

EDITORIAL

Onychomycosis: Insights in disease development

Introduction

Human nail is a tool of functional and cosmetic importance that adds subtlety and protection to the digit. It is the distal most part of the limb making it prone for external trauma and infection. The term OM is derived from the Greek word 'onychos' which means nail and 'mycosis', an infection by fungi. The common physical signs of OM are altered nail colour, nail plate separation, hyperproliferation of the nail bed, and destruction of the nail plate leading to an abnormal appearance.^[1] Description of mycotic infections of the nail appeared first in the year 1829 in a treatise on scalp ringworm, which compared 'favus of the nail' to the statue of Daphne, a beautiful woman who changed into a laurel tree to escape from amorous advances of Apollo.^[2]

Until the late 1990s, OM was a lesser discussed topic in medical science. Today, it has become a major source of interest, which can be attributed to the interesting knowledge about the epidemiology, pathogenesis, clinical presentation, diagnosis, and management of this condition.

Epidemiology

OM is a clinical term used to denote an infective condition of the nail caused by fungi namely, dermatophytes, yeasts, and moulds. The term 'tinea unguium' is used when the causative agent is identified as a dermatophyte.^[3]

OM is the most common of all nail disorders, accounting for up to 50% of all onychopathies and 30% of all superficial fungal infections.^[4,5] It has an overall incidence of 8.7% in the United States and 6.5% in Canada and an increasing prevalence worldwide showing considerable variance among different studies conducted in various parts of the country and the world.^[6,7]

Factors Influencing Fungal Nail Invasion

The many factors that have contributed to the increasing incidence of OM are attributed to the growing population of elderly and immunocompromised patients and the overuse of antibiotics.^[8] There are numerous conditions that are favorable for fungal nail invasion. They are only presumptions in some cases based on indirect relations, and in others, the influence on OM was demonstrated clinically and experimentally.

Age

The prevalence of OM is found to increase with age.^[9] A higher occurrence of OM is seen in middle-aged adults, possibly due to occupation-related trauma.^[10] It has been estimated that almost 50% of the population may be affected by the age of 70.^[11] A higher prevalence among the elderly patients above 60 years of age has been noted by some authors, who attribute to the slow growth rate of the nail, use of occlusive footwear, difficulty in maintaining foot hygiene, and peripheral circulatory insufficiency in this age group.^[12,13] Children less than 18 years of age have a much lower prevalence of OM compared to adults.^[14,15] The lower incidence of OM in children could be due to the reduced exposure to fungi, faster nail growth, smaller nail surface for fungal invasion, and lower prevalence of tinea pedis in children.^[16]

Gender

Prevalence of OM is higher in men compared to women.^[17] The higher incidence in males may be attributed to more exposure to outdoor physical activity which makes the nail prone to trauma. Inhibitory effects of progesterone on the growth of dermatophytes in women may also play a role.^[18] However, no difference in the prevalence of OM between male and female patients was found in a study, although the incidence was slightly higher in women.^[9]

Type of Nail

Toenail fungal infections are more common than fingernail infections.^[19] This could be attributed to prolonged exposure of the toenails to fungal pathogens through communal bathing, gyms, trauma by sporting activities, and occlusive foot wear. Although closed footwear is known to be a risk factor in tinea pedis and associated tinea unguium, the use of open footwear

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may also increase their chances of exposure to soil saprophytes.^[8,20] Fingernails are more commonly involved in females ascribing to their routine work performing domestic chores with water.^[21]

Genetic Factors

An autosomal dominant pattern of inheritance in the distal and lateral subungual OM caused by *Trichophyton rubrum* is noted.^[22] However, it is postulated that 'selective T cell recognition factor' could lead to differences in immunologic response to infection, or a genetic influence on the keratin itself, making the nail more susceptible to fungal infection.^[13]

Local Factors

The integrity of the corneal layer of the nail is fundamental in preventing any fungal invasion. Any process that causes the breakdown of this barrier facilitates the penetration of pathogenic fungi. Physical factors such as improper footwear, which displaces the body weight toward the toes, excessive manicure of nails resulting in loss of the protective cuticle, and continued exposure to water and detergents causing microtrauma to the nail plate appear to predispose women to develop OM. Constitutional hyperhidrosis due to the use of closed footwear which prevents transpiration and the traumatic effect of nail biting which causes micro trauma to the nail plate appear to be risk factors in the development of OM in males and children, respectively.^[23]

