The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive?

Superficial fungal infections of the skin, hair, and nail are among the most common infective dermatoses seen in dermatology outpatient clinics. Today, we are facing an onslaught of chronic and recurrent dermatophytosis in volumes never encountered previously. Over the last 3–4 years, the frequency of such cases has increased alarmingly. These cases make up at least 5–10% of new cases seen in the dermatology clinic at our center in North India. The dermatophytosis cases we see in hospitals represent just the tip of the iceberg of the epidemic that is in the community. To add to the woe there is no standard definition for the term "chronic dermatophytosis", although it is described in lay terms as "patients who have suffered from the disease for more than 6 months to 1 year duration, with or without recurrence, in spite of being treated." Recurrent dermatophytosis refers to the reoccurrence of the dermatophyte infection within few weeks, after completion of treatment.[1] Chronic and recurrent dermatophytic infections cause significant distress to the patients socially, emotionally, and financially. This editorial expounds upon various possible factors which could have led to such a menace and an emergence of antifungal drug resistance in superficial mycoses.

The pathomechanisms for chronic/recurrent dermatophytic infections are not well understood. The chronicity could be secondary to host, agent, environmental, or pharmacologic factors. Dermatophytic infections are predominant in the tropical and subtropical developing countries such as India where the hot and humid weather is favorable for the acquisition and maintenance of the disease. Dermatophytes are host-specific and this is due to the difference in the composition of keratin in host. About 90% of cases of chronic dermatophytosis have been attributed to *Trichophyton rubrum* infection.[2] Widespread *T. rubrum* dermatophytosis has often been described as *T. rubrum* syndrome, generalized chronically persistent rubrophytia, and tinea corporis generalisata. *T. rubrum* syndrome is characterized by involvement of at least four body sites such as feet (plantar), hands (palmar), nails as well as one another site with the exclusion of inguinal area with microscopic fungal detection from all four sites, and positive culture from at least three of the four sites.[3]

T. rubrum is a resilient fungus with ubiquitous presence. It is also equipped with an arsenal of factors that allows it to evade the host immune system. It survives off the body as a spore untill it finds a warm, moist area of skin, which it readily colonizes.[4] Invasion of the epidermis by dermatophytes starts with adherence between arthroconidia and keratinocytes, followed by penetration and growth. Arthroconidia adheres to the keratinized tissue and germinates producing hyphae that expand radially in multiple directions.[5] Spores must germinate and penetrate the stratum corneum at a rate faster than desquamation. This is achieved by several fungal proteases which aids in rapid expansion of the dermatophytes.[5] The dermatophytic clearance from the skin is secondary to the activation of cell-mediated immunity (CMI) and is Th1/Th17-dependent.[6] It is of interest to note that acute dermatophytosis is associated with Th1 response, whereas in cases of chronic dermatophytosis, the immunity is skewed toward Th2 cytokines with high levels of IgE and IgG4 antibodies.[5] One could propose that individuals with defective tilt of immunity toward Th2 cytokines would be more predisposed to chronic dermatophytic infection. This could also explain the increased predisposition to dermatophytosis seen in atopic population.[7,8] The exact mechanism involved in this defective shift of immunity and selective absence of CMI with respect to dermatophytosis is not well understood. Macrophages and neutrophils migrate in response to dermatophytic invasion of skin and these are capable of phagocytizing and killing the fungi in normal individuals. In patients who suffer from chronic dermatophytosis, defective phagocytosis of the fungal hyphae is observed.[6] Mannans produced by *T. rubrum* work by inhibiting the critical steps in antigen processing and presentation.[4] The free radicals and nitric oxide release have been found to be 20–30% lower than that of controls in patients of chronic dermatophytosis, indicating a defective killing mechanism as well.[6] The cellular milieu has decreased inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α, and increased anti-inflammatory cytokines such as IL-10.[6] The down-regulation of toll-like receptor 4 by *T. rubrum* further decreases the inflammatory response by decreasing pro-inflammatory cytokine production and recruitment of neutrophils.[9] The combination of ineffective phagocytosis and killing of the hyphae in the presence of anti-inflammatory milieu deviates the immunity from Th1 response to Th2 and leads to chronicity. CARD9 gene mutation, which is involved in the regulation of multiple downstream pathways having anti-fungal response, is known to be associated with severe fungal infections of varied clinical presentations ranging from candidal meningitis to recurrent dermatophytic infection of skin and nails.[10]

