AMOROLFIN NAIL LACQUER 50 mg/C.C. (5%) IN TREATMENT OF ONYCHOMYCOSIS REPORT OF A CASE

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Introduction :

Nails are affected in genetic disorders, systemic diseases, tumours, trauma, diseases that affect the nail structure and skin diseases. Fungal infection is the commonest disease to affect the nails. The commonest parts affected are proximal nail fold, the hyponychium and the nail plate either singly or in combinations. There are four types of fungal nail infections, distal subungual, white superficial, proximal subungual and candida onychomycosis. Onychomycosis comprises up to 50% of nail disorders[1]. The incidence of onychomycosis has been steadily increasing[2].

Onychomycosis has many consequences which include limitation of mobility ; exacerbate diabetic foot, may precepitate recurrent thrombophlebitis and cellulitis; act as a reservoir fungus and may trigger bacterial infection, pain and dermatophytic reaction[3].

The nails pathogens isolated were (4, 5)

1. Dermatophytes in 74% of cases mainly Trichophyton rubrum, T.mentographyte and epidemophyton floccosum.
2. Yeast's were isolated in 23% of cases - mainly candida albicans (70-90%) and other species are less commonly found such as
   - C. parapsilosis
   - C. tropicalis
   - C. Pseudotropicalis
3. Moulds account for 3% of cases. The big toe nail is more affected than other fingers or toes. The infection is mainly seen in men over 50 years of age and the causative pathogens are scopulariopsis brevicaulis, hendersonula toruloidea, acremonium, alternaria and aspergillus.

The diagnosis of onychomycosis is based on :

I The clinical pattern which is characterized by -

1) Asymmetric involvement of the nails, usually some nails are spared
2) The infection may involve any part of the nail -
   a) distal and lateral part of the nail. The fungus spreads from the hyponychium to the lateral and distal edges.
   b) may affect the superficial surface of the nail producing, white patches. This type is mostly caused by dermatophytes.
   c) Spread of chronic infection of the proximal nail fold to involve the nail plate.
   d) Total nail plate damage as seen in saprophyte infection or in chronic mucocutaneous candidiasis.
3) The nail plate becomes thickened, friable, deformed discoloured with collection of keratinous debris beneath the nail plate leading to onycholysis.

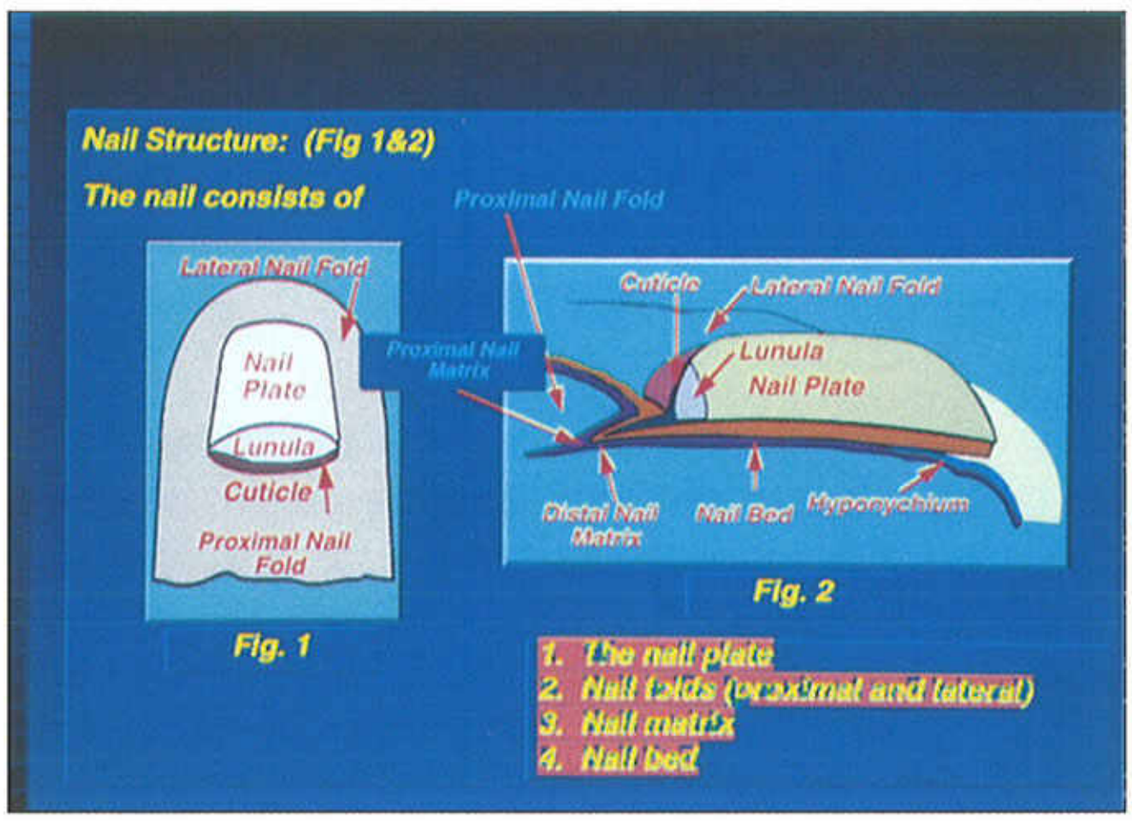
II Identification of the causative fungus by :-

1) Direct microscopy when the nail clippings are examined after being soaked in potassium hydroxide (KoH). The direct microscopy may help identifying the fungus. Dermatophyte infection will show long filaments with arthrospores,candidal infection will show both budding hyphae and yeast cells and mould will show broad sinious hyphae.
2) Culture using :
   a) Media containing cycloheximide for eg. DTM (Dermatophyte Test Medium) which contains cycloheximide, gentamycin, chlortetracycline and a phenol red indicator which changes colour from yellow to red in presence of dermatophytes.
   b) Media containing no cycloheximide to allow the growth of moulds. Selection of proper culture medium is especially important in culturing nails. DTM prevents bacterial growth and saprophytic fungi. It is of value in screening. Sabouraud glucose agar is the standard media to define colony characteristics. Mycosel agar is more selective, it contains chloramphenicol and cycloheximide. Potato-dextrose agar, corn meal agar, polished rice and trichophyton agars are used for specific characterization of the fungus.
3) Nail pathology

In order to understand nail in disease knowledge of the nail structure is essential.

