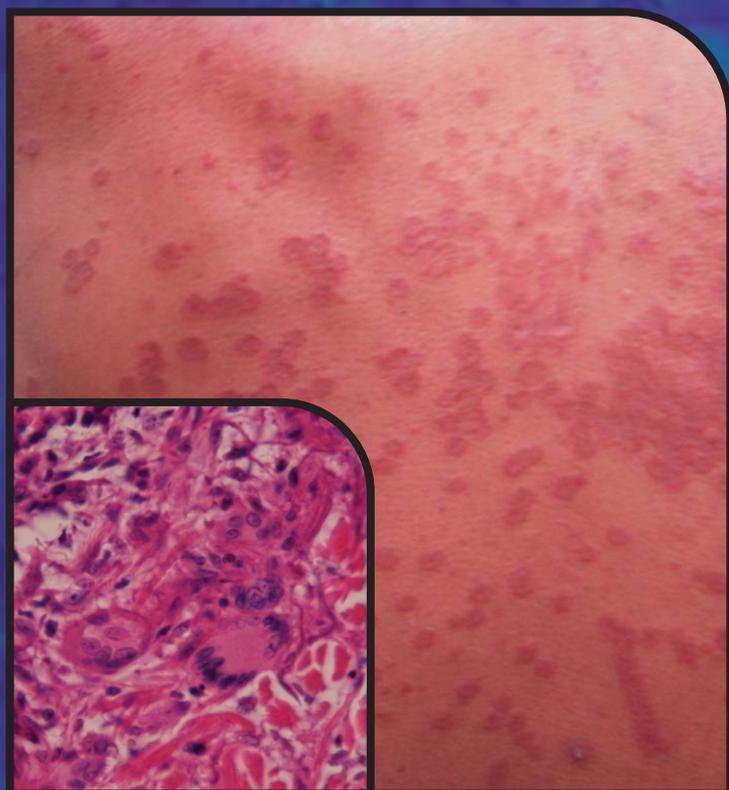


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Sunil Dogra, Savita Yadav

Nails have a functional as well as aesthetic importance. Though it is a small structural and anatomical unit, it is affected by a variety of disorders. Major advances have occurred in skin and hair disorders at a fast pace over the last two decades. Nail has received little attention compared with other dermatological disorders. Nail disorders are rarely medically serious, but provide insight into various systemic disorders. Nail diseases can lead to impairment of hand function, difficulty in walking, and cosmetic disfigurement. This article provides an update on the status of nail disorders. We have reviewed the new nail disorders described recently and advances made in the diagnosis and therapy of nail disorders over the last few years.

NEW ENTITIES DESCRIBED

In this section, we present the recently described new nail disorders and reports of uncommon involvement of nail unit by common cutaneous dermatoses. We should be aware of these rare occurrences so that the diagnosis is not missed.

New disorders

Lateral ingrowth of nail plate or onychocryptosis

Department of Dermatology, Venereology and Leprology,
Postgraduate Institute of Medical Education and Research,
Chandigarh, India

Address for correspondence:

Dr. Sunil Dogra, Department of Dermatology, Venereology and
Leprology, Postgraduate Institute of Medical Education and
Research, Chandigarh-160 012, India.
E-mail: sundogra@hotmail.com

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is a well-known and studied nail disease process. *Retronychia* is a new entity occurring as a rare complication of onychomadesis. *Retronychia* stands for the proximal ingrowth of the nail plate into the nail matrix. Berker. *et al*^[1] for the first time reported 19 patients of retronychia and the details of all the cases were presented and discussed at European Nail Society meeting (2007). The mean age of the patients was 39 years, with female preponderance (16/19). All the patients presented with complaints of proximal nail fold paronychia. The cardinal sign seen on examination was the elevation of the proximal nail plate beneath the proximal nail fold such that it was higher than the distal nail plate. In most of the patients, the nail showed yellowish discoloration due to the nail plate thickening. Granulation tissue was seen in the proximal nail fold in one-third of the cases and was most marked at the junction of the lateral and proximal nail folds. Big toe was affected in 16 of 19 subjects, whereas in three cases, hand was affected (thumb alone in two cases, thumb and index finger in one case). Around half of the patients reported an episode of trauma as the precipitating event.

