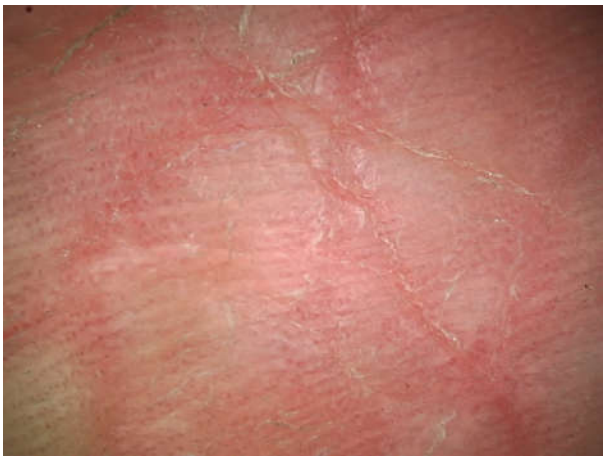

Fig. 2C:

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

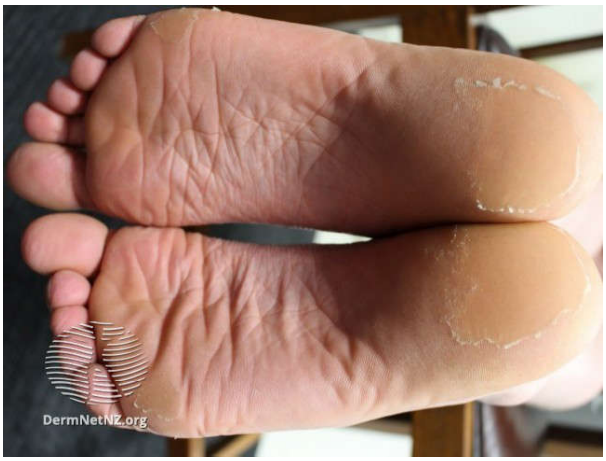

Fig. 3: Clinical image of soles showing yellowish-orange colored mildly hyperkeratotic well circumscribed focal keratoderma over pressure bearing sites in a case of Circumscribed juvenile-onset pityriasis rubra pilaris [Copyrighted watermarked image, unaltered, courtesy image library of www.dermnet.nz;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

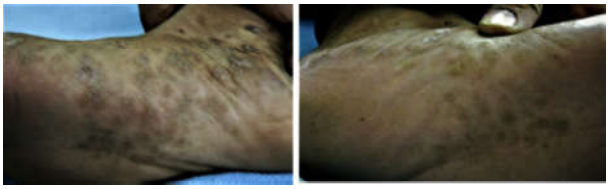

Fig. 4A:

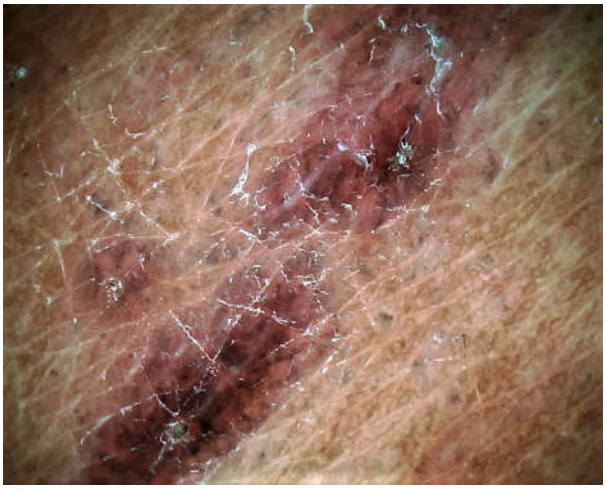

Fig. 4B:

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].

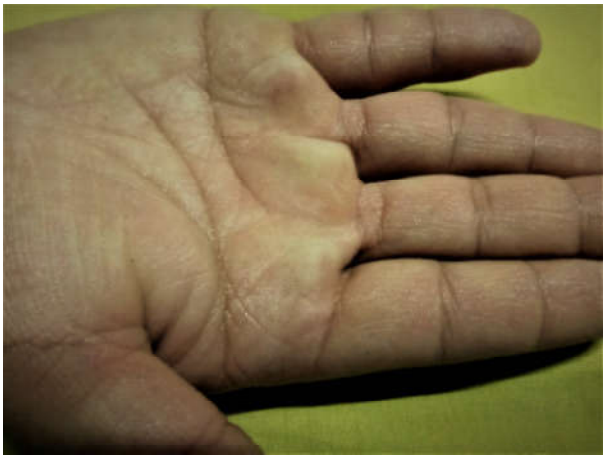

Fig. 5: Aquagenic palmoplantar keratoderma with hyperhidrosis in a 10-year old girl showing wrinkled appearance of the palms and digits and white to translucent papules; the lesions appeared after water immersion test.

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

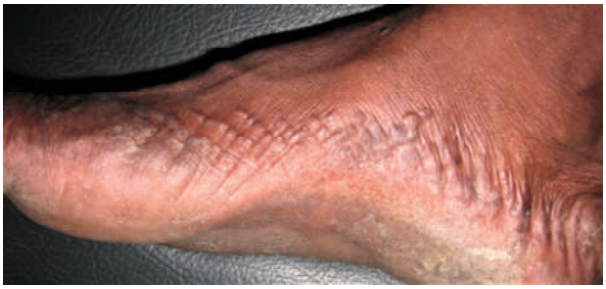

Fig. 6: Acrokeratoelastoidosis of Costa (AKC) in a 16-year old patient with the inner margin of the sole showing well defined round keratotic papules with some showing central crater. In contrast to the common autosomal dominant inheritance of AKC, this adolescent had negative family history and represents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

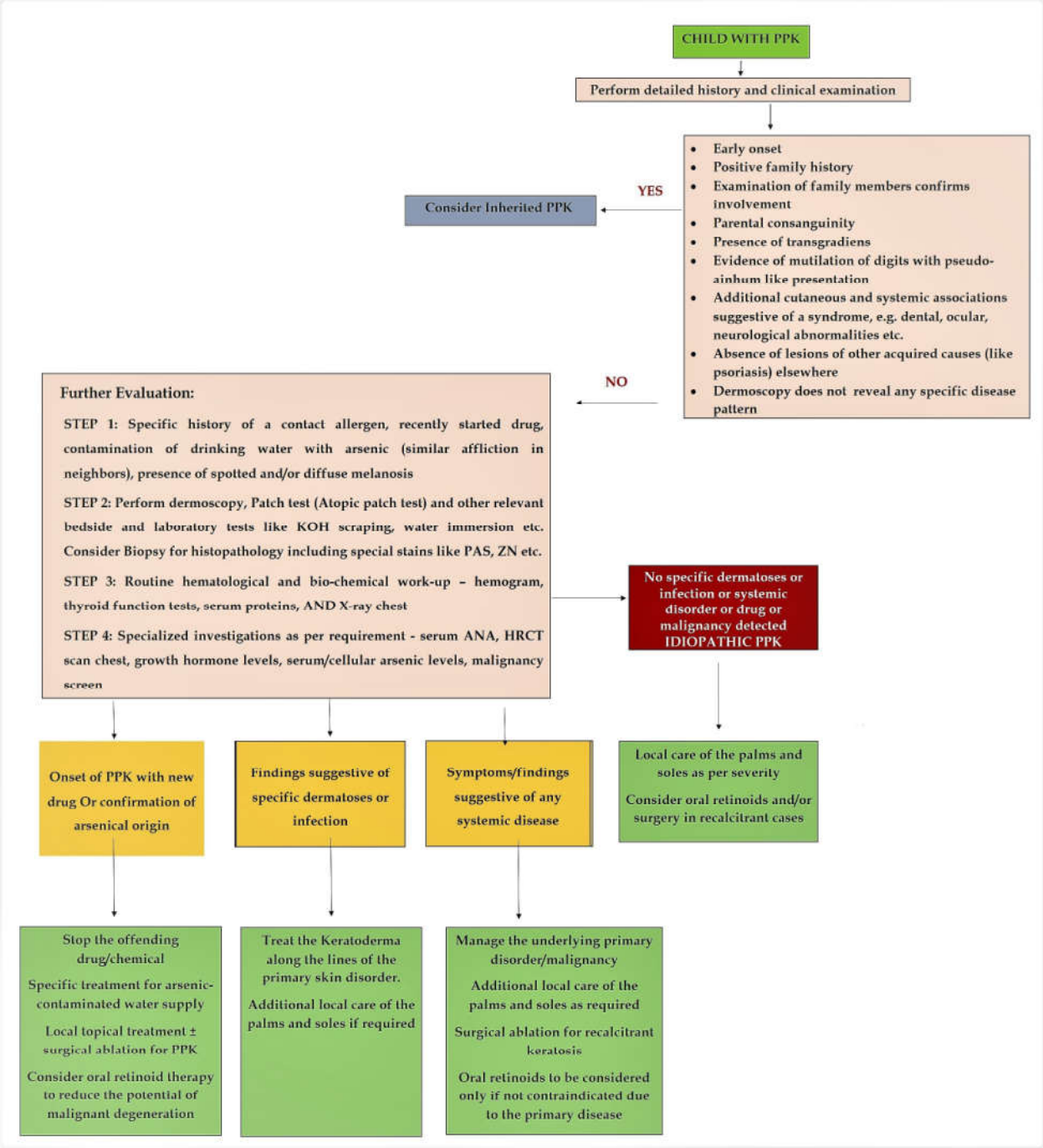

Fig. 7: Schematic flow chart outlining general approach to a child with palmoplantar keratoderma

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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Original Article

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An Etiological Study of Chronic Spontaneous Urticaria in 300 Patients at Tertiary Care Hospital in Gujarat

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Abstract

Chronic Urticaria remains a major problem in terms of etiology, investigation, and management. Chronic spontaneous urticaria affects 0.5-1% of individuals (lifetime prevalence) and significantly reduces quality of life (QOL).