Outdoor Physical Activities

The current enthusiasm for physical fitness has resulted in the widespread use of occlusive shoes (for hiking, biking, and other athletic activities) and swimming pools that provide a humid environment and traumatic exposure conducive to OM.^[13,24]

Occupation

OM and tenia pedis have been recognized to be more common in certain occupational groups like farmers, forestry workers, miners, and navy personnel owing to their greater rates of contact with pathogenic fungi present in soil, water, and animals.^[25-27]

Cutaneous Dermatophytoses

A high risk of OM is found in patients with tinea pedis. An unnoticed and stable reservoir of dermatophytes in the nail plate can lead to infection and reinfection of the surrounding cutaneous surfaces. These findings have therapeutic implications, since effective long term cure of tinea pedis may require nail-directed therapy.^[13,28]

Diabetes Mellitus

OM is said to be present in at least one-third of all patients with diabetes mellitus and diabetics are at least twice as likely to suffer from OM as compared to normal individuals. Diabetic microangiopathy leads to peripheral vascular disease, which in turn predisposes patients to OM.^[29] Sharp and brittle ends of a mycotic nail can result in injuries to the surrounding skin which can go unnoticed in a patient with diabetic sensory neuropathy, thus forming a portal of entry for bacteria.^[30]

Human Immunodeficiency Virus (HIV) Infection

The increase in infection by HIV has been associated with mycotic complications both at the cutaneous and mucosal level. HIV-positive patients may have a higher prevalence of OM that develops at a relatively younger age, spreads rapidly to the hands and feet and a higher frequency of unusual forms like proximal subungual OM and periungual involvement. Approximately 1 in 20 HIV-positive individuals may have invasive nail plate/bed fungal disease even in the presence of a normal appearing nail unit.^[31,32]

Psoriasis

Nail abnormalities can be seen in 82.3% of psoriatic patients of whom 21.5% can have OM. An infection with dermatophytes might induce a local Koebner reaction in psoriasis. However, a higher occurrence of yeast infections (*Candida* spp.) than dermatophytes is seen in psoriatic nails compared to the general population probably due to the altered subungual tissue and onycholysis which facilitates invasion of yeasts and fast turnover of the nails in psoriasis patients which may constitute an effective defense against dermatophytes.^[33]

Atopic Disorders

It has been reported that the signs and symptoms of atopic disease disappear with the treatment of OM, while in some patients untreated OM caused a disease flare. Hence, either an allergic reaction to the fungus causes atopic disease or patients with this disorder are more prone to OM.^[34]

Smoking and Peripheral Arterial Disease

Patients in a study who smoked two or more packets of cigarettes per day showed an increased risk of acquiring OM compared to non-smokers. The presence of peripheral arterial disease, indicated by a low ankle brachial pressure index (ABI), corresponds with the presence of OM.^[35]

Etiological Agents

Dermatophytes are the most common pathogens in OM, followed by yeasts and non-dermatophytic moulds (NDM).^[36] However, the incidence of isolating various etiological agents causing OM varies worldwide.

Dermatophytes

Dermatophytes causing OM belong to three different genera namely *Trichophyton*, *Epidermophyton*, and *Microsporum*. They are the causative agents in about 90% of toenails and 50% of fingernails affected with OM. Throughout the world, *T. rubrum* is the most frequently isolated organism, which can be explained by its ability to adapt to the hard keratin in the nail. *Trichophyton mentagrophytes* is the next frequently encountered dermatophyte.^[36-38] Often *Trichophyton verrucosum* is isolated from patients who came in contact with cattle as a part of their occupation.^[17]

Yeasts

Previously regarded as contaminants, yeasts are now increasingly recognized as pathogens in fingernail infections. Yeasts like *Candida* spp were the predominant pathogens (46%) in a study on OM.^[39] This high observation was due to increased prevalence of the disease among females especially those involved in kitchen work, laundering, and increased washing of the hands. *C. parapsilosis*, *C. albicans*, and *C. guilliermondii* are the most common species of *Candida* isolated.^[36]