The nail consists of -

The nail plate, nail folds (proximal and lateral), Nail matrix, Nail bed (Fig. 1 & 2)



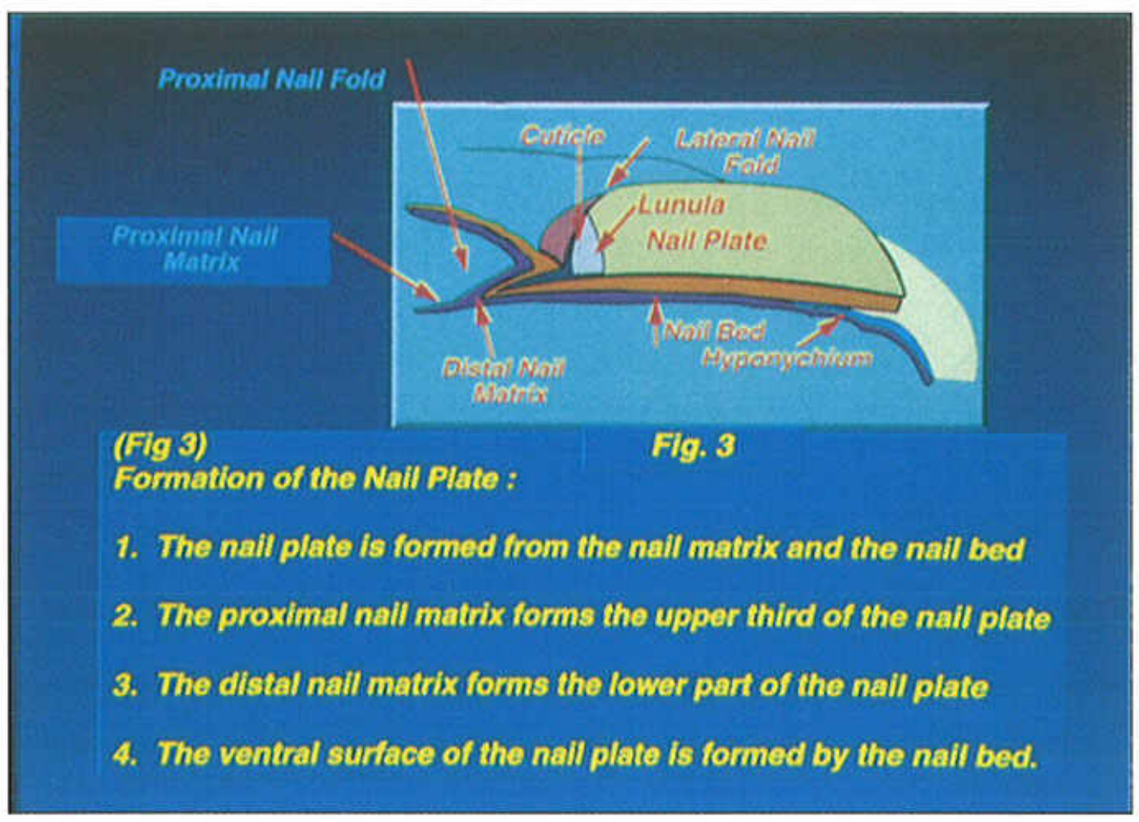


Fig. 1 & 2 : Nail Structure

Formation of the Nail Plate (6) :

1) The nail plate originates from the nail matrix and the nail bed
2) The proximal nail matrix forms the upper third of the nail plate
3) The distal nail matrix forms the lower part of the nail plate
4) The ventral surface of the nail plate is formed partly by the nail bed
5) The distal line of separation of the nail plate from its bed is known as the distal groove.
6) The nail plate gets thicken from proximal to distal varying from 0.3mm to 0.6mm
7) The most proximal part of the nail plate is 7-8 mm from the cuticle.
8) Nail plate has dorsal and ventral part. These two parts are equal proximally and as the nail grows distally the ventral part becomes thickened and the dorsal part makes the floor of the lateral nail fold.
9) The epidermis of the nail bed is ridged to fit in grooves on the under surface of the nail plate.
10) Nail bed has no pilosebaceous follicles and is rich in vascular and lymphatic supply and glomus body.
11) The nail bed epidermis produces karatin without karatohyalin in granuler cell layer.
12) The epidermis of the nail bed is continuous with that of the lateral fold. The epidermis of the lateral nail fold has granular cell layer with keratohyalin.
13) The epidermis of the nail bed is contiguous with the epidermis of the nail matrix.
14) The proximal nail fold -
    a) its dorsal part is continuous with the skin of the finger.
    b) its ventral part produces the keratin known as the cuticle or eponychium which is attached to the nail plate and moves with it.
15) The nail matrix -
    a) the proximal nail matrix lies deep to the proximal nail fold and is 1-2mm proximal to the beginning of the nail plate and gives the dorsal part of the nail plate.
    b) the distal matrix extends to the outer edge of the lunula and gives the ventral nail plate which represents 2/3rd of the plate.

