Mycokeratinophiles: Pathogens of Onychomycosis

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ABSTRACT

Mycokeratinophiles are an ecologically important group of microorganisms that have the ability to cycle keratin, which is one of the most abundant and highly stable animal protein on the earth. These are vigorous and self-sufficient saprophytes as long as environmental conditions are favourable. However, they are opportunists and may become parasitic by accident. After becoming pathogenic, they are able to survive and multiply at host’s body temperature, causing further infection by invading fresh keratinized tissues. Infection is transmitted from human to human or from animal to human by direct contact or by contact with infected hairs or epidermal cells. Infact, it is the only type of fungal infection known to be of contagious type. Mycokeratinophiles, which cause diseases of skin, hair and nails in man and animals, are commonly called as dermatophytes and their infections are known as cutaneous mycoses or dermatomycoses. The dermatophytic fungi belong to one of the three genera- Microsporum, Trichophyton or Epidermophyton. In addition to the dermatophytes, some non-dermatophytic mycokeratinophiles are emerging as leading cause of onychomycosis, that is, fungal infection of toe nails and finger nails. It is the most common nail disorder present in 2-13 per cent of general population, increasing up to 48 percent by 70 years of age. Although onychomycosis is rarely life threatening, its high incidence, prevalence and associated morbidity, makes it an important public health problem.

Key Words: Mycokeratinophiles, mycoses, onychomycosis, dermatophytes, non-dermatophytes.

INTRODUCTION

Mycokeratinophiles are an ecologically important group of microorganisms that have attracted the attention of researchers chiefly because they play an important role in the decomposition of keratin substrates and could be pathogenic to animals, including human beings causing mycosis. Secondly, since mycokeratinophiles are active producers of extracellular keratinases, they can be used in bioremediation of such wastes and waste contaminated sites. For example, several million tonnes of feather waste is generated by poultry and other livestock, which otherwise adds to environmental pollution can be converted into feather meal by using the keratinophilic/ keratinolytic fungi (Shih, 1993; Bertach and Coello, 2005). Addition of feather meal to the animal feed improves digestibility, results in bolstered growth of the poultry and can also be used as slow nitrogen releasing fertilizers (Kushwaha and Gupta, 2008). Keratinases produced by these fungi can be utilized in enzyme-based detergents, cleaning up of clogged drains, leather industry for dehairing, modification of silk and wool fibres, treatment of acne and psoriasis, additives in skin-lightening ag

A survey of literature reveals presence of keratinophilic fungi in the soil of different countries like United States (Daniels, 1954; Rippon and Medenica, 1964; Baxter, 1966, 1969), Australia and New Guinea (Duries and Frey, 1955), New Zealand and Polynsian Island (Maples, 1965), Japan (Kominami, 1961), Canada (Carmichael, 1962; Padhye et al., 1973; Currah et al., 1996), Czechoslovakia (Otsenasek and Dvorak, 1964; Repova, 1990), Egypt (Taylor et al., 1964; Abdel- Fattah et al., 1982; Youssef et al., 1992), Italy (Ajello et al., 1965; Caretta and Piontelli, 1975; Caretta et al., 1992; Mancianti et al., 1997), Pakistan (Mohammed et al., 1971; Soomro et al., 1990), Israel (Feuerman et al., 1975), Kenya (Mohammed and Lalji, 1978). Spain (Calvo et al., 1984; Guarro et al., 1981; 1987 a, b; Gene et al. 1996; Cabanes et al., 1997), France (Chabasse, 1988; Agut et al., 1995), Jordan (Ali- Shtayeh, 1988; Ali- Shtayeh and Sheikh, 1988; Ali- Shtayeh and Arda, 1989), Zambia (Simpanya and Baxter, 1997) and Iran (Soleymani et al., 2015).

In India, studies on mycokeratinophiles commenced with the work of Dey and Kakoti (1955), who isolated Microsporum gypseum from a soil sample collected from an animal house in Dibrugarh, Assam. Since then, a number of workers have reported occurrence of mycokeratinophiles from the soils of different states like Uttar Pradesh (Nigam and Kushwaha, 1985, 1987; Mitra et al., 1998), Rajasthan (Singh et al., 1994), Maharashtra (Padhye and Thirumalachar, 1968), Orissa (Ghosh and Bhatt, 2000), Madhya Pradesh (Agnihotri and
Mycokeratinophiles have the ability to cycle keratin, which is one of the most abundant and highly stable animal protein on the earth. In fact, these fungi possess the ability to degrade hard keratin and utilize it as a source of carbon, nitrogen and sulphur. Keratins (Greek word for 'horn'), which are insoluble fibrous proteins derived from the ectoderm are poorly biodegradable. According to Nelson and Cox (2005), there are two kinds of keratins (Fig. 1):