Aims of the Study: 1) To evaluate the types of chronic urticaria with reference to etiology from history and investigations. 2) To identify the specific cause of urticaria by thorough history and investigations.

Materials and Methods: Out of 300 patients with chronic spontaneous urticaria were enrolled. Autologous serum skin test (ASST) was performed after excluding physical urticaria. Routine laboratory tests were performed after ASST in all patients; and other specific investigations were done where necessary. Skin prick test was done in idiopathic urticaria.

Results: Out of 300 patients, 100 (33%) had history of angioedema. Out of 300 patients, auto-immune condition was present in 48 (16%) patients. Provocating factors were present in 81 (27%) patients. In our study 123 (41%) patients showed infective focus on routine screening investigation. ASST was positive in 60% of patients. Physical urticaria were found in 47 (15.66%) patients by challenge test, most common was dermographism. In prick test, maximum number of patients reacted positively to food allergens followed by pollen, dust, fungus in decreasing frequency.

Conclusion: Nearly half of the patients had chronic autoimmune urticaria on the basis of ASST. Chronic spontaneous urticaria requires extended diagnostic measures based on the patient's history.

Keywords: Auto antibodies; Autoimmune disease; ASST; CSU; Skin prick test.

Introduction

Urticaria is a common, heterogeneous group of disorders with a large variety of underlying causes. It is characterized by the sudden appearance of fleeting wheals, each of which last 1-24 hours and/ or angioedema lasting up to 72 hours [1].

Chronic Urticaria, with or without angioedema, has traditionally been defined as daily or almost daily symptoms recurring for more than 6 weeks [2]. affecting 0.1% of the population. Mast cell degranulation and histamine release is of central importance in the pathogenesis of CU. In contrast, acute urticaria is a single episode lasting for < 6 weeks.

Although the condition is rarely life-threatening, it generates anxiety and embarrassment and has an impact on quality of life comparable with that of severe coronary artery disease and exceeding

that associated with respiratory allergy. It is a disease with a high burden for patients disrupting sleep, diminishing work/school productivity [4]. It also has high direct and indirect healthcare costs with large socio-economic implications due to a reduction in performance by 20-30% [3].

Chronic Urticaria remains a major problem in terms of etiology, investigation, and management. Unfortunately, this troublesome condition is often trivialized, though it may cause considerable distress and may last for years. However, the good news is that, it can often be alleviated by appropriate management [5].

Materials and Methods

This prospective observational study was carried out in department of Dermatology, Venereology and Leprology. Three hundred patients, 99 male and 201 female between the age group of 1-80 years with chronic spontaneous urticaria were enrolled. Clinical details of all patients were recorded using a standard proforma.

Approval of Institutional Ethics Committee (IEC) was obtained.

Informed written consent and photographs were taken.

History regarding onset, frequency of disease, infection, gastrointestinal symptoms, aggravating and associated factors were taken.

Baseline investigations (CBC, ESR, urine and stool), RBS and CRP were done for all the patients. whereas specific investigations (ANA, Thyroid Profile, IgE, Anti H. Pylori IgG, skin biopsy, prick test) were done in selected cases. ASST was performed in all patients after excluding physical urticaria.

Exclusion Criteria

1. Acute urticaria (less than 6 weeks).
2. Urticarial vasculitis.
3. Pregnant or lactating women.
4. Severely ill and immuno-compromised patients,
5. Non complaint patients.

Statistical methods:

Descriptive statistical analysis was carried out. Chi- square was used to find association between ASST, ANA, Thyroid- antibodies, IgE and Helicobacter pylori IgG.

Results

The male: female ratio among all urticaria subgroups was 2.03:1. Maximum patients were between age group of 20-40 years (reproductive age). Patients <20 years show infective focus in majority of cases. Out of 300 patients, 100 (33%) had history of angioedema. There was no history of provocative factors in 219 (73%) patients. Eighty one (27%) patients had history of provoking factors such as food, pollen, and drugs. In 69 (23%) patients infections were the provocating factors. In 60 (20%) patients food was a provocating factor. In 55 (18.33%) patients drugs were the provocating factor. Urticaria followed by non steroidal anti inflammatory drug (NSAID) was observed in 40 (13%) patients and 2 (0.6%) patients presented with urticaria followed by in take of oral contraceptive pills and 13 (4%) patients presented with urticaria followed by antibiotic therapy. Out Of 40 NSAIDS induced urticaria 10 were aspirin sensitive. Diabetes mellitus was seen in 20 (6%) patients, 30 (10%) had gastritis, 12 (3.6%) had hypertension, 18 (5.4%) were hypothyroid. 5 (6%) had systemic lupus erythematousus. 5 (6%) had rheumatoid arthritis **(Table 1)**. In our study 123 (41%) patients showed infective focus on routine investigations. ASST was performed in all patients of CSU after excluding those with physical urticaria. Out of 300 patients 250 patients who underwent ASST, 60% showed a positive test **(Table 2)**. In this study lesions lasting for a significantly longer duration and frequency correlated to a higher incidence in ASST positive patients as compared to ASST negative patients. H. pylori antibodies were significantly higher (29%) for ASST positive patients when compared to ASST negative patients, which show significant p value (<0.00001). Similarly, antinuclear antibodies (ANA) were positive in 4% of patients who were ASST positive, which showed significant p value (<0.00001). Thyroid antibodies were present in 7% of patients with positive ASST, which showed significant p value (<0.00001). IgE was elevated in 32% of ASST positive patients, which showed significant p value (<0.01). **(Table 3)**. Challenge tests were performed in 47 (15.66%) patients with clinical features of physical urticaria. 15 (5%) patients showed cholinergic urticaria, 15 (5%) had symptomatic dermographism, 5 (1.6%) had cold urticaria with ice cube test, 6 (2%) showed delayed pressure urticaria, 4 (1.3%) had solar urticaria and 2 (0.66%)patients showed localized heat Urticaria **(Fig. 1).** Skin Prick test was done in 40 patients who had idiopathic urticaria of which 12 patients had history strongly suggestive of

food and dust induced aggravation. Among them 60% patients showed reactions to more than five antigens with maximum reaction to foods (in 15 patients), followed by dust (in 5 patients), pollen, mites, fungi (1 patient)and insect in 2 (1 each to cockroach & yellow flask) with 12 patients showing no reaction **(Fig. 2).**

Discussion

Chronic Urticaria remains a major problem in

Table 1: Probable Etiological Factor for Cronic Sponteneous Urticaria

Probable etiological factor	Present study (N=300)	Krupshankr *et al*. study [8] (N=150)	Rakshapatel *et al.* study [17] (N=500)
Food	60 (20%)		136 (27.7%)
Dust	12 (4%)		7 (1.4 %)
Drugs	55 (18.33%)		128 (25.6%)
Infestation	27 (9%)		14 (2.8%)
Infection	123 (41%)patients	38%	16 (3.2%)
Physical	47 (15.66%)	23 (15.55%)	83 (16.6%)
Atopy	45 (15%)	18.8%	4 (0.8%)
Malignancy	2 (0.66%)		1 (0.2%)
Autoimmne condition	48 (16%)	22.5%	3 (0.6%)

Table 2: Frequency of Attacks in Asst Positive and Asst Negative Patients

Frequency of attacks	ASST positive	ASST negative
Every day attack	70 (23.33%)	58 (19%)
Every alternate day	44 (14.66%)	21 (7%)
Every 3 day	22 (7.33%)	18 (6%)
Once a week	14 (4.66%)	3 (1%)