    NB: The ventral surface of the plate is produced also by the nail bed.
16) The distal end of the nail plate as it separates from the nail bed overlies the hyponychium.

Patient & Method

(A.H.), 27 years old Qatari male patient was seen in the The Long Term Care Unit for the handicapped in Rumaillah Hospital. He is mentally retarded and had onychomycosis of toe nails and moccasin type tinea pedes of both soles of 4 years duration. The ten toe nails were thickened, crumbled, discoloured with affection of the proximal nail and subungual hyperkratosis. The skin of both soles and toe webs was diffusely hyperkeratotic and scaly. (Fig. 3,4).

He did not receive any form of antifungal therapy neither local nor systemic.

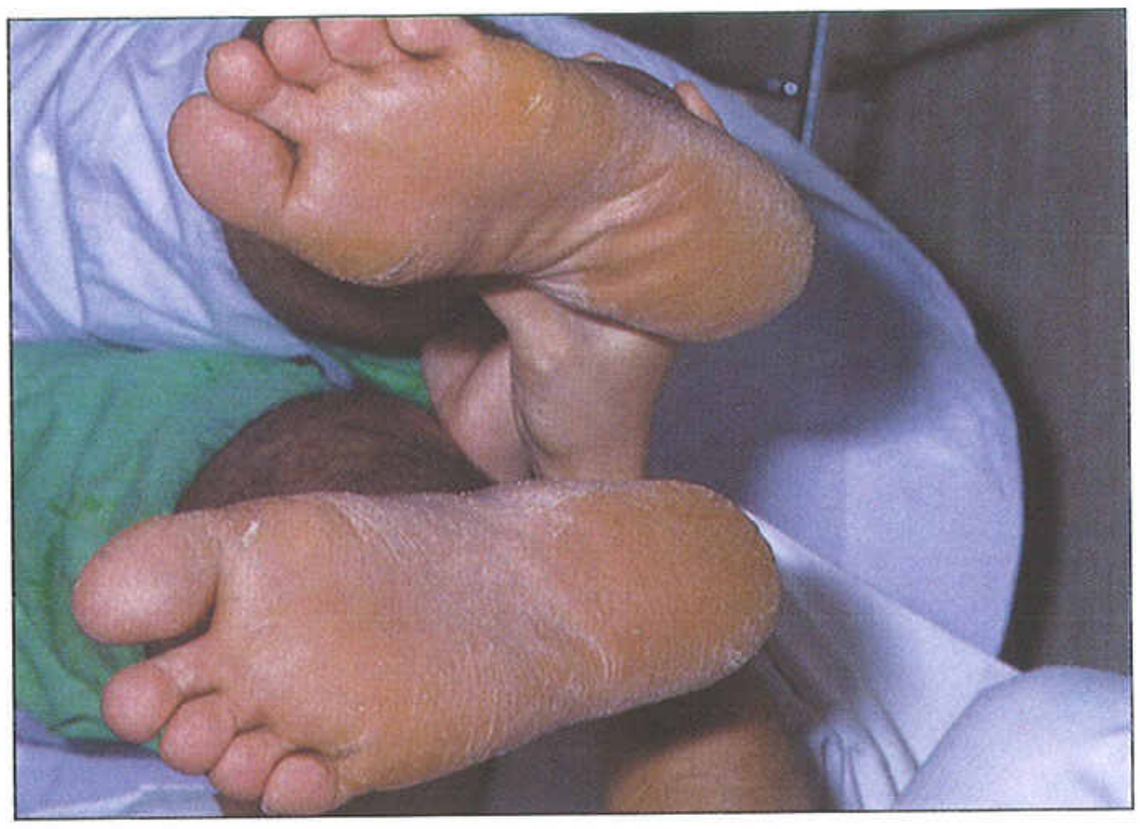


Fig. 3 : Tinea pedes left and right feet

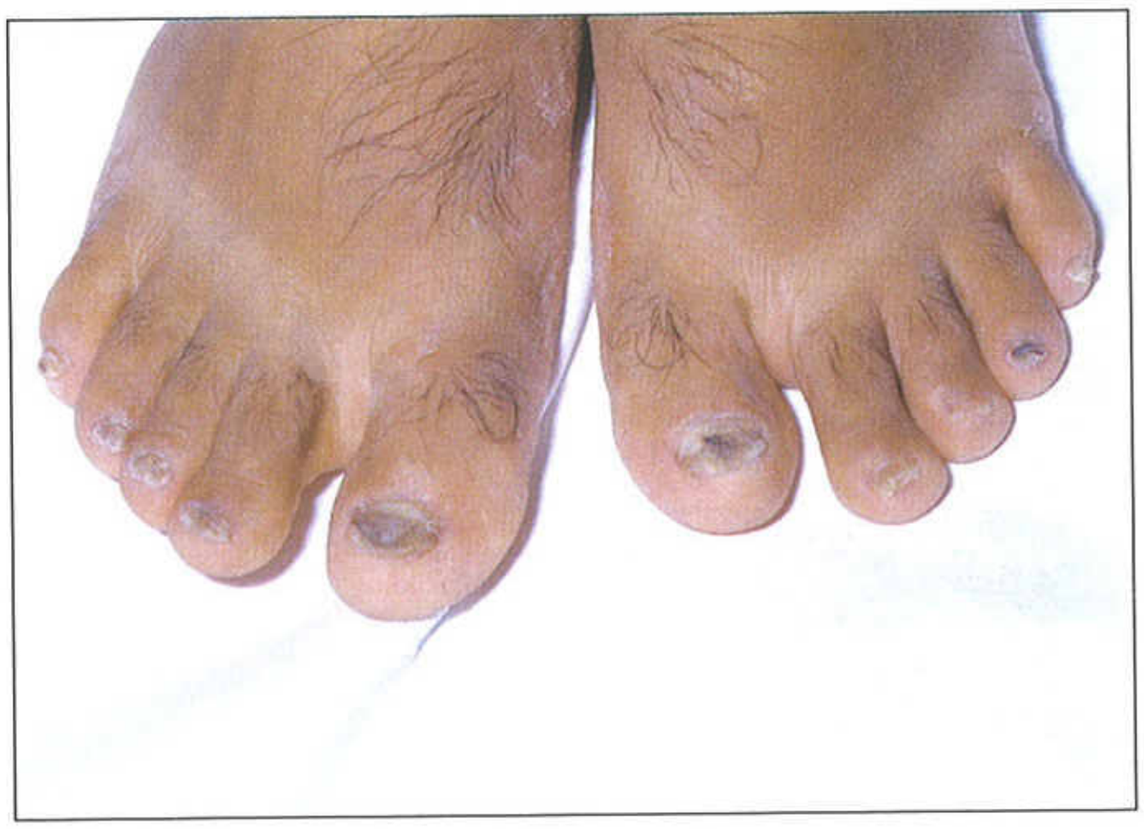


Fig. 4 : Onychomycosis of the toe nails

The diagnosis was further confirmed by direct microscopic examination of nail fragments soaked in 20% KoH for one hour when long septate mycelia were seen (Fig. 5). Histopathology of the nail showed fungal elements by PAS stains, (Fig. 6) Grocott stain (silver nitrate impregnation which stains fungal element black) Culture on DTM grew Trichophyton rubrun.

The patient was in good general health and laboratory tests for blood count and biochemistry were normal.

The nursing staff fulfilled the following advised treatment.

First

Systemic griseofulvin was given orally after lunch in the dose of one gram daily for the first 2 months of treatment.

Second

Local treatment using Loceryl cream and nail Lacquer supplied to us by La Roche representative in Doha, Qatar.

1. Loceryl cream (0.25% Amorolfine) containing 2.5 mg per gram was applied to both feet and interdigital spaces once daily for 2 weeks.
2. Loceryl nail lacquer contiaining 50 mg Amorolfine per c.c. (5%) was supplied in kit containing - Loceryl nail lacquer, nail files, presoaked pads for cleaning affected nails, spatulas for applying the medication.

the instructions followed were :

a) File the affected nails to eliminate infected keratin. The files should only be used to diseased nails to avoid spread of infection.

b) Use the pre-soaked pads to clean affected nails before application of the Loceryl lotion. This cleaning enhances penetration of the lacquer.

c) The spatula is dipped in the lacquer and not wiped off at the rim of the bottle.

The lacquer is applied evenly over the entire surface of the nail and allowed to dry for about 3 minutes.

The lacquer is not affected by soap and water but removed by organic solvents.

The spatulas are reusable and have to be cleaned well with the pre-soaked pads each time they are used.

The treatment and its effect was checked weekly by the dermatologist.

Results :

1. The tinea pedes cleared after 2 weeks and direct KoH preparation became negative and the cream was discontinued Fig (7, 8) nails were still infected.
2. After 3 months of local treatment nails showed marked improvement. They became less thickened and less discoloured . KoH preparation from the nail were still positive.
3. After 6 months of local treatment the nails grew normal direct KoH, culture on DTM was negative (Fig.9 & 10).
4. No systemic or local side effect were observed
5. The patient is still under follow up

Discussion :

Fungal infections in Qatar have an incidence of 11.4% [7] and onychomycosis of 0.35%. In USA