i) **Alpha-keratins**: These contain most of the common amino acids but are primarily rich in cystine residues and disulphide bridges. The rigid and brittle forms like horns and nails contain up to 22 per cent cystine, whereas the soft and flexible forms in the skin, hair and wool contain only 10 to 14 per cent. The alpha- keratins constitute an ecological problem as they are resistant to degradation by most of the microbes due to the tight packing of their polypeptide chains in the alpha-helix structures and due to their linkage by disulphide bridges (Marchisio, 2000).

ii) **Beta-keratins**: These lack both cystine and cysteine but are rich in amino acids with short side chains, especially glycine, alanine and serine. They are found in the fibers of spiders and silkworms, and in the scales, claws and beaks of reptiles and birds.

Due to the strength and stability of keratin, very few organisms are able to break it down and utilize it. These include few insects (e.g., the larvae of wool, feather and fur moths), helminths, bacteria (e.g., *Bacillus* species, thermophilic *Fervidobacterium pennavorans* and some actinomycetes), birds of prey, water mounds and some geophilic fungal species. Among these, the biggest group of organisms that can utilize keratin as the sole source of carbon, nitrogen and sulphur are the mycokeratinophiles belonging to *Ascomycetes, Zygomycetes and Chytridiomycetes* (Noval and Nickerson, 1959; Tribe and Abu-El-Souod, 1979).

Most of the ascomycetous keratinophiles belong to families *Arthrodermataceae and Onygenaceae* of the order *Onygenales* (Currah, 1985). The *Arthrodermataceae* and *Onygenaceae* are unusual in that majority of them are associated with birds and mammals. These are true mycokeratinophiles that vigorously degrade keratin and include important human and animal pathogens. Other commonly recovered mycokeratinophilic genera include *Chrysosporium, Geomyces, Malbranchea, Microsporum, Oideodendron, Sporendonema, Trichophyton* and their telomorphs (Kushwaha and Gupta, 2008).

### Degradation of keratins by mycokeratinophiles

Mycokeratinophiles have the ability to cycle keratin, which is
Ecological and biological significance

The ecological role of geophilic mycokeratinophiles is undoubtedly of prime importance as they degrade the keratinized material, which may be added to the soil from various sources in the form of feathers, hairs, nails, hoofs, horns, wool and related appendages as wastes. Hence, soil provides most conducive habitat for the growth and multiplication of keratinophilic fungi. In the soil, these fungi usually exist in their telomorphic (sexual) state, whereas on the keratinized material, they usually exist in an amanomorphic (asexual) state in which they develop only a very simple morphology. When there is ample of keratin substrate available in the soil, these fungi multiply by asexual means by producing enormous number of conidia (aleuronconidial and arthroconidial). However, when the keratin substrate is depleted, these fungi reproduce by sexual means and form characteristic sexual fruiting bodies. The thick-walled sexual and some asexual spores are the propagules for the next generation and can remain dormant until fresh keratin or an alternative source of nutrition becomes available. In natural environments, keratinophilic fungi are involved in recycling of carbon, nitrogen and sulphur present in keratins by the action of three factors (Kunert, 2000):

i) Deamination. Creating an alkaline environment needed for swelling, sulphitolysis and proteolytic attack.

ii) Sulphitolysis. Denaturing the substrate by removing its disulphide bridges.

iii) Proteolysis. Cleaving the denatured substrate to soluble products.

Mycokeratinophiles are vigorous and self-sufficient saprophytes as long as environmental conditions are favourable. However, they are opportunists and may become parasitic by accident. After becoming pathogenic, they are able to survive and multiply at host’s body temperature, causing further infection by invading fresh keratinized tissues. Infection is transmitted from human to human or from animal to human by direct contact or by contact with infected hairs or epidermal cells. Infact, it is the only type of fungal infection known to be of contagious type. Such mycokeratinophiles, which cause diseases of skin and hair in man and animals, are commonly called as dermatophytes and their infections are known as cutaneous mycoses or dermatomycoses. These fungi, by virtue of their ability to colonize epidermal appendages, may become a source of sanitary danger to human health and accordingly, from time to time they have drawn the attention of various medical and veterinary epidemiologists. The dermatophytic fungi are keratinolytic in nature and belong to one of the three genera- Microsporum, Trichophyton or Epidermophyton. In addition to the dermatophytes, the non-dermatophytic mycokeratinophiles are emerging as leading cause of onychomycosis (Elewski, 1998; Raghavendra et al., 2015).