Authors proposed that *retronychia* results due to the malalignment of the nail plate following its detachment from the matrix. The detached nail plate is pushed upward into the matrix and the new nail plate grows beneath it, further pushing the old nail plate upward. Subsequently, two to four new nail plates may get sandwiched beneath the old nail plate in the proximal nail fold. This malalignment most commonly occurs as a result of repeated distal trauma from the footwear which pushes the nail plate proximally and upward. Definitive treatment is the total nail plate avulsion which leads to subsidence of nail fold inflammation. The new nail plate growth is often normal and the recurrences are not seen as in lateral ingrowth of nail plate. Wortsman *et al*.^[2] reported a case of triple finger *retronychia* resulting from trauma and the diagnosis was established using 3D ultrasonography (USG).

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Worn down nail syndrome, also known as bidet nails, was first reported by Baran and Moulin.^[3] They reported three unrelated women who had nail disorder characterized by a triangular defect of the fingernails with its base at the free edge of the nail. All these females had obsession for genital hygiene and nail changes were the result of excessive rubbing of nails against the porcelain of bidet while cleaning their genital area. Piraccini *et al.*^[4] reported this nail disorder in 14 of their patients and Patrizi *et al.*^[5] described it as a tic disorder in an 8-year-old girl child. The child had habit of scratching the school desk with his nails and finger tips. In this disorder, there is triangular thinning and erythema of the distal nail plate. On dermoscopy, dilated capillaries and pinpoint hemorrhage can be seen. Nails improve once the behavior is changed.

Lacquer nail described by Rigopoulos *et al.*^[6] has significant overlap with worn down nail syndrome. Lacquer nail are the result of excessive rubbing of nail plate with nail filers provided with the topical antifungal nail lacquers.

Hair growth at ectopic sites like glans penis^[7] and oral cavity^[8] has been reported before. *Onycotrychia* has been recently described by Ferreira *et al.*^[9] as a growth of hair follicle longitudinally underneath the nail plate. Their patient presented with single longitudinal brownish ridge of the right thumb nail plate evolving for last three months. The ridge started under the cuticle and in the distal third, it formed a hyperpigmented band. Nail biopsy revealed the presence of hair structure in the nail bed in contact with the nail plate. Immunocytochemistry with keratin 9 better defined the nail structure. Cerman^[10] have reported *onycotrychia* in 16-month-old child as an isolated abnormality. Child presented with longitudinal black streak underneath the nail plate of second right toe. The nail plate was not affected unlike the case reported by Ferreira *et al.* Authors could not provide a satisfactory explanation for the occurrence of this anomaly.

Nail degloving was recently described by Baran and Perrin having three main clinical presentations and multiple etiologies.^[11] First is the typical thimble-shaped nail shedding in which the walls of the thimble are composed of the skin of the distal digit including the nail plate (circumferential skin shedding). Second, a partially sloughed-off nail plate with its surrounding tissue composes nail degloving. In third presentation,

shedding is restricted to the entire nail apparatus and its components (matrix, nail bed, hyponychium, and ventral aspect of the proximal nail fold) while the surrounding epidermis of the distal digit is spared. Various causes of nail degloving syndrome include trauma, toxic epidermal necrolysis, and digital gangrene. Lichen planus can rarely present with nail degloving type of involvement.^[11]

Common disorders—uncommon site

Seborrheic keratosis (SKs) is a common benign epithelial cell tumor which commonly occurs in head and neck area and upper trunk. Bon-Mardion *et al.*^[12] for the first time have reported SKs involving the nail bed. Their case was a 58-year-old man who had 1-year history of nail involvement in the form of longitudinal leukoxanthychnia. Dermoscopic examination showed longitudinal leukoxanthychnia with filiform hemorrhages and milia-like cysts. Histopathological examination revealed typical findings of SKs. So, SKs should be included in the differentials of leukoxanthychnia which includes squamous-cell carcinoma, subungual warts-induced lesion, onychomatricoma, and onychopapilloma.