Patients with immuno-compromised status, diabetes mellitus, atopy, and intake of systemic corticosteroids are also predisposed to chronic dermatophytosis.[1] Diabetic patients are more likely

to develop onychomycosis after having tinea pedis.[11] There is an increased prevalence associated with the disorders of keratinization such as ichthyosis vulgaris where retained keratin often acts as a nidus for infection.[7] The differences in the incidence of superficial infections between the age groups and sexes reflect the differing rates of sebum production and fluctuations of immunity with aging. Ethnic susceptibility has also been noted, eseially in tinea capitis.[12] Recurrent dermatophytosis was more frequent in low socio-economic group, and tinea corporis and cruris were found to be the most common clinical forms associated with chronicity.[13] Further research is awaited to fully understand the pathomechanisms of the persistence of dermatophytic infections in certain patient population.

Over the past few years, antifungal resistance has emerged due to irrational use of antifungal agents in cutaneous mycoses. Studies around the world are noticing an increasing rise in resistance to common antifungal drugs used for the treatment of dermatophytic infections.[14-17] Antifungal resistance can be defined as microbiologic or clinical resistance or as a composite of the two. Microbiologic resistance refers to nonsusceptibility of a fungus to an antifungal agent by *in vitro* susceptibility testing, in which the minimum inhibitory concentrations (MICs) of the drugs exceed the susceptibility breakpoint for that organism. Primary resistance is found naturally among certain fungi without prior exposure. Secondary resistance develops among previously susceptible strains after exposure to the antifungal agent and is usually dependent on altered gene expression. Both primary and secondary resistance to antifungal agents have been observed.[18,19] However, it is interesting to note that though there are several instances of clinical resistance, microbiologically proven resistance is demonstrated sparingly.[14]

Clinical resistance has been defined as the persistence or progression of an infection despite appropriate antimicrobial therapy. In other words, it is the failure to eradicate a fungal infection despite the administration of an antifungal agent with *in vitro* activity against the organism. Such failures can be attributed to incorrect diagnosis, immunosuppression, and suboptimal dose or duration of therapy. A successful clinical response to antimicrobial therapy depends not only on the susceptibility of the pathogenic organism, but also relies on the host immune system, drug penetration and distribution, patient compliance, and absence of a protected or persistent focus of infection.[20,21] Re-infection from the contacts or fomites may also be a contributing factor, as majority of patients with chronic/recurrent dermatophytosis have multiple affected family members. Overcrowding, sharing of clothes and footwear, poor hygiene, tight clothes, and migrants are also some predisposing factors in Indian scenario.

In vivo resistance is also correlated with antifungal misuse because patients often fail to complete the full course of treatment. Thus, the inadequate use or dosage of drugs contributes to the failure in eliminating the disease agent completely, encouraging growth of the most resistant strains, which may lead to hard-to-treat fungal infections. Even considering a low frequency of gene mutation, the selective pressure exerted by the constant use of antifungal agents eventually selects a resistant strain that will become predominant in the population. This has been further substantiated in an interesting study done by Hryncewicz-Gwózdz *et al*. from Poland.[22] The study demonstrated that *T. rubrum* develops resistance on prolonged exposure to itraconazole and fluconazole. In addition, cross resistance between both the azoles has been observed in the same study.[22] Various biochemical mechanisms contribute to the phenotype of drug resistance in fungi. The most frequent ones involve a decrease in drug uptake, structural alterations in the target site, and an increase in drug efflux or combination of these in intracellular target levels. The over-expression of the drug efflux pump transporters *Tru*MDR1 and *Tru*MDR2 has been seen in the dermatophytes in the presence of azoles and this might contribute to drug resistance.[22] From a molecular viewpoint, these biochemical changes can result from gene amplification, gene transfer, gene deletion, point mutations, loss of cis- and trans-acting regulatory elements, and transcriptional activation.[23] Another mechanism of resistance has been attributed to biofilm production by the dermatophytes. Both *T. rubrum* and *T. mentagrophytes* have been demonstrated to produce biofilms. Biofilms are known to confer resistance to both antimicrobial agents and host immunity. Hence, the antifungal resistance and recurrence of dermatophytes, along with the necessity for prolonged and high dose therapy could be attributed to the biofilms produced by this organisms.[24]