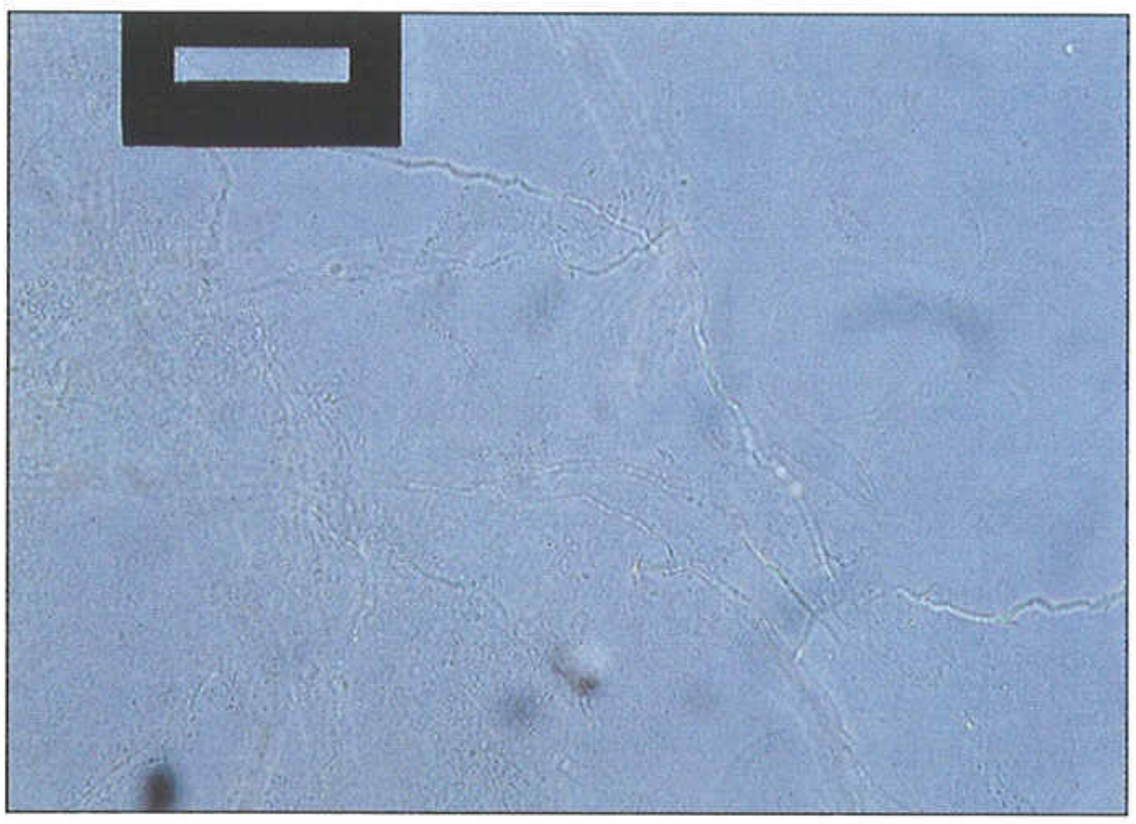


Fig. 5 : Direct microscopic examination (Koh preparation)