Table 3: Special Investigation

Investigation	Asst +VE N=150	Asst –VE N=100	Chi square value at Df=1	p value
ANA			24.04	<0.00001
Negative	144 (96%)	100 (100%)		
Positive	6 (4%)	0 (0%)		
Thyroid			339.56	<0.00001
Negative	124 (93%)	98 (98%)		
Positive	26 (7%)	2 (2%)		
IgE			5.76	<0.01
Negative	102 (68%)	70 (70%)		
Positive	48 (32%)	30 (30%)		
H. Pylori			784	<0.00001
Negative	106 (71%)	94 (94%)		
Positive	44 (29%)	6 (6%)		

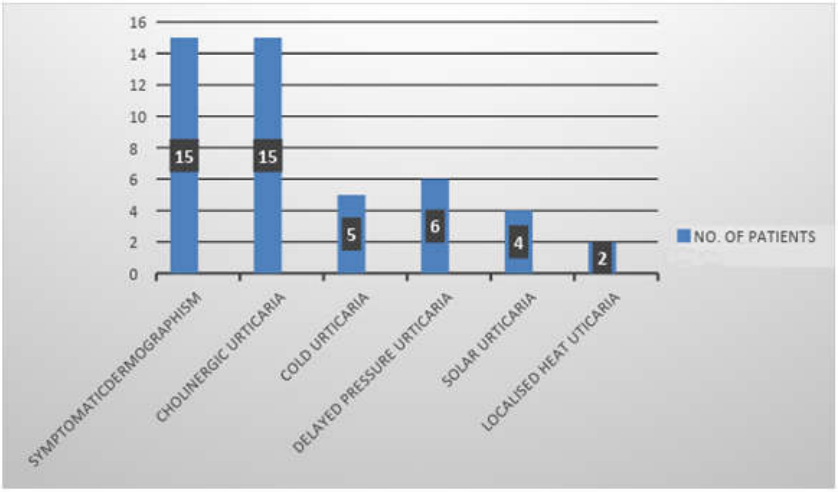

Fig. 1: Proportionate number of patients with specific type of Physical Urticaria

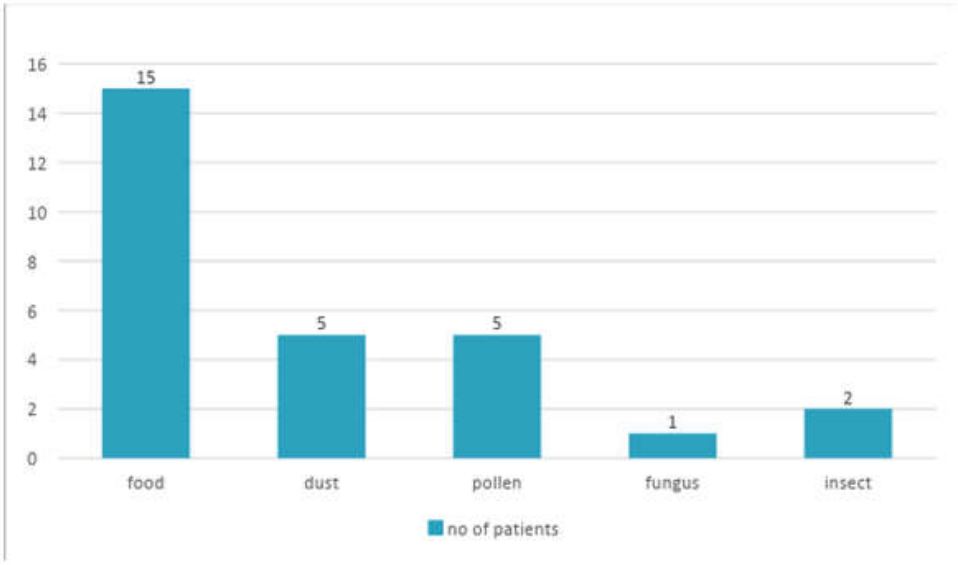

Fig. 2: Results of the Skin Prick Test demonstrating specific allergen positivity and corresponding number of patients

terms of etiology, investigation, and management. In this prospective observatinal study of 300 patients was done over a period of three year. The youngest patient was a one-year-old and the oldest was 80, with mean ages of 21- 40 years. Male to female ratio was 1:2.03. Compairable with study done by krupashankar *et al.* [8]. There was no history of provocating factors in 219 (73%) whereas a provocating factor such as food, pollen, and drugs was found in 81 patients. Urticaria following non steroidal anti inflammatory drug (NSAID) was observed in 40 (13%) patients with 2 (0.6%) patients presenting with urticaria following intake of oral contraceptive pills and 13 (4%) patients following antibiotic therapy, Comparable with the study done by krupa Shankar *et al.* [8]. Out Of 13% NSAIDS induced urticaria, 33% were aspirin induced compared with the reference quoted by Heavey DJ, Kobza and Stevenson DD [6,7]. Aspirin is the most common drug causing urticaria [6] and accounts for 30-60% of all NSAIDs implicated [7]. In our study 123 (41%) patients showed infective focus on routine investigations, comparable with the study done by Krupa Shankar *et al.* [8] showing 38% with infective focus on routine screening investigation, CSU frequently flared by intercurrent infection. This is due to non-specific effect of circulating pro-inflammatory cytokines or chemokines, either on mast cells or the expression of adhesion molecules on endothelial cells. According to Krupa Shankar *et al.* [8] 4-35% of such affected patients, cure of infections leads to improvement of urticaria.

It has already been reported that the ASST with positive test being defined as one with serum induced wheals, which is both erythematous and has a diameter of 1.5 mm greater than saline response at 30 minutes is a reasonably predictive clinical test to reveal functional circulating antibodies with a sensitivity of 65-71% and specificity 78-81% [10].

In this study, lesions lasting for a significantly longer duration and with higher frequency correlated to a higher incidence of ASST positivity as compared to ASST negative patients. *H. pylori* antibodies were significantly higher (29%) for ASST positive patients when compared to ASST negative patients showing a significant P value (<0.00001). It is postulated that *H. pylori* infection may induce development of pathogenic auto antibodies by molecular mimicry [12,13]. Appelmelk *et al.* [12,13] first demonstrated the molecular mimicry between *H. pylori* and lipopolysaccharide (LPS) anti Lewis antibodies in autoimmune type-B gastritis.

Similarly, antinuclear antibodies (ANA) was positive in 4% of patients who were ASST positive with a significant P value.

Thyroid antibodies were present in 7% of patients with positive ASST, with a significant P value (<0.00001) IgE was elevated in only 32% ASST positive patients which is significant. This may indicate induction of autoimmunity through cross reactivity or other mechanisms in a population prone to immunological hyper reactivity.

A study by Sabroe *et al.* [9]. concludes that patients with auto antibodies showed frequent attacks. There is a statistically significant difference in TSH, thyroid antibodies and ANA between the ASST positive and negative groups, indicating a correlation between a positive ASST and auto immunity. This implies that markers of autoimmunity may be found in many

types of chronic urticaria, but ASST is the only clinically demonstrable evidence of autoimmunity. Patients with autoimmune urticaria have no distinctive, diagnostic clinical or histopathological features which differentiate it from non autoimmune cases, although they tend to have more severe urticaria [11]. Patients with positive ASST have more severe urticaria, more prolonged duration, more frequent attacks, angioedema and GI symptoms than negative ASST patients. Identification of autoimmune urticaria may permit the use of an immunotherapy in severe disease unresponsive to anti-histamine therapy.

In our study dermographism and cholinergic urticaria accounted for 15%, which was the most common type of physical urticaria. Cold urticaria was diagnosed in 1.6%, delayed pressure urticaria in 2% corresponding to the study done by Krupa Shankar *et al*. [8] showing cholinergic urticaria and dermographism accounting for 4.7% cases, Cold urticaria in 2%, and Delayed pressure urticaria in 2%.

In our study maximum number of patients reacted positively to the food allergens followed by pollen, dust, fungi and insect comparable with the study by Krupa Shankar *et al*. [8] were in maximum reaction was seen to foods, followed by dust, pollen, mites, fungi, epithelia and insect.

Skin prick test is the most convenient and least expensive method of allergy testing and result can be made available within 15-20 minutes. Prick testing helps to trace out type 1 (immunoglobulin E) mediated hypersensitivity specifically [14,15]. Patients with idiopathic urticaria, who were willing and had a high degree of suspicion towards particular food items or aero allergens, and in whom all other clinical and laboratory findings were non contributory, underwent skin prick testing. Standardized extracts for many antigens are readily available. These tests are generally well tolerated with mild erythema and edema that usually subsides within one to two hours. More severe swelling is treated with oral antihistamines, topical steroids and ice-packs. It was possible to identify cause and eliminate it in 20 patients.

A positive skin test indicates that the subject is allergic to the particular substance. In general, skin tests are most reliable for diagnosing allergies to airborne substances, such as pollen, epithelia, and dust mites.