The potential pathogenicity of mycokeratinophiles has been considered as a natural evolution from its presence in the soil (geophilic species) to invasion of cornified substrata in animals (zoophilic species) and man (anthropophilic species). Based on habitat, nature and epidemiology, dermatophytes are classified into three broad categories (Ajello, 1960):

i) Geophilic, which are saprobic, occur mainly in soil and are rarely pathogenic.

ii) Zoophilic, which are mainly parasitic to lower animals and are transmitted through contact.

iii) Anthropophilic, which are mainly parasitic to humans and cause dermatomycoses.

Molecular studies based on the DNA sequence analysis of the ribosomal ITS (Internal Transcribed Spacer) region have shown that these three groups are also phyllogenetically distinct (Graser et al., 2000). The PCR based nucleic acid amplification procedures such as arbitrary primed PCR (AP-PCR) amplification techniques can rapidly distinguish dermatophytes and other keratinophilic fungal species examined through the generation of characteristic band patterns. Development of species-specific primers and probes for individual dermatophytes are more practical and precise methods for molecular detection (Pakshir et al., 2013). In molecular identification, similarity and phylogeny of internal transcribed spacer (ITS) sequences of two related species is also studied (Woodgyer, 2004). These ITS regions of ribosomal DNA are used as primer and amplified. For isolation of a particular ITS region, specific restriction enzymes are used. Location of a specific gene in the genome is also used for molecular identification. Molecular markers also known as DNA markers which play important role for identification of particular species and are either PCR based or non PCR based methods. Molecular markers include Restriction Fragment length Polymorphism (RFLP), Random Amplified Polymorphic DNA (RAPD), Amplified Fragment length Polymorphism (AFLP), Simple Sequence Repeats (SSR), Inter Simple Sequence Repeats (ISSR), and Single Nucleotide Polymorphism (SNP), etc. Identification of dermatophytes by Matrix Assisted laser desorption ionization time-of-flight (MALDI-TOF) is reported by Erhard et al., 2008. Molecular identification of mycokeratinophiles can also be done by purification of keratinase. Keratinase is separated by SDS-PAGE technique. The protein separation by SDS-PAGE is based on molecular weight of the compounds. In this technique polyacrylamide gel is used for separation. When electric field is applied, keratinase is separated according to molecular weight. For identification, the gel is stained with coomassie blue for 2 hours (El-Gayar et al., 2012).

Mycokeratinophiles in causing Onychomycosis

Mycokeratinophiles cause infection of the nails also called as ungual mycosis or onychomycosis, a term derived from the Greek word “Onychos”, which means nail, and “mycosis” is an infection by fungi. The fungal invasion frequently causes hyperkeratosis reaction and a greater or lesser degree of destruction to the external layers or other structures of the nails (Fig. 2).

Onychomycosis generally means chronic fungal infection of toe nails and finger nails caused by different species of dermatophytes, saprophytic moulds, yeasts and yeast-like
fungi. It is the most common nail disorder present in 2-13 per cent of general population, increasing up to 48 per cent by 70 years of age (Lilly et al., 2006). Onychomycosis caused by dermatophytes is called *Tinea unguium* (Anaisi et al., 2003) and the dermatophytic fungi causing it include species of *Trichophyton, Microsporum* and *Epidermophyton*. Other accountable non-dermatophytic species are yeast and yeast-like fungi, such as, species of *Candida, Geotrichum, Trichosporon* and saprophytic fungi like species of *Aspergillus, Alternaria, Cephalosporium, Scopulariopsis, Fusarium, Acremonium* and *Penicillium* (Khosravi and Mansouri, 2001). Mycokeratinophiles (both dermatophytes and non-dermatophytes) reported so far as causal agents of onychomycosis are listed in table 1 and table 2.

Onychomycosis caused by dermatophytes is often symptomatic and can cause functional impairment. Its clinical appearance involves hyperkeratosis with thickening and discoloration of the nail plate. Other disorders such as nail psoriasis, lichen planus and nail trauma may yield a nearly identical picture (Scher and Baran, 2003). On the basis of their clinical appearance, onychomycosis is classified into four types (Roberts et al., 2003; Kaur et al., 2008):

**i) Distal subungual onychomycosis (DSO):** It is the most common form of *Tinea unguium*, in which the fungal infection invades the nail bed and the underside of the nail plate (Fig 3A).