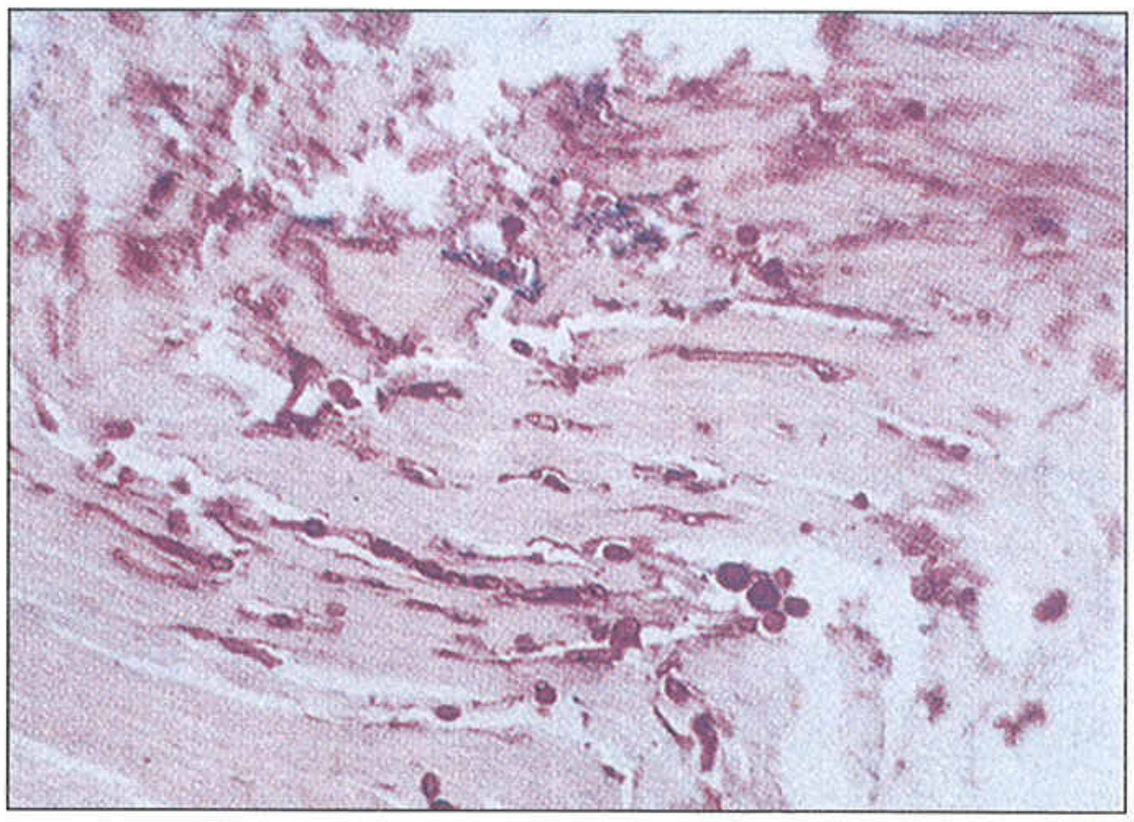
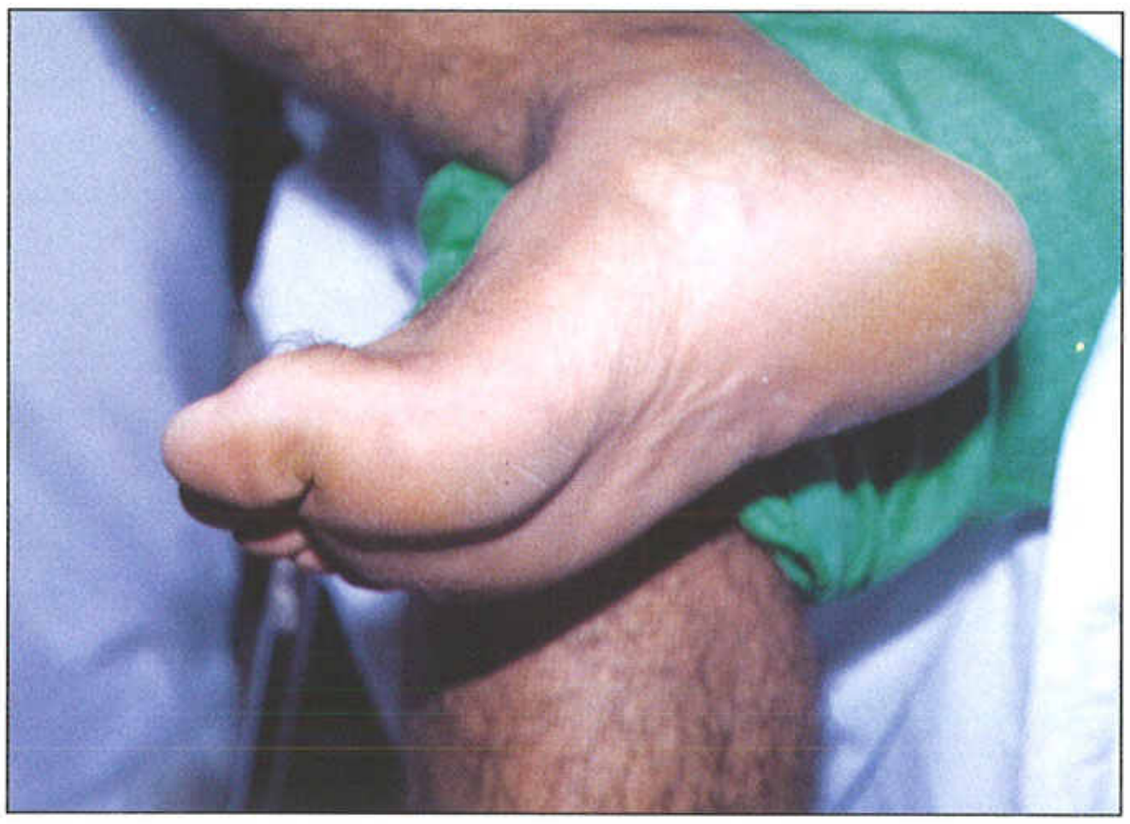