Diagnosing food allergies can be complex, and may need additional tests or procedures. In our study maximum number of patients reacted positively to yeast out of the food allergens but due to the small case numbers for prick test, no conclusion can be made. In pollen, maximum number of patients reacted positively to parthenium which is the most common aeroallergen in India.

Conclusion

Food was the most common cause found in 20% of the patients followed by drug in 18.33% & physical urticaria was present in (16.%). History of atopy was found in 16% patients and infestation in 27%. ASST was positive in 60% of the patients out of 250 screened and patients with positive ASST show more frequent attack (23.33% had daily attack) of urticaria compare to ASST negative in our study. IgE and IgG against h. pylori were raised in 32% and 29% of the patients respectively. Dermographism and cholinergic urticaria were the most common type found in 15% of the patients with physical urticaria. Skin prick test shows maximum reaction to food (37.5% patients).

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Original Article

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Autologous Serum Skin Test in Chronic Urticaria

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Abstract

Background: Chronic urticaria is a distressing condition which affects the quality of life of patients. Majority of chronic urticaria patients have no external cause and termed as chronic idiopathic urticaria. Approximately 30-40% of patients with chronic idiopathic urticaria have autoimmune urticaria. Asst is a simple inexpensive test which helps to classify chronic urticaria into idiopathic urticaria and autoimmune urticaria.

Aims: To identify autoimmune urticaria amongst the chronic idiopathic urticaria.

Methods: A total of 100 cases of chronic urticaria, attending the skin opd from march to February were taken up for the study. After a detailed clinical history and examination laboratory investigations like Complete haemogram, Blood sugars, Erythrocyte Sedimentation Rate (ESR), Absolute eosinophil count (AEC) was sent for all the patients. ASST was done. A positive test was defined as a serum-induced wheal response with a diameter of 1.5 mm or more than the saline induced response at 30 minutes.

Results: Of all the patients studied 41% of the patients showed a positive reaction. Most of whom were females and in the age group of 21-30 years. The mean urticaria activity score was 5.11 in the ASST positive patients compared to 4.39 in the ASST negative group. In the ASST positive group, 80.48% had daily occurrence of lesions while 62.71% of the asst negative group got lesions daily. Patients with positive ASST had larger extent of body involvement.

Conclusion: We concluded that autoimmune urticaria has greater frequency and larger extent and higher urticarial activity score than other types of urticaria.

Keywords: Chronic urticaria; ASST; Autoimmune urticaria.

Introduction

Chronic urticaria is defined by presence of wheals on most days of the week for a period of 6 weeks or longer [1,2]. In about 80% cases, no external allergen is identified and thus termed chronic idiopathic urticaria (CIU) [1]. Approximately 30-40% of patients with chronic idiopathic urticaria have histamine-releasing autoantibodies directed against either the high-affinity IgE receptor, or less frequently, IgE called autoimmune urticaria [3].

These antibodies can be detected using autologous serum skin test (ASST). With a sensitivity of 70% and a specificity of 80% it is a simple inexpensive reasonably predictive clinical test for functional circulating auto antibodies [4]. Chronic urticaria is a frustrating skin disease that affects the patient's quality of life [5]. It may last for years but it can be alleviated by appropriate management [6]. Patients with autoantibodies may need higher dose of antihistamine or additional immunomodulators [7]. With this in mind we did

the present study to identify autoimmune urticaria by ASST and study its clinical patterns.

Aims and Objectives

1. To study the clinical aspects of chronic urticaria.
2. To identify autoimmune urticaria amongst the group and study its clinical pattern.

Methods

A total of 100 cases of chronic urticaria, attending the skin opd from march to February were taken up for the study. After a detailed clinical history and examination laboratory investigations like Complete haemogram, Blood sugars, Erythrocyte Sedimentation Rate (ESR), Absolute eosinophil count (AEC) was sent for all the patients.

Two millilitres of venous blood was taken from the antecubital vein and the blood was allowed to undergo clotting at room temperature. Serum was separated by centrifugation (2000 rpm for 10-15 min). Approximately 0.05 mL of serum was injected intradermally into the volar aspect of the forearm, avoiding the areas of whealing within the past 24 hours. Equal amount of normal saline (negative control) was injected intradermally 3 to 5 cm apart in the volar aspect of the same forearm. Wheal and flare responses were measured at 30 min. A positive test was defined as a serum-induced wheal response with a diameter of 1.5 mm or more than the saline induced response at 30 minutes.

Results

A total of 100 cases of chronic urticaria, attending the skin opd were taken up for the study. Of all the patients studied 41% of the patients showed a positive reaction to the autologous serum skin test in the form of wheal and flare and 59% patients had a negative ASST. Chronic urticaria was predominantly seen in the age group of 21 to 30. Majority of the ASST positive patients were also in the 21 to 30 years age group (34.09%). But there was no significant difference in the age distribution between ASST positive and negative patients.The incidence of chronic urticaria was higher in females (68) compared to males (32). Of the 41 ASST positive patients, 31 (75.60%) were females indicating that a statistically significant proportion of females showed positive response to ASST **(Table 1).** UAS score was obtained by adding the scores for the number of wheals and the score for the intensity of itching. It is a subjective score to assess urticarial activity. The mean urticaria activity score was 5.11 in the ASST positive patients compared to 4.39 in the ASST negative group. This difference was statistically significant **(Fig. 1)**. The ASST, positive patients had a mean duration of onset of 29 months and ASST, negative group had 20 months.

Out of the 100 patients, 70 patients had daily occurrence of urticarial lesions. In the ASST positive group, 80.48% had daily occurrence of lesions while 62.71% of the ASST negative group got lesions daily. There was astatistically significant difference between the two groups indicating that the frequency of appearance of lesions was higher in the ASST positive subgroup **(Table 2)**. In our study we noticed patients with positive ASST had larger extent of body involvement.

Table 1:

	Asst+	Asst -	Total
Males	10	22	32
Females	31	37	68
Total	41	59	100

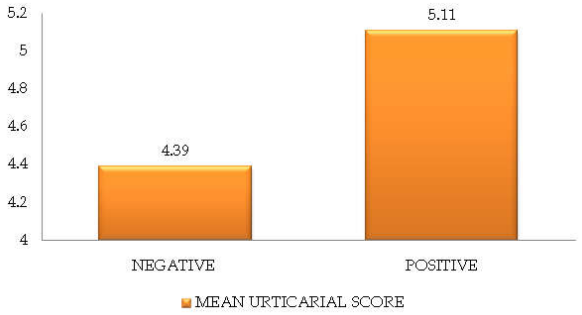

Fig. 1: Graphical correlation of the mean urticarial score and ASST positivity

Table 2:

Extent	Asst		Total
	Negative	Positive	
<10% (Score 1)	8 13.55%	0 (0%)	08 (8%)
11-50% (Score 2)	29 49.15%	13 (31.70%)	42 (42%)
>50% (Score 3)	22 37.28 %	28 (68.29%)	50 (50%)
Total	59 (100%)	41 (100%)	100 (100%)

Discussion

Out of the 100 cases studied 41 patients were tested positive for ASST. While studies done by Beevi AS *et al.* [4] showed 69.4% and Vohra et al.

[8] showed 46% positivity, Mamatha *et al.* [9] and M Abd El Azim *et al.* [10] showed 34% and 39.6% respectively.

The mean age of ASST positive patients is 32.9 which is similar to the study done by Zeinab Abdel Azim *et al.* [11] (34.3) and M Abd El Azim *et al.* [10] (36.4).and Beevi SA *et al.* [4] (35.9) years.

The proportion of positive ASST was more in females (75.60%) compared to males (24.39%) in our study. In all studies [4,9,11] including the present study, the incidence of autoimmune urticaria is more in females compared to males. The higher incidence of positive ASST in females can be explained by the hypothesis of increased autoimmune diseases in the female sex in general [12].

In our study ASST, patients had alonger duration of disease (29 months) compared to ASST negative patients (20 months) although the difference was not statistically significant.

In a study by by Zeinab Abdel Azim *et al.* [11] it was higher (48 m) and lower compared to a study by Abd El Azim M *et al.* [10] (27.4 months) in the autoimmune urticaria group.

Majority of patients with autoimmune urticaria have a higher mean urticaria score. In the present study, the mean urticaria activity score was 5.11 in ASST positive patients compared to 4.39 in ASST negative patients. This value is higher when compared to the study by Zeinab Abdel Azim *et al.* [11] with 4.5 in ASST positive. Our values were lower compared to study by Vohra *et al.* [8] (6.13). We noticed that autoimmune urticaria patients (80.48%) had more frequent urticarial attacks (>5/ week or daily). This finding is consistent with the results of the studies done by Abd El Azim M *et al.* [10] and Zeinab Abdel Azim *et al.* [11] Majority (68.29%) of the ASST positive patients in the present study had >50% of their body surface area involved by urticarial lesions. This is comparable with the study done by Mamatha *et al.* [9] This implies that patients with a positive ASST have more frequent attacks and more extensive disease.