**Table 2:** Non-dermatophytic fungi associated with onychomycosis.

<table>
<thead>
<tr>
<th>Non-Dermatophytic fungi</th>
<th>Country</th>
<th>References</th>
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<tr>
<td>Aspergillus flavus</td>
<td>Spain, India</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000), Asadi et al. (2009), Raghunandan et al. (2011), Gupta et al. (2011), Shirihas et al. (2012)</td>
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<td>A. sydowii</td>
<td>India, Spain</td>
<td>Wadhwan and Srivastava (1985), Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td>Italy, Spain, India</td>
<td>Romano et al. (2005), Torres-Rodríguez and Lopez-Jodra (2000), Asadi et al. (2009), Shirihas et al. (2012)</td>
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<td>Wadhwan and Srivastava (1985), Shirihas et al. (2012)</td>
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<td>A. madura</td>
<td>Nigeria, India</td>
<td>Shirihas et al. (2012)</td>
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<td>A. tenuis</td>
<td>Denmark</td>
<td>Kristensen et al. (2005)</td>
</tr>
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<td>A. versaceps</td>
<td>Spain</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td>A. canadensis</td>
<td>Spain</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td>A. terreus</td>
<td>Spain, Nigeria</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000), Shirihas et al. (2012)</td>
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<td>A. peguensis</td>
<td>Italy</td>
<td>Zott et al. (2007)</td>
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<td>A. niger</td>
<td>Spain</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td>A. nomius</td>
<td>India</td>
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<td>Alternaria alternata</td>
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<td>A. niger</td>
<td>Nigeria, India</td>
<td>Wadhwan and Srivastava (1985)</td>
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<tr>
<td>F. oxysporum</td>
<td>Canada, Brazil, Italy, India</td>
<td>Gupta et al. (2000), Gedoy et al. (2004), Romano et al. (2005), Shirihas et al. (2008), Shirihas et al. (2011)</td>
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<tr>
<td>F. solani</td>
<td>Canada, Brazil, India, Pakistan</td>
<td>Gupta et al. (2000), Gedoy et al. (2004), Wadhwan and Srivastava (1985), Farwa et al. (2011), Shirihas et al. (2015)</td>
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<td>F. pseudonodosum</td>
<td>India, China, India</td>
<td>Shirihas et al. (2015)</td>
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<td>F. nivuliforme</td>
<td>Nigeria</td>
<td>Shirihas et al. (2014)</td>
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<td>F. dimorium</td>
<td>Pakistan, India</td>
<td>Farwa et al. (2011), Ramsawak et al. (2015), Ray et al. (2016)</td>
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<td>F. roseus</td>
<td>India</td>
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<td>F. psallotrichum</td>
<td>India, China</td>
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<td>F. chlamydosporum</td>
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<td>F. pseudonodosum</td>
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<td>Farwa et al. (2011), Shirihas et al. (2015)</td>
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<td>Shi et al. (2016)</td>
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<td>Cryptococcus albidos</td>
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<td>C. unguiatilis</td>
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<td>C. laurentii</td>
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<td>C. keratinophilum</td>
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<td>C. gloeosporioides</td>
<td>India</td>
<td>Tadepalli et al. (2015)</td>
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**Table 1:** Dermatophytic fungi associated with onychomycosis.

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<th>Dermatophytic fungi</th>
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<tr>
<td><em>Trichophyton rubrum</em></td>
<td>Iceland, Italy, India, Iran</td>
<td>Gudnadottir et al. (1999), Romano et al. (2005), Kaur et al. (2008), Veer et al. (2007), Asadi et al. (2009), Farwa et al. (2011)</td>
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<tr>
<td><em>T. mentagrophytes</em></td>
<td>Iceland, Italy, India, Iran</td>
<td>Kaur et al. (2008), Veer et al. (2007), Asadi et al. (2009), Farwa et al. (2011)</td>
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<tr>
<td><em>T. violaceum</em></td>
<td>Italy, India, Iran, Pakistan</td>
<td>Romano et al. (2005), Asadi et al. (2009), Farwa et al. (2011)</td>
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<td><em>T. rubrum</em></td>
<td>Italy, India, Iran</td>
<td>Asadi et al. (2009), Farwa et al. (2011)</td>
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<td><em>T. verrucosum</em></td>
<td>Iran</td>
<td>Asadi et al. (2009)</td>
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<td><em>T. mentagrophytes</em></td>
<td>Spain</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td><em>T. concentricum</em></td>
<td>Spain</td>
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<td><em>T. mentagrophytes</em></td>
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<td><em>T. hominis</em></td>
<td>Spain</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000)</td>
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<td><em>T. tonsurans</em></td>
<td>Spain, Pakistan</td>
<td>Torres-Rodríguez and Lopez-Jodra (2000), Farwa et al. (2011)</td>
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<td><em>M. canis</em></td>
<td>France</td>
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<td><em>M. audouinii</em></td>
<td>Tehran, Iran</td>
<td>Nowrozii et al. (2008)</td>
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<td><em>Epidemiphorum floccosum</em></td>
<td>Italy, India, Iran</td>
<td>Romano et al. (2005), Kaur et al. (2008), Asadi et al. (2009)</td>
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Fig. 2: Internal structure of the nail.