Nondermatophyte Moulds

Nondermatophyte moulds are filamentous fungi that are commonly found in nature as soil saprophytes and plant pathogens.^[40] The NDM which were previously being considered as mere contaminants have recently emerged as potential nail pathogens capable of causing OM indistinguishable from dermatophyte infections.^[41] With the number of immunosuppressed patients escalating each day, the incidence of OM being caused by nondermatophytes has increased. Increased susceptibility to nondermatophyte infection is seen in HIV-positive patients due to immunosuppression and in tropical regions like India due to increased humidity which favors the growth of NDM, active lifestyle increasing susceptibility to trauma and contact with soil and the presence of varied species of fungi in the environment.^[31,41]

Nail invasion by NDM is considered uncommon, with prevalence rates ranging from 1.45% to 17.6%. This variation may reflect geographic differences in

mould distribution, differences in the criteria used for diagnosing mould OM and use of mycological methods inappropriate for mould growth. Traditionally, they have been considered as secondary pathogens of nails which are already diseased, although they act as primary pathogens in a small number of cases. The important NDM involved in OM as primary pathogens appear to be *Scopulariopsis* and *Scytalidium*. It is said that OM caused by *Scytalidium* and *Aspergillus* may often be suspected by clinical examination; the pattern usually seen is proximal OM associated with inflammation of the proximal nail fold. Periungual inflammation may be quite marked and painful, and in some cases associated with purulent discharge. Therefore, the presence of inflammation should strongly suggest a mould OM.^[42]

The relation between dermatophytes and NDM in OM may be similar to the situation as in tinea pedis interdigitalis. Dermatophyte infection of the toe webs (dermatophytosis simplex) may create a hospitable environment for the bacteria that normally would not colonize the area; these bacteria can overgrow and mask the underlying dermatophyte infection (dermatophytosis complex). Similarly, dermatophyte infection of the nail may create conditions favourable to both bacteria and saprophytic moulds, which on culture often overgrow dermatophytes, impeding their isolation. Therefore, a saprophytic mould growing from a patient with a clinical impression of OM may not be the original pathogen, but may represent valid growth. This phenomenon in the nail could be called 'onychomycosis complex'. Hence, repeat cultures of nail specimen may be necessary to detect the presence of a dermatophyte or to validate NDM as a primary pathogen.^[43]

Pathogenesis

Nail unit is a site of relative immune privilege due to a very low level of expression of major histocompatibility complex Class 1a antigens, local production of potent immunosuppressive agents, dysfunction of antigen presenting cells and inhibition of natural killer cell activity. Moreover, fungi-invading skin, hair and nails are strongly keratinophilic, and use keratin as nutrients for their development. Due to a lack of effective cell-mediated immunity, the nail apparatus is susceptible to invasion by fungal organisms. The nail plate offers an ideal niche for fungal organisms where they can persist for long durations. Hence, OM is usually a chronic infection not associated with inflammation.^[44,45]

Natural infection is acquired by the deposition of viable arthrospores or hyphae on the surface of the nail. The

clinical type of OM is determined by the route of invasion of fungi into the nail. Once the fungi are inoculated onto the nail, the arthroconidia (infectious elements) get attached with the help of expression of adhexin molecules. The arthroconidia then germinate to produce short and long projections called hyphae which play a role in fungal invasion. Enzymes like proteases, metallo-endoproteases (fungalysins), lipases, and ceramidases help fungi digest keratin into assimilable oligopeptides.^[46]

Impact on Quality of Life

The common perception is that OM is more of a cosmetic nuisance than a significant disease. Similar to other cutaneous disorders, OM has detrimental effects on quality of life and possibly predisposes persons to more serious medical disorders. Patients have fear of spreading the disease to others. The stigma associated with it causes embarrassment. This may be accompanied by distress, low self-esteem, and loss of self-confidence. The physical consequences of OM may be considerable. When fingernails are affected, daily functions such as manipulating small objects and repetitive finger use (e.g., typing) is severely compromised. When toenails are affected, prolonged standing and walking can be impaired.^[47]

Conclusions

Physicians need to appreciate the true nature of OM. It is not just a cosmetic nuisance but a painful and potentially disabling disorder that merits more medical attention than it has thus far received. It is of great value to identify the associated risk factors in the prevention and treatment of OM.

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Editorial

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