Fixed drug eruption (FDE) is a common pattern of cutaneous drug reaction reported with a variety of drugs. Drug reaction occurs within 30 minutes to 8 hours of drug administration. The sites most commonly involved are mucosa and the limbs. Benton and McGibbon^[13] have reported a case of FDE with amoxicillin-clavulanic acid in a 75-year-old man who presented with painful periungual and subungual erythema. On examination, circumscribed macules of erythema involving the paronychia fold and the nail bed were seen.

Pyogenic granuloma commonly involves the nail folds presenting as a bleeding exophytic growth. Rarely, it can present in the nail bed and then it has to be differentiated from amelanotic subungual melanoma.^[14] There is a single report of subungual pyoderma gangrenosum.^[15]

NEW DIAGNOSTIC IN NAIL

Diagnosis of nail disorders is based mainly on clinical examination, but some nail disorders need a further workup to establish the diagnosis and/or plan the treatment. Nail scraping is most commonly performed laboratory test in the clinical setting. Nail biopsies

are occasionally done for the diagnosis of nail bed and matrix disorders but they are time consuming, unpleasant to the patient, and result in scarring and disfigurement of the nail. Nail apparatus has been deprived of investigative medical imaging until recently when there has been a growing interest in noninvasive techniques which could supplement the clinical examination of the nails. This includes USG, magnetic resonance imaging (MRI), optical coherence tomography (OCT), confocal laser scanning microscopy (CLSM), and improvised dermoscopy instruments.

Since onychomycosis (OM) is the most common nail disorder accounting for around 50% of total nail disease patients,^[16] we have dealt with new advances in its diagnosis separately.

ADVANCES IN MEDICAL IMAGING OF NAIL

Ultrasound

Nail unit is well suited for USG study as it consists of well-defined tissues of different densities.^[17] USG of nail requires a high-resolution ultrasound machines and high-frequency ultrasound probe. This modality is available since long time, but is finding place in the diagnosis of nail disorders only recently probably because of greater availability of machines with high resolution. USG is a good tool to diagnose cystic tumors of nail unit including myxoid cyst, synovial cyst, and collections like subungual hematoma or abscess. USG is not a good tool for the diagnosis of solid tumors like melanoma and squamous-cell carcinoma as they appear as nonspecific hypoechoic areas.^[17]

Wortsman *et al.*^[18] presented the ultrasonographic findings in retronychia nails in which the distance between the nail plate origin and distal interphalangeal (DIP) joint is reduced, proximal nail fold is thickened and hypoechoic, and sometimes multiple nail plates embedded into the proximal nail fold can be visualized.

Blood flow in the nail unit can be studied with color Doppler and power angio. These techniques are useful in the diagnosis of vascular tumors like glomus tumor. Imaging of vascular lesions can be further enhanced by means of using contrast media.

Newer technique called real-time compound spatial imaging is evolving.^[19] It provides instantaneous integration of several overlapping ultrasound scans

taken at different angles to produce a compound image with better information content.

Magnetic resonance imaging

High-resolution MRI provides an accurate analysis of the nail apparatus with detection of even 1 mm lesions. Use of MRI for nail disorders started in 1990s with the availability of small surface coils, mainly devoted to the diagnosis of glomus tumor.^[20,21] Nail unit tumors have atypical presentations as the lesion in nail matrix present with secondary nail plate changes and nail bed tumors are obscured by the nail plate. MRI has been used mainly for the diagnosis of nail unit tumors, glomus tumor being the commonest indication. Indications for MRI in relation to nail pathologies are still evolving.^[22] Other indications include myxoid cyst, implantation epidermoid cyst, ganglion cyst onychomatricoma, exostosis, and osteochondromas.