Conclusion

We concluded autoimmune urticaria has greater frequency and larger extent and higher urticarial activity score than other types of urticaria.

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Conflict of interest: none

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Original Article

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Crane Principle Revisited

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Abstract

Background: Reconstructing defect is the goal of the plastic surgeon which is done on the principle of reconstruction ladder but certain defect needs coverage requiring improvising on the principles, once such is crane principle. In this study, we would like to highlight the use of crane principle in reconstructing defect of hand and protecting vital structures.

Methods: 18 year male with full thickness defect of a volar and dorsal aspect of wrist post electrical burn injury underwent flap cover for the defect.

Results: Marginal necrosis of flap noted, flap debrided, healthy wound bed noted.

Conclusion: Covering of defect employing crane principle though described in earlier days is still relevant in the management of defect with limited donor site.

Keywords: Crane principle; Defect; Hand

Introduction

Traumatic/ infective cause leading to exposure of vital structure like bone, joint, tendons, vessels, nerves compounds the initial insult sustained. Coverage of such tissue is a prime concern and reconstructive ladder based approach is jumped to achieve coverage of these exposed structures. The problem arises when Peter can't afford to pay to Paul; in such scenario, the use of a carrier or crane was described by Gillies and Millard' in their text, "The Principles and Art of Plastic Surgery" in 1957. They showed the use of one flap, a tubed pedicle flap, to carry another flap to its final resting place, referred to this as a living crane [1].

In this case study, we would like to elaborate on the age-old principle used to treat our patient who sustained high voltage electrical burn injury.

Methods

Our patient is an 18 year old male who sustained accidental high voltage electrical burn injury. Entry point being right hand and exit point left hand. The patient had full thickness burns over the dorsum of right wrist with compartment syndrome of the right hand, right forearm. Fasciotomy was done; deep muscles of the forearm were unhealthy, discolored and edematous. Patient Wound grossly infected with exposed flexor tendons and median nerve. The patient underwent serial debridement and Hypogastric flap cover **(Figs. 1,2)**.

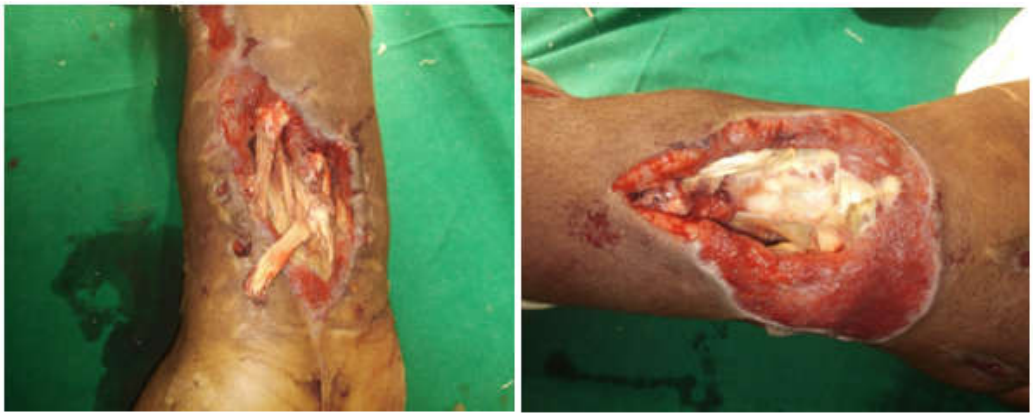

Fig 1: Volar and dorsal defect of hand

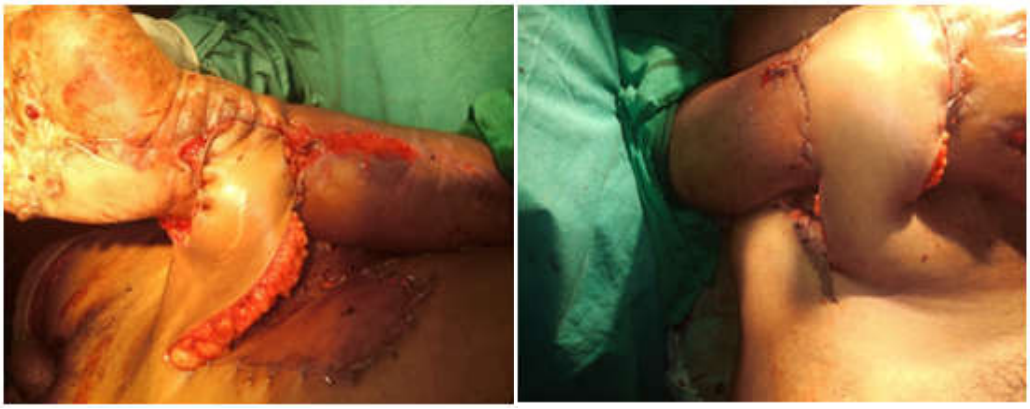

Fig 2: Hypogastric flap reconstruction of defect

Results

Margin necrosis of flap was noted, on postoperative day 7, the entire flap was dismantled. The bed of the flap had completely granulated which could be covered by skin graft **(Fig. 3)** but flap was reinserted in view of the defect, aesthetic and plan for secondary reconstruction.

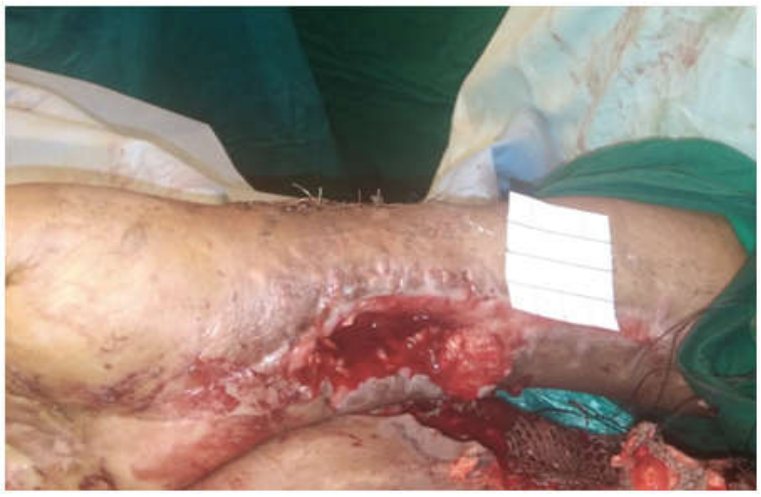

Fig 3: Wound bed after flap dismantle

Discussion

Traditionally reconstructive plastic surgeons approach tissue reconstruction by paying due attention to the reconstructive ladder. This was viewed as a ladder with each successive rung representing an increasingly complex mode of treatment. This concept was principally introduced as an aid to obtaining wound closure. Thus the simplest method represented on the ladder is by the primary closure and the most sophisticated is by way of free tissue transfer. It was envisaged that one "climbed" this "ladder" when attempting to close wounds. Thus only after the simplest technique has failed should one try the next level of complexity [2].

Millard in 1969 expanded Crane principle to transport and deposit subcutaneous tissue to cover exposed vital structures of hand and after a week the skin flap is returned to its bed, leaving behind a quarter of its thickness as a vascular bed which can be covered by a skin graft [3].

Erol [4], in 1976, used vascular pedicle to carry tissue; a skin graft was placed over the superficial temporal vessels and later transferred as a pedicle flap based on these vessels. This work demonstrated the utility of vascular pedicles to transfer tissue locally.

Shens [5] prefabricated flaps using the facial vascular bundle and Hyakusoku et al. prefabricated a hair-bearing skin flap for lip reconstruction.

Reconstructive methods using crane principle has been advanced from random flap transfer to prefabrication but the basic principle remain the same. In our study, the crane principle was used to protect the flexor tendon of the hand and neurovascular structures.

Conclusion

Covering of defect employing crane principle though described in earlier days is still relevant in the management of defect with limited donor site.

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Case Report

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Jodhpur Technique for Chronic Non-Healing Leg Ulcer

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Abstract

Chronic non healing ulcer (NHU), especially over the legs pose a management conundrum to the doctor. Etiology of NHU over the legs is predominated by diabetes, leprosy, venous stasis, arterial insufficiency, decubitus ulcer, vasculitis and certain infections. The ulcer may not heal for a long time despite the diagnosis and treatment of the underlying disease. The problem becomes compounded in idiopathic NHU of the legs. Various approaches, including skin grafting have been used with variable results. We describe for the first time, the use of the Jodhpur Technique, our innovation synonymous with autologous non-cultured non-trypsinised keratinocyte and melanocyte grafting to attempt healing of a chronic NHU over the lower leg of a 52-year old man with treated leprosy. The patient's persistent and treatment-refractory NHU of 3 years duration healed completely within 5-6 weeks of the procedure. No adverse effects were observed. We propose the use of JT as an extremely low cost and simple procedure to induce healing of chronic NHU, especially on the leg.

