Chapter

1

Introduction to Fungal Infections: Focus on Dermatophytoses

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Among the 50,000 to 2,50,000 species of fungi that have been described, fewer than 500 have been associated with human disease, and no more than 100 are capable of causing infection in otherwise normal individuals. The remainder is only able to produce disease in hosts that are debilitated or immunocompromised in some way. In general these organisms are free living in nature and are in no way dependent on humans (or animals) for their survival. With a few exceptions, fungal infections of humans originate from an exogenous source in the environment and are acquired through inhalation, ingestion or traumatic implantation.

CLASSIFICATION

Fungi are conventionally classified as superficial, deep and systemic infections. In recent years, fungal infections have been grouped according to their clinical presentation, subdividing them into superficial, subcutaneous, systemic, and opportunistic mycoses. The term "deep" is sometimes used as synonymous for systemic, and at other times, it is used to describe subcutaneous and systemic disease. To clear this it is useful to classify subcutaneous mycoses as mycotic infections that mainly involve subcutaneous tissue, even though they can occasionally spread to other sites because of disseminated or systemic infection.

SUPERFICIAL MYCOSIS

The superficial mycoses are infections limited to the outermost layers of the skin, the nails and hair, and the mucous membranes (Table 1.1). The principal infections in this group are the dermatophytoses and superficial forms of candidiasis. The dermatophytes are limited to the keratinized tissues of the epidermis, hair and nail. Most are unable to survive as free-living saprobes in competition with other keratinophilic organisms in the environment and thus are dependent on passage from host to host for their survival. These obligate pathogens seem to have evolved from unspecialized saprobic forms. In the process, most are now no longer capable of sexual, and some even asexual, reproduction. In general, these organisms have become well adapted to humans, evoking a little or no inflammatory reaction from the host.

Table 1.1: Superficial cutaneous mycoses*

Disease	*Causative agent*
Tinea (pityriasis) versicolor, seborrheic dermatitis, including dandruff and *Malassezia* folliculitis	*Malassezia* spp (a lipophilic yeast)
Tinea nigra	*Exophiala werneckii*
White piedra**	*Trichosporon asahii*
Black piedra	*Piedraia hortae*
Dermatophytosis, ringworm of the scalp, glabrous skin, and nails	Dermatophytes (*Microsporum, Trichophyton, Epidermophyton*)
Candidiasis of skin, mucous membranes and nails	*Candida albicans* and related species
Dermatomycosis	Nondermatophyte moulds, *Hendersonula toruloidea, Scytalidium hyalinum, Scopulariopsis brevicaulis*

*Arenas R, *et al.*
**White piedra caused by *T. ovoides* earlier called beigelii.

The etiological agents of candidosis, like the dermatophytes, are largely dependent on the living host for their survival, but differ from them in the manner by which this is achieved. These organisms, of which *Candida albicans* is the most important, are normal commensal inhabitants of the human digestive tract or skin. Acquisition of these organisms from another host seldom results in overt disease, but rather in the setting up of a commensal relationship with the new host. These organisms do not produce disease unless some change in the circumstances of the host lowers its natural defences. In this situation, endogenous infection from the host's own reservoir of the organism may result in mucosal, cutaneous or systemic infection.

SUBCUTANEOUS MYCOSES

Subcutaneous mycoses, previously known as deep mycosis, belong to a group of infections acquired from ubiquitous saprophyte fungi that affect the skin and subcutaneous tissue (Table 1.2). These infections are usually acquired as a result of the traumatic implantation of organisms that grow as saprobes in the soil and on decomposing vegetation. These infections are most frequently encountered among the rural populations of the tropical and subtropical regions of the world, where individuals go barefoot and wear the minimum of clothing. The disease may remain localized at the site of implantation or spread to adjacent tissue. More widespread dissemination of the infection, through the blood or lymphatics, is uncommon, and usually occurs only if the host is in some way debilitated or immuno-compromised.