Optical coherence tomography

OCT works in analogy to USG; the infrared light reflected from the skin is measured and the intensity is imaged as a function of position. The OCT probe is applied directly to the nail, scanning lasts for few seconds, and does not cause discomfort to the subject studied. This technique provides images of tissue pathology *in situ* with a high axial resolution.^[23]

Mogensen *et al.*^[24] found OCT technique to have low coefficients of variation compared with 20 Hz USG in measurements of nail plate thickness. Ayden *et al.*^[25] recently reported OCT to provide higher resolution changes compared with nail USG in nail psoriasis. Abuzahra *et al.*^[26] detected fungal elements noninvasively *in vivo* using OCT in 10 patients with histologically proven OM. Fungal elements were detectable as highly scattering elongated structures inside the nail plate, in the middle of the areas of homogeneous decrease in signal intensity.

Confocal laser scanning microscopy

CLSM is a new noninvasive diagnostic tool which is becoming increasingly popular. It can visualize cell structures of the skin up to a depth of 300 μm *in vivo*. It is based on the principal of increasing optical resolution and contrast of a micrograph by using point illumination and a spatial pinhole to eliminate out-of-focus light in specimens that are thicker than the focal plane. It also enables the reconstruction of three-dimensional structures from the obtained images. Researchers have found it to be faster and

more accurate than the conventional microscope used in potassium hydroxide (KOH) preparations in the diagnosis of OM.^[27,28]

Dermatoscopy

Dermatoscopy is also known as dermoscopy and epiluminescence microscopy. It is the examination of skin using dermatoscope and is mainly used for distinguishing pigmented benign and malignant lesions. In nail unit, it is mainly used for patients presenting with melanonychia. Park *et al.*^[29] have introduced a handy portable hand-held digital dermoscope (USB Microscope M2, Scalar Corporation, Tokyo, Japan) which can be used to study the nail fold capillary changes while sitting in a high-volume outpatient setting. It has the advantages of obtaining microscopic images on a computer monitor in real time; this makes the system more practical than other conventional dermoscopy systems using a camera that requires the development process. In addition, it has a polarizing light mode that minimizes the light reflection from the stratum corneum caused by the difference in the reflective index between the air and the stratum corneum. Thus, it does not require mineral oil or other immersion agents to reduce the light reflection.

ADVANCES IN DIAGNOSIS OF ONYCHOMYCOSIS

OM is a common problem, accounting for up to half of all diseases of the nail, with an estimated prevalence of 10% of the general population and approaching 60% in the elderly.^[30,31] Hay and Baran^[32] have revised its classification because of the recognition of new pathways of nail infection, new pathogens and variations in the appearance of diseased infected nail.

KOH preparation and culture together have been considered as the gold standard test for OM diagnosis.^[33] Nail sampling is done by means of curettage. In a study by Semer *et al.*,^[34] they compared sampling by means of nail drilling vis-a-vis curettage. They found that culture sensitivity was significantly higher when sampling was done by means of drilling technique as compared with conventional curettage technique. Direct microscopic examination using KOH preparation has low sensitivity. Fungal culture technique has high false-negative rate, requires long incubation period, risk of obscuration by bacterial overgrowth, and contamination with foreign material.

Periodic acid-Schiff (PAS) staining is a good diagnostic

tool for the diagnosis of OM but probably less utilized by the dermatologist. Recently, it has been considered as the gold standard for the diagnosis of OM by some authors and is beginning to supplant KOH and culture in the diagnosis of OM.^[35,36] Wilsmann *et al.*^[37] found histopathological staining to have highest sensitivity (82%), followed by culture (53%) and KOH preparation (48%). The results with PAS staining are faster compared with culture. It should be the preferred diagnostic tool, especially in cases where the diagnosis of OM is not certain and in those already on antifungal treatment.

Diagnosis of OM caused by non-dermatophyte molds is challenging, requiring more stringent criteria than that of dermatophytes. Based on the available data in literature, Gupta *et al.*^[38] concluded that at the moment, traditional mycology remains the gold standard for diagnosing non-dermatophyte mold OM. This includes obtaining positive results from KOH and culture. Repeated isolations (2 or 3) in the absence of a dermatophyte increase the probability of accurate identification of the causative non-dermatophyte mold. Still, there is controversy over the number of inocula required to confirm the causative diagnosis. Histopathology can be of assistance in establishing the penetration of the non-dermatophyte mold into the nail plate; however, this method does not provide identification of the organism.