Keywords: Jodhpur technique Non-healing ulcer Diabetes Leprosy Venous stasis Vasculitis Skin grafting Autologous non-cultured non-trypsinised keratinocyte and melanocyte grafting.

Introduction

Chronic non healing ulcer (NHU) is defined as the loss of skin and soft tissue which takes more than 6 weeks to heal [1]. A chronic NHU is most commonly seen over the legs (NHUL) and may arise from diverse etiologies. Leprosy (even after successful completion of multi-drug therapy or MDT), poorly controlled diabetes, chronic venous stasis, arterial insufficiency arising out of a peripheral vascular disease (PVD), vasculitis, certain infections, and pressure sores (decubitus ulcers) constitute major etiological reasons for a chronic NHU. Although targeting the primary pathology may lead to complete remission, many chronic NHU pose a therapeutic challenge. The ulcer may not heal owing to undiagnosed or untreatable underlying condition as well as despite apparent success in controlling the same. Irrespective of the etiology, the lack of necessary growth factors seems to contribute hugely to persistence and chronicity of substantial number of NHUs [2].

Autologous non-cultured non-trypsinised keratinocyte and melanocyte grafting also known as Jodhpur Technique (JT) is a novel method of epidermal grafting innovated by us. We have demonstrated its successful use in repigmentation of stable vitiligo lesions [3]. Owing to the bounty of various growth factors in the 'donor paste' (*vide infra*), we extrapolated the concept and attempted its use in inducing healing of a chronic NHLU over the leg of a 52-year old Indian man, a treated case of leprosy.

Case Details

A 52-year-old Indian man, known case of treated borderline lepromatous (BL) leprosy presented to us with a 3-year old NHLU over the lateral aspect of his right lower leg around the ankle. The patient was non-diabetic, and had no clinical suggestion of varicose veins or vasculitis, or intermittent claudication. He was a non-smoker, and did not have any concurrent or past history of vasculitis. The patient successfully completed 12 month MB-MDT around 6 month back. Examination revealed a solitary 5cm × 2.5cm painless, non-tender polygonal ulcer with scant serous discharge located over the lateral malleolus of right foot **[Fig. 1(A)].** The ulcer had, slightly indurated sloping edges and pale unhealthy granulation tissue at the base. The surrounding akin was hyperpigmented and scaly.

Clinical examination of the peripheral nervous system revealed bilateral mildly thickened fibrotic ulnar, radial, and lateral popliteal nerves. Moderate glove-and-stocking pattern of hypoesthesia was present. The patient had bilateral partial claw hands and hammet toes but no foot drop.

Routine hematological and biochemical investigations, X-Ray chest, and USG Doppler were normal. Slit skin smear for Acid fast bacilli (AFB) was negative. Pus-swab from the ulcer was negative for bacterial growth. An ulcer edge biopsy revealed a non-specific ulcerated lesion with hyperkeratosis, irregular acanthosis, and dense diffuse and perivascular lymphohistiocytic infiltrate in the dermis. AFB stain was negative. The patient had received daily collagen wound dressings, honey-phenytoin dressings, and platelet rich fibrin treatments in the past 2.5-3 years with modest improvement followed by relapse.

Materials & Methods

In view of the chronic treatment-refractory non-healing trait of his leg ulcer, we took his special consent for attempting ulcer healing with JT, i.e. our innovation of autologous non-cultured non-trypsinised keratinocyte and melanocyte grafting. Principles of ethical human research outlined in the Declaration of Helinski 2013 were adhered to.

Donor (lateral thigh region) and recipient areas were prepared under aseptic precautions. 2% lidocaine (without adrenaline) was used for local anaesthesia followed bymicromotor dermabrasion as detailed below at 4000-5000 rpm.

First, the ulcer margin was dermabraded with pin-point bleeding as the end point. The area of the donor site (lateral thigh region) that was prepared for graft extraction was roughly calculated asmeasuring around 'one-third to one-half of recipient area' of the dimensions of the recipient ulcer. A 2% mupirocin ointment was thoroughly smeared over the donor region, followed by motor dermabrasion of the site till the endpoint of pin-point bleeding. This approach ensured enmeshment of the epidermis and upper dermis onto the ointment applied at the site, expectedly containing a mix of keratinocytes, melanocytes and fibroblasts. The dermabraded 'skin graft' was collected in a spatula and was homogenized by adding carboxymethyl cellulose to enhance the ease of spreading. The homogenized graft was then applied at the recipient ulcer as a paste.

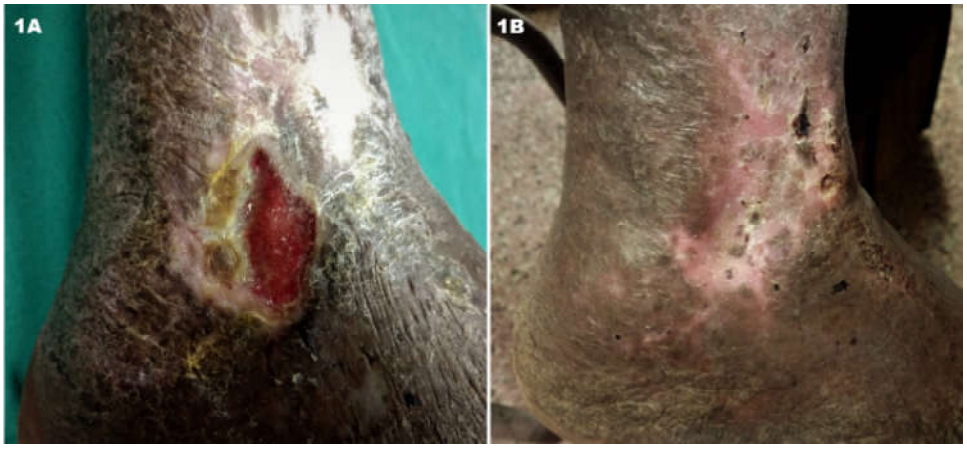

Fig. 1: (A) Chronic non-healing leg ulcer over the lateral malleolus of the right foot of a post-MDT leprosy patient (baseline); **(B)** Almost 100% healing seen at 6th week after a single session of Jodhpur Technique – an innovative autologous non-cultured non-trypsinised keratinocyte and melanocyte grafting technique.

Post procedure dressing (non-absorbable) was done and bandaged with gauge with instructions of strict avoidance of wetting of the dressing till seven days. Post procedure, course of oral augmentin was given for a week. Additionally, oral vitamin C 500 mg BID and Multivitamin capsule containing at least 22.5 mg zinc OD were recommended for 4 weeks. The first follow-up visit was after seven days and then once-a-week. Weekly visits for follow up were done for upto 8 weeks and consisted ofglobal clinical photography as well as arithmetic follow-up of healing in terms of reduction in the ulcer volume as per the formula - ***length× breadth× 0.7854***, which is taken for an ellipsoidal structure [4]. After achieving complete healing, two more follow-up visits were done, after 6 and 12 weeks to monitor for relapse.

Primary outcome criterion was percentage reduction in ulcer volume at 6th week measured by (1) arithmetic formula for ulcer volume, and (2) global photography. Secondary outcome was measured as patient satisfaction on the visual analogue scale (VAS), with 10 suggesting total non-healing and 0 referring to complete healing.

Results

The baseline: The ulcer volume was 9.82 cm^3. Gross photography is shown in **Fig. 1(A).** Patient's VAS was 9.

Follow-up:

On the seventh day follow-up visit, there was no pus or discharge on opening of the dressing. A healthy granulation tissue was seen within the entire ulcer, which was only mildly tender suggesting initiation of good healing. The site was left open, but with the instructions of strict avoidance of any trauma and scratching. Twice-daily application of mupirocin 2% ointment was suggested for next 1-2 weeks.

At the 3rd week (2 weeks after opening the dressing) the ulcer volume reduced to 3.7 ×1.4 × 0.7854 = 4.1 cm^3, i.e. 58.2% reduction was sustained. At the 5th week, ulcer volume was reduced to 0.3 × 0.2 × 0.7854 = 0.047 cm^3, calculated to 99.5% reduction. The healing of the ulcer was 100% complete at the 6th week by formula as well as appreciable on global photography **[Fig. 1(B)].** Excepting mild scarring, no complication such as infection or otherwise was noted. The patient's satisfaction on VAS reduced from 9 (at the baseline) to 6 (at the 3rd week) and 0 at the 5th week itself and persisted thereafter. Mild pruritus was compliant of after the 3rd week, which was managed by gentle application of coconut oil and Tab cetirizine SOS. There was no relapse on the follow-up visits.