Fig. 6 : Histopathology of infected nail (PAS stain)



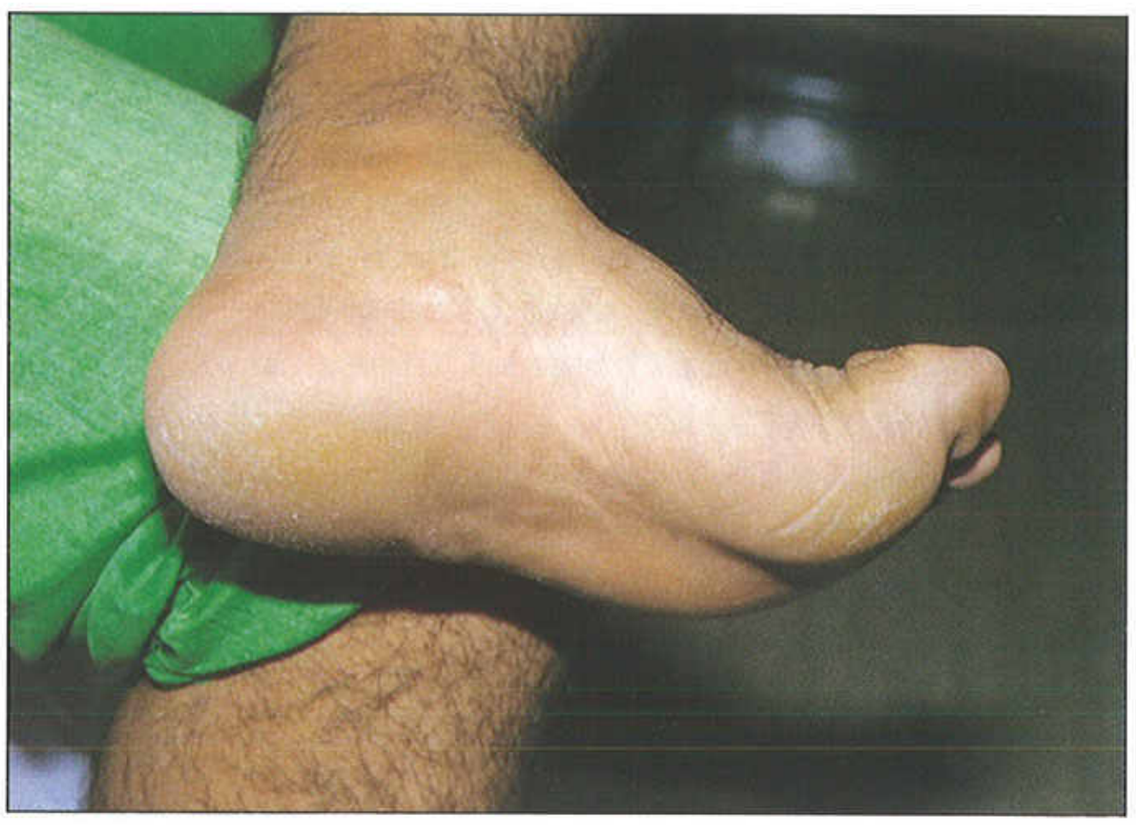
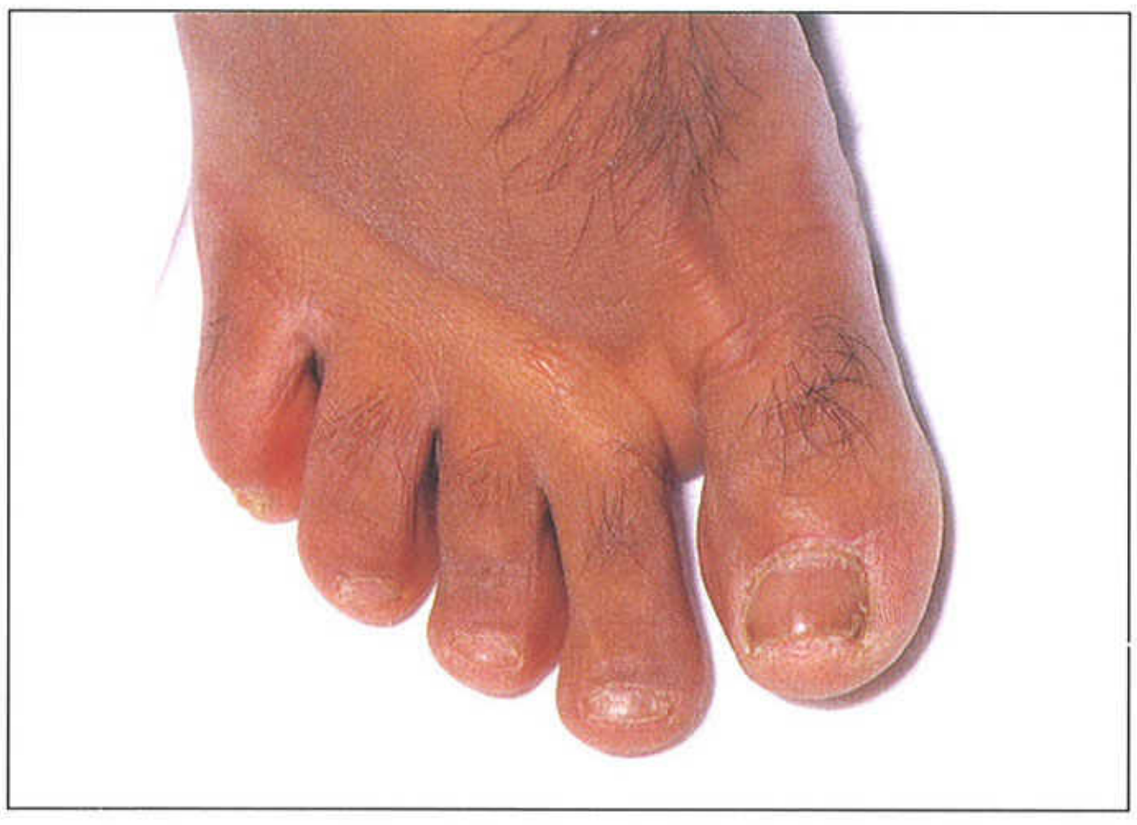