Development of newer techniques like polymerase chain reaction (PCR),^[39] OCT,^[26] flow cytometry,^[40,41] and immunohistochemistry^[42] for the diagnosis of OM is underway. The routine use is impractical at present because of some limitations. Litz and Cavagnolo^[39] have devised a quick inexpensive PCR test to detect dermatophyte DNA in nail specimens. They compared their PCR with KOH, fungal culture, and PAS staining. A total of 559 nail specimens were tested and PAS, PCR, KOH, and culture were positive in 54%, 37%, 40%, and 22% of specimens, respectively. PCR was negative in all non-dermatophyte and yeast isolates. PCR is specific, requires no morphologic expertise, has relatively good sensitivity, and gives faster results. This molecular approach is developing and with wider availability, it may prove to be a useful tool in future.

OTHER ADVANCES IN NAIL DISORDER DIAGNOSIS

Nail biopsy is sometimes done to diagnose those conditions which are not clear on clinical examination

or history alone. As nail is a highly vascular structure, bleeding from biopsy site is difficult to manage. Hwa *et al.*^[43] reported easy control of post-biopsy bleeding using gelatin sponge saturated with aluminium chloride.

While doing nail procedures, digital block using plain lidocaine is the most common mode of administering anesthesia. Many authors have reported safe use of lidocaine-epinephrine mixture for digital block in good number of patients.^[44-46] They did not observe digital necrosis in any of their patients, rather there were added advantages of combining with epinephrine. Epinephrine facilitates faster onset of anesthesia, prolonged post-procedure pain relief, and lesser amount of local anesthetic required without much need of tourniquet placement to control bleeding. So, lidocaine with epinephrine can be used for giving digital block, but caution should be exercised in patients with peripheral vascular diseases.

NEW THERAPEUTICS IN NAIL

In this section, new advances are discussed in the management of OM, inflammatory disorders of nail, surgical treatment of nail disorders, and various other new approaches in the treatment of nail disorders.

New in onychomycosis treatment

OM is a common disorder caused by dermatophytes, non-dermatophyte molds, and yeasts. It is managed with topical and systemic antifungal therapy. At present, oral terbinafine is considered the treatment of choice for OM caused by dermatophytes.^[47,48] Ciclopirox and amorolfine are the two topical compounds used for mild to moderate OM or as an adjunct to systemic therapy. With standard therapies, response rate is less than 50%.^[49] There is a continuing search for a convenient, cost-effective agent with high and long-lasting cure rates. Currently, many new therapies for OM are under investigation which includes new azoles, improvement of existing topical treatments through addition of unguinal penetration enhancers and new topical drugs with better nail permeation. Several means to enhance unguinal penetration are under investigation.^[50] This includes the following:

- I. Physical enhancers - transungual laser therapy, electrokinetic transungual system iontophoretic application of terbinafine gel;
- II. Chemical enhancers - NM100060, econazole 5%/SEPA18% nail lacquer, nanoemulsion (NB-002), IDP-108, Ciclopoli™ 8% nail polish, AN-2690.

New triazole drugs (second generation triazoles) under trial for the treatment of OM include pramiconazole, posaconazole, ravuconazole, and albaconazole.^[50] Voriconazole has high antifungal activity against dermatophytes as well as non-dermatophytes but its use is mainly directed to invasive fungal infections in immunocompromised individuals. Echinocandins and sordarins are two new groups of antifungals which are effective against azole-resistant fungi, but they are also under development for mainly invasive fungal infections.

Besides the topical and systemic medical therapy, investigators are devising new means of treatment of OM

1. Photodynamic therapy (PDT) - Cases resistant to standard antifungal therapy and those who cannot take oral antifungals have been treated with photodynamic therapy.^[51-53] Watanabe *et al.*^[51] treated two with 20% solution of aminolevulinic acid (ALA) as photo sensitizer and irradiated with pulsed laser light at a wavelength of 630 nm at 100 J/cm² using an excimer-dye laser. Both the patient had complete clearance after 6 and 7 weekly sittings. Similar results have been reported by other authors.^[52,53]
2. Dual wavelength device – uses optical energy for the treatment of OM.^[54]
3. Ultraviolet C (UVC) irradiation an *in vitro* study indicate that germicidal UVC irradiation may be a less invasive treatment option for onychomycosis, when the appropriate consideration is given to safety.^[55]

These devices provide a non-drug approach and are undergoing testing for the treatment of OM.