A study from North India showed that there were nonresponders to gold standard drug griseofulvin among the tinea capitis patients.[25] In 2002, Mukherjee *et al*. found a *T. rubrum* strain exhibiting primary resistance to terbinafine.[14] This resistance was attributed to a single missense amino acid substitution at L398F. This missense substitution made the *T. rubrum* resistant to all antifungals that act on squalene epoxidase enzyme.[15] In a study of 100 isolates of onychomycosis, Sarifakioglu *et al*. found itraconazole and fluconazole having the greatest variation in MIC for itraconazole and fluconazole.[17] Azambuja *et al*. found high MIC values for fluconazole and itraconazole (66.7% and 25%, respectively) in 100 isolates of *T. rubrum* from patients with onychomycosis.[16]

What has led to such a catastrophic situation in the Indian scenario is a hot topic of epidemiological and clinical research. Some predisposing factors particularly relevant to India are wide over-the-counter (OTC) availability and rampant use of topical steroid and antifungal combinations by the patients themselves or unrestricted prescription of

these products by quacks and general practitioners. Topical and oral antifungals in suboptimum and irrational regimens are the most often misused medications in India, which are prescribed by various medical specialists who tend to label a majority of skin lesions as "fungal infections." The availability of such medications OTC is adding to the current situation. Cost of these medications may also be a factor for nonadherence or poor compliance. Topical antifungal creams are generally available as 10–15 g which may not last 2–3 weeks and they are expensive as compared to cheaper OTC available formulations (steroid-containing combinations) which give quick relief, but with time make the disease worse and unresponsive to standard antifungals. Taking commercial cognizance of the rapidly increasing problem of chronic/recurrent dermatophyte infections, almost every other pharmaceutical company in India has started manufacturing itraconazole and terbinafine. Unfortunately we do not have any precise bioavailability studies for most of these formulations.

Dermatologists are perplexed by such complex behavior of dermatophyte infections. Many postgraduate thesis dissertations and research projects on chronic/recurrent dermatophytosis are underway at many centers in India. In almost all major regional and national conferences in India, a dedicated session is being devoted on chronic/recurrent dermatophyte infections. We will not be surprised if in near future a theme-based conference happens exclusively to discuss the intricacies of the ongoing menace. Tinea corporis and tinea cruris, once considered to be easy to manage skin conditions, are gradually becoming a dermatologist's nightmare. Patients with chronic/recurrent dermatophytosis are posing treatment challenges similar to the one observed with chronic dermatoses like psoriasis, vitiligo, and pemphigus. There are no consensus guidelines for the management of these cases; dermatologists are using a combination of oral antifungals, higher doses of antifungals, longer duration of treatment, and even retinoids for the management of these recalcitrant tinea cases, but it is more of hit and trial rather than evidence-based approach. Well-designed studies comparing different antifungals which could elucidate the most effective drug as well as dose and duration of therapy.

It has been a well-observed phenomenon among dermatologists irrespective of their place of work, be it institution or clinic-based practice that the burden of such difficulty to treat dermatophytosis is growing in India. It is a pertinent need of the hour to increase our understanding on the molecular mechanisms of antifungal drug resistance and the genetic and host factors that make us more susceptible to recurrent dermatophytosis. In times ahead, we look forward more academic exploration into this menace for the benefit of the patients and the dermatologist.

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