Discussion

Healing chronic NHULs has become a major therapeutic challenge. Venous and diabetic foot ulcers account for 70–90% of these ulcers, leprotic foot ulcers due to peripheral neuropathy continue to contribute a substantial proportion off NHUL in developing countries.These ulcers typically afflict geriatric population who often have multiple pathophysiological factors that impede wound healing despite best treatments.

Prompt wound healing is essential to prevent irreversible damage. Moreover, the longer it takes to heal an ulcer, the greater the severity and the financial burden [4].

Although the involvement of growth factors was discovered decades ago with subsequent development of recombinant growth factors, these molecules are expensive, needed in combination, and often not available. PRP, PRFM, and newer adjuvant modalities attempt to provide ingenious growth factors, but suffer from their own coterie of limitations [5,6].

We previously demonstrated that the Jodhpur Technique was an inexpensive, simple and convenient approach to attain repigmentation in vitiligo patches [3]. We attempted repurposing this approach, on a plausible ground for induction of healing of NHUL in this patient and got excellent result with no Adverse effect.

The successful healing of a treatment-refractory NHUL after a single session of Jodhpur Technique has prompted us to use it in other NHULs as well. And pending publication, we have had an almost 100% healing after a single session in most of the ulcers. The postulated mechanism of induction of healing is that the healing tissueat NHU site provides the base on which the grafts clutches. The graft provides a rich extra-cellular matrix (ECM) containing glycosaminoglycansas well as a cellular component of keratinocytes, melanocytes and fibroblasts. Additionally, dermabrasion is conjectured to have promoted the release of cytokines and growth factors like epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), etc from the enmeshed keratinocytes, melanocytes and fibroblasts of the donor graft that accelerate

the proliferation and migration of keratinocyte and melanocytes at the recipient site, enhance neoangenesis and activate other ulcer-healing mechanisms resulting in a completely healed ulcer with scarring. Hence our technique offers ease, pace and negligible complications and engages small donor area to heal large ulcers.

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I don't want to Apply Minoxidil: Hairsplitting this Common Complaint

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Abstract

Minoxidil (MNX), the first drug approved for androgenetic alopecia (AGA) in both genders by the US-FDA is most commonly prescribed as 2% or 5% minoxidil topical solution (MTS) for local scalp application. However, the cosmetic unacceptability and other local adverse effects including allergic contact dermatitis associated with the conventional alcoholic MTS often results in markedly reduced patient compliance. Although a patch test is essential to differentiate between allergic reaction to the solvents, namely ethanol and/or propylene glycol (PG) versus MNX molecule, the most common source of the allergic reactions and flaking of scalp with MTS is the alcoholic solvent vehicle. Alcohol-free MTS formulations have been launched but brands with tall claims need to be scrutinized before prescription. Shifting to the aerosolized foam preparation is one viable option, albeit a little costlier. Low dose oral MNX may be tried in patients recalcitrant to topical MNX or developing intolerable local adverse effects. Nanoxidil 5%, the new congener with a lower molecular weight and expectedly better penetration and tolerance may offer a leap over MNX but needs to be validated in large randomized controlled trials.

Keywords: Minoxidil topical solution; Androgenetic alopecia; Female pattern hair loss; Male pattern hair loss; Hair loss; Allergic contact dermatitis; Alcoholic solution; Propylene glycol; Patch Test; Minoxidil foam; Oral minoxidil; Nanoxidil

Introduction

Topical minoxidil (MNX) was the first drug to receive US-FDA approval for treatment of androgenetic alopecia (AGA) both in men and women [1]. The 2% and 5% topical formulations of the product were first marketed in the United States for hair regrowth in men with AGA in 1986, and 1993 respectively [2]. But it was not until August 1988 and November 1997, that the topical 2% and 5% solution of MNX received FDA-approval for treatment of AGA in men [3,4]. While the 5% 'extra strength for men' solution got approved in November 1997, approval of the same strength solution for women was given in 2006. In the latter year, the foam (aerosol) preparation of 5% MNX also got FDA-approval for men with

the benefit of being less irritating than the solution due to lack of propylene glycol [5]. The 5% foam got FDA-approved for once-a-day use for AGA in women much later in 2014 [6]. Topical MNX has also been in use for diverse off-label indications in trichology including (AA), telogen effluvium (TE), chemotherapy-induced alopecia (CIA), post hair transplant, monilethrix, hereditary alopecia/ hypotrichosis, and even scarring alopecias [7].

The exact mechanism of action of MNX remains to be confirmed, but it has been postulated that its hair growth stimulation effect results from opening ATP-sensitive potassium channels and promoting synthesis of VEGF in dermal papilla cells [8].

Problems with the conventional minoxidil topical solution

Despite the satisfactory results of minoxidil topical solution (MTS) in AGA, the occurrence of scalp irritation, flakiness, worsening of seborrheic dermatitis, and scalp allergic contact dermatitis (ACD) in a substantial number of patients constitutes a huge problem. The cosmetic unacceptability of MTS stemming from the aforementioned local adverse effects often leads to patient non-compliance.

The role of ethanol and propylene glycol in MTS

Conventional MTS consists of propylene glycol (PG)–water–ethanol solution [9]. The rationale of having an ethanol-based solution was that ethanol would reinforce the thermodynamic activity of MNX onto the stratum corneum *in situ* after the solvent evaporates, and also enhance the diffusion of the drug through the layers of the skin to the deepest levels possible [10]. Allergic reactions to topical MNX solution such as scalp dryness, irritation, burning, redness, and ACD may arise from either the vehicle (ethanol, PG) or the molecule, i.e. MNX itself the latter being less common [11].

Differentiating between ACD to solvent vehicle VS minoxidil

Patch test has been used to distinguish between the two [12]. It is important to understand that true ACD to MNX molecule ultimately depends on the cutaneous delivery of the allergen. Thus, the ideal patch testing should include the 'as it is' proprietary minoxidil preparation, minoxidil in propylene glycol, minoxidil 5% in ethanol, PG, and ethanol. In patients with allergy to the solvent (ethanol and/ or PG), many therapeutic approaches may be tried and have been propounded.

Strategies to maintain patient compliance on minoxidil therapy

Shifting the patient from MTS to the aerosolized foam preparation (which is free of PG) has been trial-proven to reduce the local scalp adverse effects and enhance cosmetic acceptability [13].

Alcohol-free preparations of MTS are being manufactured by replacing ethanol and PG with an alternative solvent vehicle such as polysorbate, or glycerol, or multilamellar liposomes prepared from soy phosphatidylcholine and cholesterol, or niosomes containing mixture of alkylpolyglucoside (APG) surfactants, cholesterol, and dicetylphosphate, or alginate-based hydrogel containing MNX/β-Cyclodextrin Inclusion Complex [14-16].

However, it is important to note that although many pharmaceutical companies are marketing 'alcohol-free' MTS, many of them are only ethanol free and contain PG. Chemically PG is 1,2-propanediol, a synthetic organic alcohol with potent humectant property. And as stated above, an ethanol-free but PG containing solution of MNX is neither truly alcohol-free nor free from the possibility of solvent (i.e. PG) induced ACD. Recently a proprietary alcohol and PG-free brand of MNX 5% solution called ANASURE 5% has been launched in India by Sun Pharmaceuticals in which the vehicle used is Volarest™ F**,** an acrylate-based polymer**.**

Sticking to lower and US-FDA approved concentrations of MTS (not exceeding 5%) is helpful in patients who are otherwise comfortable with the 5% preparation. There is no evidence favoring higher efficacy of 10% or 15% MTS over 5% solution. Infact, a higher concentration of MNX requires more amount of ethanol/PG to dissolve it in solution form. This explains the higher incidence of scalp dryness, flaking, dandruff, and overall cosmetic unacceptability of 10-15% MTS.

Moreover, US-FDA issued a drug alert in 2012 [17] advising strictly against the use of these high concentrations of MTS owing to the risk of systemic absorption leading to low blood pressure, palpitations and associated cardiac symptoms.

Oral minoxidil for hair loss – Dose, Efficacy, Safety, and Evidence

A 'recalled' option worth exploring is oral administration of low dose (0.25-2.5 mg/day) MNX tablets for upto 12 months. Recent studies have shown improvement in patients with CTE, FPHL, as well as other hair loss conditions many of which were refractory to long-term MTS application [18-20]. Except for manageable facial hypertrichosis in few patients, authors did not report any other significant adverse effect. Importantly, oral MNX did not lead to clinically significant lowering of blood pressure or any biochemical abnormality. In the author's personal observation of administering 2.5 mg MNX tab/day to 8 patients (5 males, 3 females) with AGA for upto 12 months, no adverse effects were noted, except for 2 patients complaining of dizziness around half an hour after the tablet. Thus, I recommend the tablet preferably be taken at bedtime.