With the currently available treatment options, recurrences are common occurring in 10 to 53% of cases.^[56,57] Sigurgeirsson *et al.*^[58] studied the utility of topical amorolfine nail lacquer (ANL) for prevention of recurrence. The patients who were cured of confirmed OM were divided into two groups. One group applied ANL 2 weekly and the other group did not receive any treatment. Recurrence occurred more quickly in the untreated group and at end point, 70.8% remained cured in treated group, while 50% in the untreated group. Author concluded that ANL can serve as a good prophylactic tool to prevent recurrence of OM. However, in another long-term follow-up study, recurrence rate was not found to be related to

presence of predisposing factors, use of nail lacquer as a prophylactic treatment, and the dermatophyte strain isolated.^[59]

Non-dermatophyte OM is less common, incidence ranging from 1.45% to 17.6%.^[60] Epidemiologically, the top five organisms in terms of published confirmed isolations worldwide are (in descending order) *Scopulariopsis brevicaulis*, *Fusarium* species, *Aspergillus* species, *Scytalidium dimidiatum*, and *Acremonium* species.^[38] Non-dermatophyte show a poor response to topical as well as systemic antifungal therapy. Gupta *et al.*^[38] reviewed various studies on treatment of non-dermatophytes. Oral terbinafine and itraconazole have greatest amount of efficacy data. Both have shown efficacy in treating *S. brevicaulis* and *Aspergillus* species infections. A smaller amount of data supports the use of oral fluconazole and ketoconazole for treating *S. brevicaulis*. Griseofulvin should not be used for treating non-dermatophyte (NDM) OM. Topical ciclopirox may be effective in treating *S. brevicaulis* and *Acremonium* species infections. Systemic and/or topical therapy combined with periodic chemical or surgical nail debridement/avulsion may be the best option in the management of non-dermatophyte mold OM.

New in inflammatory disorders of nail

Treatment of nail psoriasis has received little attention compared with cutaneous psoriasis despite the significant burden it places on patients as a result of functional impairment of manual dexterity, pain, and psychological stress. Also, the treatment response of nail psoriasis is slow and incomplete. Sanchez-Regana *et al.*^[61] retrospectively reviewed the data of 84 psoriasis patients who had received classical systemic therapy (acitretin, methotrexate, cyclosporin, photo (chemo) therapy) or biologics (infliximab, efalizumab, etanercept, adalimumab) for moderate to severe skin disease or psoriatic arthritis and had concomitant significant nail involvement. The author found that the NAPSI score fell significantly with all classical treatments (except NBUVB) as well as with the biological treatments. Among all the classical treatments, cyclosporine produced the highest improvement. In the biological treatment group, infliximab and adalimumab lead to significantly greater improvement at 12 and 24 weeks. The author did not find relation between response to treatment and type of nail involvement (matrix, bed, mixed). Also, the percentage of improvement in the

NAPSI score was significantly greater with biological treatments compared with classical treatment.

Many new topical formulations and combinations have been tried for the treatment of nail psoriasis.^[62,63] Pulsed dye Laser (PDL) has been used to treat psoriatic plaques, and recently, PDL has been shown to improve nail psoriasis as well.^[64]

Chronic paronychia is a common problem among the females which is multifactorial in origin. Initially, it was attributed to fungal infection primarily, but now the role of irritants and allergens in its development and propagation has been realized. Rigopoulos *et al.*^[65] compared the response of chronic paronychia in 45 patients treated with tacrolimus or betamethasone-17-valerate or emollients. Treatment was given for three weeks and patients were followed up for further 6 weeks. Both betamethasone and tacrolimus groups achieved statistically significantly greater improvement when compared with the emollient group. This study stresses the importance of treatment with anti-inflammatory agents in addition to antifungal therapy in chronic paronychia patients.