Chromoblastomycosis, sporotrichosis, and eumycetoma are more common. Lobomycosis and conidiobolomycosis (entomophthoromycosis) are rare and have a low association with immunosuppression, even though these fungi are considered to have low virulence.

Table 1.2: Clinical classification of subcutaneous and systemic mycoses*

Disease	*Causative agent*
Subcutaneous mycoses	
Sporotrichosis	*Sporothris complex*
Chromoblastomycosis	*Fonsecaea, Phialophora, Cladosporium*
Phaeohyphomycosis	*Cladosporium, Exophiala, Wangiella, Bipolaris, Exserohilum, Curvularia*
Eumycetoma	Genera *Madurella, Acremonium, Exophiala, Scedosporium* spp.
Subcutaneous zygomycosis (entomophthoromycosis)	*Basidiobolus ranarum* *Conidiobolus coronatus*
Subcutaneous zygomycosis (mucormycosis)	Genera *Rhizopus, Mucor, Rhizomucor, Mycocladus, Saksenaea*
Lobomycosis	*Lacazia loboi*
Dimorphic systemic mycoses	
Histoplasmosis	*Histoplasma capsulatum, Histoplasma capsulatum* var *duboisii*
Coccidioidomycosis	*Coccidioides immitis,* *Coccidioides posadasii*
Blastomycosis	*Blastomyces dermatitidis*
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
Opportunistic systemic mycoses	
Candidiasis	*Candida albicans* and related spp.
Cryptococcosis	*Cryptococcus neoformans* (var *neoformans*, var *gattii*)
Aspergillosis	*Aspergillus fumigatus*, other spp.
Pseudallescheriasis	Genera Scedosporium (*Pseudollescheria boydii*)
Zygomycosis (mucormycosis)	Genera *Rhizopus, Mucor, Rhizomucor, Mycocladus*
Fusariosis	*Fusarium* spp.
Penicilliosis	*Penicillium marneffei*
Trichosporonosis	*Trichosporon* spp.
Hyalohyphomycosis	Genera *Penicillium, Paecilomyces, Beauveria, Fusarium, Scopulariopsis*
Phaeohyphomycosis	Genera *Cladosporium, Exophiala, Wangiella, Bipolaris, Exserohilum, Curvularia*

*Arenas R, *et al.*

SYSTEMIC MYCOSES

These are infections that usually originate in the lungs (Table 1.2), but may spread to many other organs. These infections are most commonly acquired as a result of inhaling spores of organisms that grow as saprobes in the soil or on decomposing organic matter, or as pathogens on plants. The main organisms causing them are depicted in Fig. 1.1. The organisms that cause systemic fungal infection can be divided into two distinct groups: The true pathogens and the opportunists. The first of these groups consists of