![Image](58x103)
Table. 2 Contd……

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<th>Non-Dermatophytic fungi</th>
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<td>Curvularia spp</td>
<td>India</td>
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<td>E. olgae</td>
<td>Taiwan</td>
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<td>Acyrthosiphon dianthi</td>
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<td>Belgium, Italy, India, Pakistan, Korea, Guatemala</td>
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Figs. 3(A-E): Different Types of Onychomycosis- (A) Distal subungual onychomycosis (B) Proximal subungual onychomycosis (C) White superficial onychomycosis (D) Candidal onychomycosis and (E) Total dystrophic onychomycosis forming "white islands" on the plate (Fig.3C).

iv) Candidal onychomycosis (CO): It refers to the invasion of fingernails by Candida species. It normally requires the prior damage of the nail by infection or trauma (Fig. 3D).

v) Total dystrophic onychomycosis (TDO): It refers to the total destruction of the nail plate, which usually may be the end result of any of the four main patterns of onychomycosis. The entire nail unit becomes thick and dystrophic. TDO is used to describe end-stage nail disease, although some clinicians consider it as a distinct subtype (Fig. 3E).

The most common symptom of a fungal nail infection is the thickening and discoloration of the nail, which takes up many colours like white, black, yellow or green. As the infection progresses, the nail may become brittle, with pieces breaking off or coming away from the toe or finger completely. If left untreated, the skin can become inflamed and painful underneath and around the nail. There may also be white or yellow patches on the nail bed or scaly skin next to the nail. The capacity of mycokeratinophiles to metabolise keratin of the nails is due to the production of extracellular keratinases, collagenases and elastases along with endopeptidases, lipases, glucosidases and nucleases (Torres-Rodriguez and Lopez-Jodra, 2000). These enzymes allow easy penetration and development of the mycelium, which further allows pathogenesis.

Until the late 1990s onychomycosis was a poorly discussed topic of medical science. Even in financially more advanced Asian countries, onychomycosis has been highlighted only in the last decade (Kaur et al., 2007). Onychomycosis affects approximately 5% of the population worldwide (Murray and Dawber, 2002) and represents 20-40% of onychopathies and about 30% of mycotic cutaneous infections (Achten and Wanet, 1978). In developing countries, higher priorities in socioeconomic concerns and health issues for other diseases, have resulted in low awareness of onychomycosis by physicians and the general public alike. In spite of improved personal hygiene and living environment, onychomycosis

ii) Proximal subungual onychomycosis (PSO): It refers to fungal penetration of the newly formed nail plate through the proximal nail fold. It is least common in healthy people, but more common when the patient is immuno-compromised (Fig.3B).

iii) White superficial onychomycosis (WSO): It is caused by fungal invasion of the superficial layers of the nail plate
continues to spread and persist. The worldwide incidence of onychomycosis is increasing day by day and a number of factors contribute to this rise (Kaur et al., 2007). Firstly, as the population ages, there are corresponding chronic health problems that emerge, such as diabetes and poor peripheral circulation. Secondly, the number of persons who are immune-compromised because of infection with human immunodeficiency virus and the use of immunosuppressive therapies, cancer chemotherapy or antibiotics continue to expand. Thirdly, avid sports participation is increasing the use of health clubs, communal swimming pools and occlusive footwear for exercise. Additionally, in a small percentage of persons, onychomycosis may be caused by a genetic defect that causes alteration in immune function (Odom, 1994).

Though there is a clearly diseased appearance associated with this condition, onychomycosis is often regarded as merely a cosmetic problem of relatively minor importance that is hardly worth the effort to seek treatment in many cases. This belief may have been supported by the adverse effects and long dosing courses associated with some of the earlier antifungal agents (Kaur et al., 2008). However, in the last two decades there have been safe, effective systemic treatment regimes available for this chronic superficial fungal disease that can have significant negative effects on patients' emotional, social and occupational functioning. Although onychomycosis is rarely life threatening, its high incidence, prevalence and the associated morbidity, makes it an important public health problem.

REFERENCES