Nanoxidil 5% - The New Kid on-the-block

Another novel option is the use of nanoxidil 5%, a congener of MNX with lower molecular weight; which may provide better penetration and absorption, although no there is lack of robust evidence to support this assumption [21]. In an open labeled study 49 female patients with trichoscopically proven early FPHL who complained of increased hair shedding were treated with a novel proprietary nanosomal delivery system called Spectral. DNC-N® (DS Laboratories, Inc.) containing combination of 5% nanoxidil with numerous hair growth promoters and anti-inflammatory molecules, including pyrrolidinyl diaminopyrimidine oxide, azelaic acid, lysophosphatidic acid, copper tripeptide-1, myristoyl pentapeptide-17, adenosine, piroctone olamine, retinol, and caffeine [22]. There was a statistically significant decrease in hair shedding and a corresponding increase in hair mass index at 3 months. By the end of 6 months, the hair shedding score was reduced further and the hair mass index was maintained [22]. The treatment was very well tolerated.

Conclusion

In absence of a definitive and consistently efficacious medical option for hair restoration in AGA, the huge experience with the possible adverse effects of MNX – MNX shall continue to remain on the frontiers of trichotherapy. Dermatologists need to assess their patient's requirement, psychology and prefer to give them alcohol-free preparations instead of the convention MTS based protocol. The only problem with the former (aerosolized foam, alcohol-free MTS) is the modestly higher cost of these formulations. Low-dose oral MNX is worth trying, but under utmost care. The new congener nanoxidil 5% may be a true advancement over MNX, but needs validation with many more planned randomized controlled trials with large cohort size.

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What's Your Dermoscopic Diagnosis?

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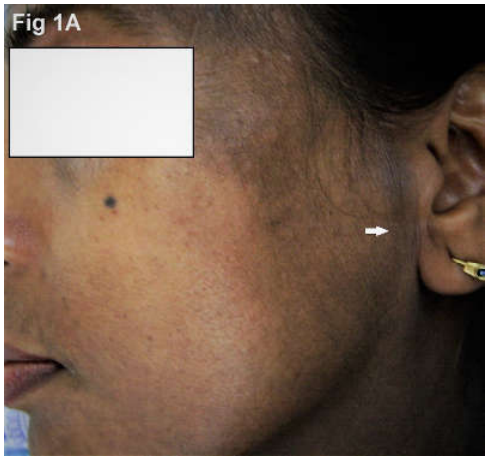
Case Details

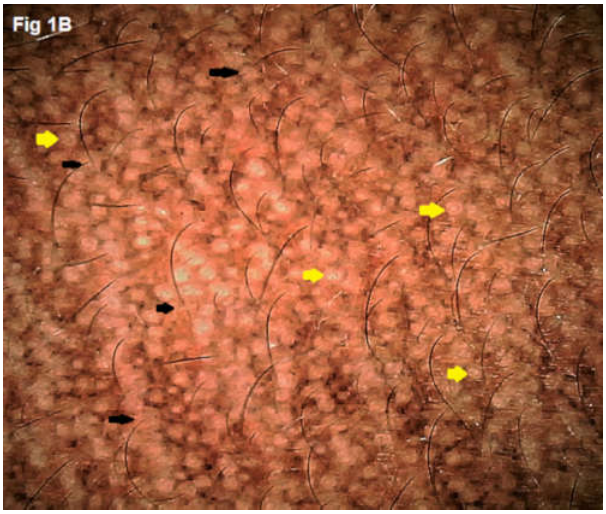
Clinical - Observe the clinical image of a 40-year old Indian lady who developed gradually progressive asymptomatic dark brown to greyish-blue pigmentation with ill-defined margins involving her forehead, lateral aspect of cheeks, preauricular region extending down till middle neck over the past 3 years. [Fig. 1A]. As a home maker, her sun-exposure was minimal and she denied being very fond of or frequent user of cosmetics and fragrances. She gave history of having used Indian gooseberry (*amla*) oil over her scalp for many years; and had started using an ammonia-free propriety hair color around 4-5 years back. Being unmarried, she did not use vermillion powder in the scalp parting line. There were no other lesions elsewhere, and examination of mucosae, scalp and hair, and nails was unremarkable. No treatment had been sought or taken till now. A patch and photopatch test with the Indian Standard series and cosmetic series revealed 2^+ and 3^+ positive allergic reactions to paraphenylenediamine (PPD) and fragrance mix respectively.

Dermoscopy – Dermoscopic image taken from the pre-auricular area (marked with white solid arrow in **Fig. 1A**] using E-scope [USB videodermoscope, Timpac Healthcare Pvt. Ltd., New Delhi, India] in polarized mode at 30× magnification is shown in **Figure 1B.**



What is the Most Likely Diagnosis?

(A) Lichen Planus Pigmentosus (LPP)
(B) Pigmented Contact Dermatitis (Riehl's Melanosis)
(C) Pigmentary Demarcation Line (PDL)-F
(D) Nevus of Ota



Answer

(B) Pigmented Contact Dermatitis (Riehl's Melanosis)

Comment

Facial melanoses are of diverse etiologies but often have overlapping clinical presentation. Biopsy for histopathological diagnosis is often refused by the patient, especially women owing to the risk and fear of scarring. That's why dermoscopy offers a distinct advantage in non-invasive diagnosis of facial melanoses [1].

The clinical image shows coalescing areas of brown-to-greyish blue hyperpigmentation involving the face and neck, more along the margins suggestive of Riehl's melanosis (RM) as well as LPP as the most likely clinical possibilities. Dermoscopy aided in a relatively more convincing diagnosis of RM. Dermoscopy **(Fig. 1B)** showed an exaggerated pseudo reticular pigmentary network, diffuse brown to faint erythematous background, brown-to-grey colored dots, granules, and globules scattered both discreetly and at places accentuated around the eccrine openings, perifollicular whitish halo (*black arrows*), follicular plugs within the hair follicles (*yellow arrows*), and few telangiectatic vessels. These features have been reported to be highly suggestive of RM [2]. Dermoscopic findings of RM and PCD display substantial overlap. However, a more brownish hue of the background, high degree of accentuation of pigmented dots and globules around the openings of the hair follicles and eccrine glands often arranged in a hem-like, arcuate or reticular pattern, and reduction in the lesional hairs are more typical of LPP. Patch test positivity was earlier considered to be pathognomonic for RM. However, it has been conclusively reported that patch test positivity, e.g. to PPD present in hair color and fragrance mix may also be seen in LPP. PDL-F does not show any specific dermoscopic features, excepting perifollicular and peri-eccrine blotchy brownish areas [3]. Lastly, dermoscopic features of Nevus of Ota and other dermal dendritic melanocytic proliferations remain poorly defined. The description is based along thelines of the blue nevi; characterized by a homogeneous bluish to steel-blue pigmentation [4].

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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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Primary Contact Dermatitis to Nickel: A Classical Presentation

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Through the medical image

A 20-year-old atopic female presented with multiple, itchy, grouped minimally erythematous papules and hyperpigmented macules over midline and both sides of chest, and just below the umbilicus for 2 years. A history of wearing artificial pendent, brassiere with metal clips and jeans was elicited. Patch test with Indian standard series was positive (2+) for nickel. Thus, a diagnosis of allergic contact dermatitis to nickel was made. Patient was advised to avoid contact with nickel containing substances. The lesions responded to topical mometasone cream within 2 weeks leaving behind post inflammatory hyperpigmentation without any relapse in the 2 month follow up.

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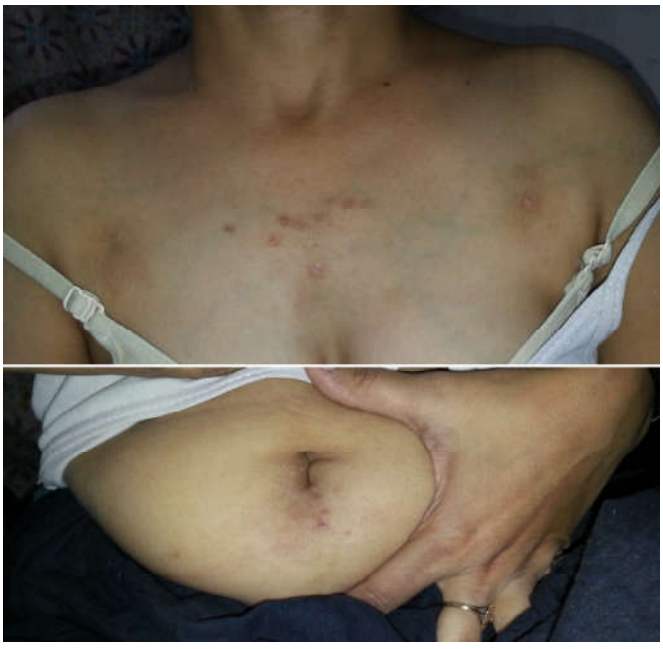

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