Fig. 7 & 8 : Tinea pedes right and left feet after cure



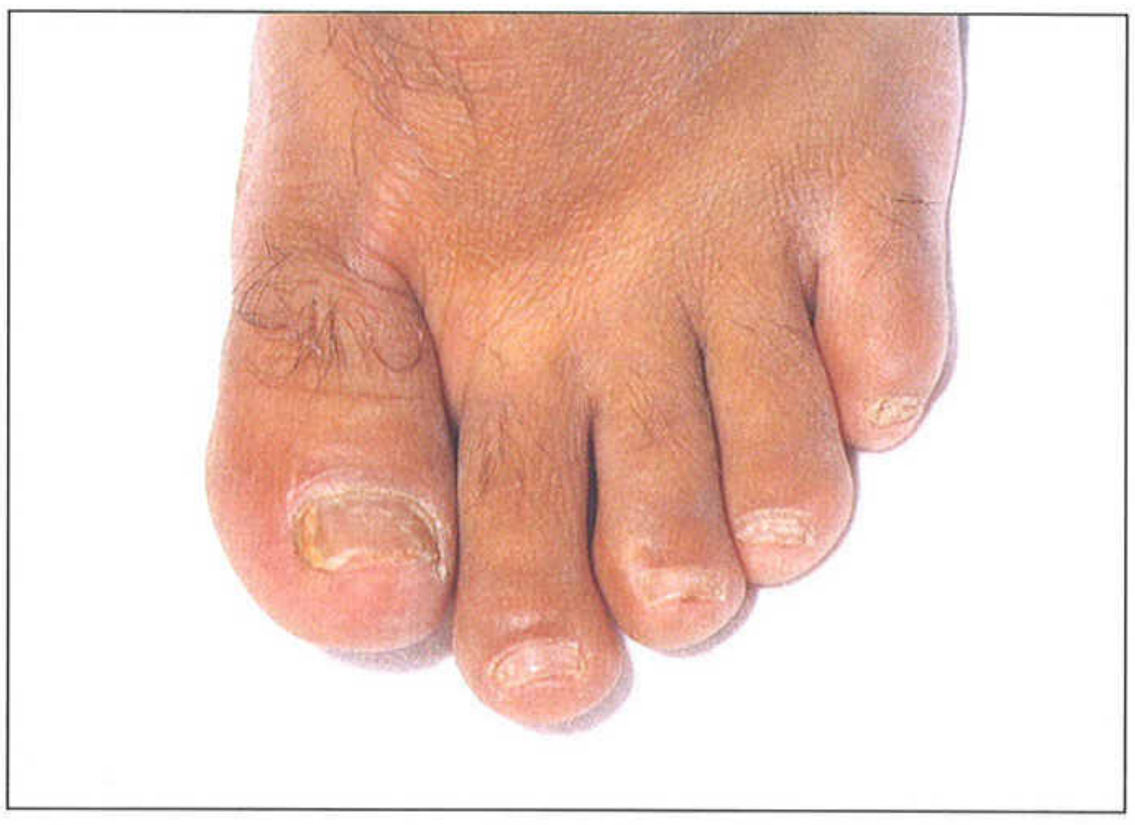


Fig. 9 & 10 : Onychomycosis right and left feet after 6 months of treatment with loceryl.

fungal infection is the second most common skin disease[8] and onychomycosis accounts for one third of all fungal skin infections [4,9] There is a wide variety of antifungal drugs used to treat fungal diseases as shown in table 1. There is no doubt that the newer antifungal agents itraconazole, fluconazole, terbinafine and amorolfine have improved the treatment of fungal infections.