New in surgical management of nail disorders

Ingrown toe nail, also known as onychocryptosis, is a common nail disorder. It is managed with either conservative approach or by surgical treatment, depending upon the clinical presentation and severity. Conservative approaches include antibiotics, silver nitrate cautery, proper nail trimming techniques, and flexible tube splinting (sleeve method). New non-surgical techniques using VHO-osthold nail brace,^[66] resin splint,^[67] super-elastic wire^[68] have been described. All these techniques are based on same principle that is to keep the lateral nail plate pulled by making use of some equipment, so that it does not impinge into the lateral nail fold. Advantages of these techniques are that they are easy and faster to perform, good for elderly and diabetic individuals in whom surgery may otherwise be contraindicated, and lastly the nail anatomy remains unaltered. Disadvantages are that basic pathology is not corrected and recurrences can occur on removing the equipment, patient has to take care of device, and his activities may be limited because of it.

Ozdil *et al.* have described a new non-surgical procedure called angle correction technique in eight patients with ingrown toe nail.^[69] The major

principal of the technique is to correct the dome shape (convexity) of the nail by reducing its thickness 50 to 75%.

Different techniques of surgery for ingrown toe nail include Winograd method, whole nail plate avulsion, Emmert procedure, ablation of the nail matrix using phenol or sodium hydroxide or Lasers, and Zadik's procedure. Payvandi *et al.*^[70] compared Winograd and sleeve methods for the treatment of ingrown toe nails in 100 patients. They found that the participants treated with sleeve method experienced shorter surgery duration, less work day loss, and the recurrence rate were similar in two groups.

Pincer nail kind of deformity has been treated by nail plate avulsion followed by complete destruction of nail matrix by either chemical cautery or surgical matricectomy or laser. Ghaffarpour *et al.*^[71] has described a new nail-saving surgical technique for correction of pincer nail deformity. The technique is a combination of nail bed cutting and splinting. First nail plate is removed, fibrous nail bed excised, and then widened. Remaining nail bed is sutured to the margins and then splint is applied, which ensure that the new nail growth is not deformed.

Glomus tumor has to be surgically excised. Roan *et al.*^[72] have reported a new surgical approach for removing glomus tumor with nil recurrences and good cosmetic results. Author recommends cutting into the nail plate and nail bed over the tumor together without separating the nail plate from the nail bed. The tumor pops out when the nail plate and nail bed are split and then nail plate is sutured without the need of nail bed repair. This is easy to perform, gives good cosmetic results, and there were no recurrence in 17 reported patients.

OTHER ADVANCES

Pachyonychia congenita (PC) is a rare autosomal-dominant keratin disorder caused by dominant negative mutations in keratin genes KRT6A/B, KRT16, or KRT17. It is characterized by painful plantar keratoderma and hypertrophic nail dystrophy. It is notoriously difficult to manage and systemic retinoids have been the main stay of therapy. But because of the rarity of the disorder, the optimum use of retinoids is not described. Gruber *et al.*^[73] surveyed 30 patients of PC who had received oral retinoids (acitretin/isotretinoin 10-50 mg/day for

1-240 months). Nail changes ameliorated in 14% while 79% did not experience any nail change. In 50% cases, there was thinning of plantar hyperkeratosis and 33% had decreased plantar pain. Most of the patients (83%) discontinued retinoids because of the adverse effects. Risk benefit analysis favored low dose (≤ 25 mg/d) for longer period (> 5 months) compared with higher dose (> 25 mg/day) given for shorter period (≤ 5 months). The data indicate that acitretin may have a slight edge over isotretinoin in treating PC.

Sirolimus (rapamycin) is an mTOR inhibitor and mainly used presently in organ transplant recipient patients. Hickerson *et al.*^[74] have treated keratinocyte cell line with mTOR inhibitors and this lead to decreased expression of K6a. Three PC patients given oral rapamycin had subjective improvement and change in callus character. Further research including topical formulations is warranted in this regard.

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