Terbinafine (Lamisil) is given in onychomycosis in the dose of 250mg daily for 4 months and achieves cure in 92.8% of cases [10]. Fluconazole in onychomycosis is given in the dose of 150mg single dose per week for 9-12 months and causes a cure rate of 100% in finger nails and 92% in toe Topical treatment for onychomycosis have been generally ineffective. They are best used after nail avulsion surgical or chemical, a procedure that is not well accepted by the patients. Chemical avulsion is done by applying 40% urea paste under acclusion daily for 10-14 days. The nail becomes soft and easily filed so that topical antifungal effect increases.

The topical antifungal preparations that are currently used are 28% tioconazole in alcohol base, 8% ciclopirox solution and cream, 0.1% bifonazole, topical terbinafine, 2% Tolnaftate and 20% urea and amorolfine 5% lacquer. For topical treatment to be effective in onychomycosis the active antifungal agent must penetrate through the nail plate, the infected keratin and the nail bed and remain there for a prolonged period and must not be washed off by soap and water.

Amorolfine nail lacquer 5% fulfils these requirements [15, 16].

Amorolfine is a morpholine derivative developed to treat dermatomycosis and onychomycosis in humans. It is chemically unrelated to azole derivatives and allylamines. Amorolfine strongly inhibits ergosterol biosynthesis in the cytoplasmic membrane of the fungi [11]. Ergosterol controls the membrane permeability and is essential for the proper functioning of the enzymes bound to the membrane.

Inhibitions of ergosterol synthesis will result in permeability changes and dysregulation of the fungal metabolic processes. Amorolfine also may lead to abnormal deposition of chitin within the cell membrane and this may have a role in its fungicidal activity [17]. Amorolfin at high concentration causes considerable damage to the ultrastructure of the yeast and dermatophyte. The damage involves the cytoplasm, the cytoplasmic membrance and the cell wall [17, 18, 19].

Amorolfine in low concentrations has a potent fungistatic activity against common agents of dermato and onychomycosis particularly candida, dermatophytes and some moulds. Amorolfine fungicidal activity against the same pathogen is time and concentration dependent [17, 18, 19]. Amorolfine cream 0.25% is effective in treatment of dermatomycoses when applied once daily for 3-4 weeks [11].

In the present case report the wide spread hyperkeratotic tinea pedes cleared clinically and mycologically after 2 weeks of local Loceryl cream applied once daily. No recurrence occured during the follow up period of 22 weeks.

If the nail matrix is not affected in onychomycosis the use of 5% amorolfine nail lacquer once weekly will achieve cure after 6 months in finger nails and 9-12 months in toe nails.

If the nail matrix is diseased it is suggested to give combination of systemic antifungal therapy and topical amorolfine lacquer until a healthy growth of the proximal nail occurs[20]. Systemic treatment could then be discontinued with ongoing amorolfine lacquer treatment.

In this presentation the ten toe nails were affected together with the nail matrix, we gave combined treatment using amorolfine nail lacquer locally once weekly and griseofulvin systemically for 2 months and amorolfine lacquer alone for 4 more months. By the end of 6 months treatment, all nails were cured clinically and mycologically. No adverse effects were observed from both the cream and the lacquer.

It is reported that repeated application of loceryl cream upto 3 weeks and nail lacquer upto 13 months is not associated with significant absorption and no systemic side effects have been reported [16]

Conclusion :

1. The once daily application of loceryl cream for dermatomycosis and the once weekly application of Loceryl lacquer in onychomycosis is a convenient dose regimen and is expected to be readily accepted by the patients whose compliance is an essential requirement for the success of any line of treatment.
2. Amorolfine is effective against dermatomycosis and in onychomycosis griseofulvin was given in the first 2 months for the patient to control the nail matrix affection. Clinical and mycological cure occured after 6months use of Loceryl Lacquer.
3. No systemic or local side effects were observed.

Table (1) : Classification of antifungal agents

Polyenes	Miscellaneous	Azoles	Allylamines	Morpholines
Systemic Amphotericin B Mystatin	Flucytosine Griseofulvin Potassium iodide	Imidazoles Miconazole Ketoconazole Triazoles Itraconazole Fluconazole	Terbinafine	Amorolfine
Topical Amphotericin B Nystatin Natamycin	Specific Ciclopirox olamine Haloprogin, Tolnaftate Ciloquinol (iodochlorhydroxyquin) Nonspecific Whitfield's ointment Castellani's paint Gential Violet Compound undecylenic acid Potassium permanganate Selenium sulfide Zinc pyrithione Propylene glycol	Imidazoles Bifonazole Butoconazole Clotrimazole Econazole Fenticonazole Ketoconazole Miconazole Oxiconazole Sulconazole Tioconazole Trizole Terconazole	Naftifine Amorolfine	Terbinafine

Table (2) : Symmary of systemic antifungal agents

Drug	Griseofulvin	Ketoconazole	Triazole Itraconazole Fluconazole	Terbinafine
Dose daily	500-1000 mg (micronized	200-400 mg	200 mg	250 mg
Sensitivity	dermatophytes (fungistatic)	dermatophytes Candida M furfur (fungicidal)	dermatophytes Candida moulds M furfur (fungicidal)	dermatophytes ? Candida (fungicidal)
Pharmacokinetics/ dynamics	inhibits fungal cell mitosis	inhibits synthesis of ergosterol and P-450-dependent enzymes (fungal and human	inhibits synthesis of ergosterol and P-450-dependent enzymes (fungal only)	inhibits squalene; no interference with P-450- dependent enzymes
Reaches nail plate via	matrix	?	matrix and nail bed	matrix and nail bed
Toxic/side effects	headache photosensitive rash	hepatotoxic headache rash	headache dyspepsia rash	dyspepsia rash

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