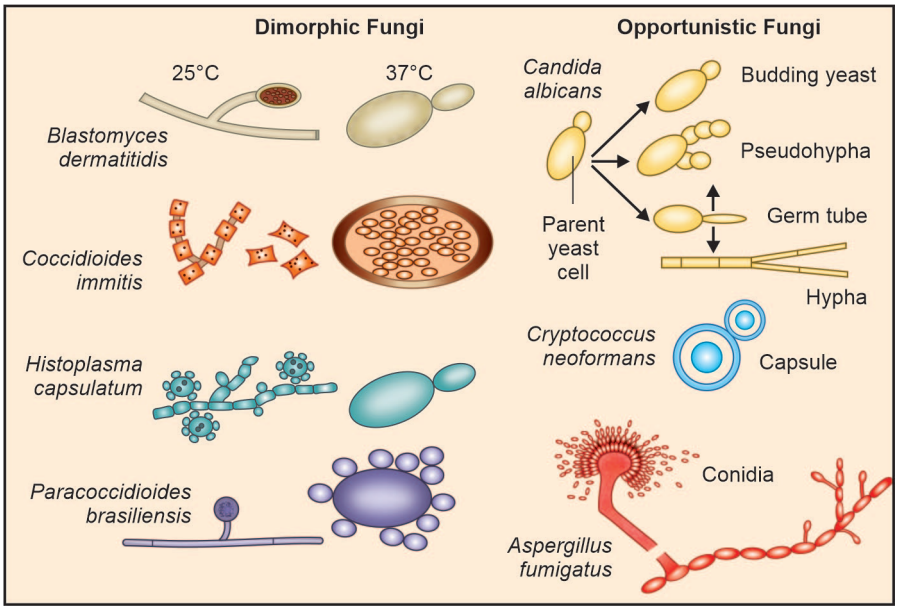

Fig. 1.1: A diagrammatic depiction of common organisms causing systemic fungal infections

a handful of organisms such as *Histoplasma capsulatum* and *Coccidioides immitis*, that are able to invade and develop in the tissues of a normal host with no recognizable predisposition. Often these organisms possess unique morphological features that appear to contribute to their survival within the host. The second group, the opportunists, consists of less virulent and less well-adapted organisms, such as *Aspergillus fumigatus*, that are only able to invade the tissues of an immunocompromised host.

In many instances, infections with true pathogenic fungi are asymptomatic or mild and of short duration. Most cases occur in geographical regions where the aetiological agents are found in nature and follow inhalation of spores that have been released into the environment. The host must encounter the fungus while sporulation occurs. After this, the fungi exhibit a morphologic transition from the mycelial (saprophytic) form to the parasitic form found in infected tissues. This transformation is determined by the temperature of incubation (called thermal dimorphism), which is seen in most fungi that cause systemic infections. Individuals who recover from these infections enjoy marked and lasting resistance to reinfection, while the few patients with chronic or residual disease often have a serious underlying illness. In addition to their well-recognized manifestations in otherwise normal persons, infections with true pathogenic fungi have emerged as important diseases in immunocompromised individuals. Histoplasmosis and coccidioidomycosis, for instance, have been recognized as AIDS-defining illnesses. Both have been seen in significant numbers of human immunodeficiency virus (HIV)-infected persons.

Opportunistic fungal infections occur in individuals who are immunosuppressed as a result of an underlying illness or treatment. In most cases, infection results in significant disease. Resolution of the infection does not confer protection, and reinfection or reactivation may occur if host resistance is again lowered. In contrast to

the restricted geographical distribution of most of the true pathogenic fungi, many opportunistic fungi are ubiquitous in the environment worldwide, being found in the soil, on decomposing organic matter and in the air. Although new species of fungi are regularly being identified as causes of disease in immunocompromised patients, four diseases still account for most reported infections: Aspergillosis, candidosis, cryptococcosis and mucormycosis. Others include infections due to *Penicillium marneffei*, *Trichosporon* spp., and Fusarium spp. The fungi in this group include moulds and yeasts that are characteristically not dimorphic. These infections are associated with high mortality rates, but estimates of their incidence are thought to be quite conservative in comparison with their true magnitude because many cases go undiagnosed or unreported.

THE CHANGING PATTERN OF FUNGAL INFECTION

Over the past few years, major advances in health care have led to an unwelcome increase in the number of life-threatening infections due to true pathogenic and opportunistic fungi. Population at risk includes persons with HIV infection, transplant recipients, cancer patients and other individuals receiving immunosuppressive treatment.

In addition to the rise in prevalence of opportunistic fungal infections due to such well-recognized organisms as *A. fumigatus* and *C. albicans*, an everincreasing number of fungi, hitherto regarded as harmless saprobes, are being reported as the cause of serious or lethal infection in immunocompromised individuals. For instance, *Fusarium* species. The emergence of these organisms as significant pathogens has important implications for diagnosis and management, not only because the clinical presentation can mimic a more common disease, aspergillosis, but also because the organisms are usually resistant to amphotericin B, the drug of choice for empirical treatment of suspected fungal infections in febrile neutropenic patients.

DERMATOPHYTOSIS: A RECALCITRANT "EPIDEMIC"

Although dermatophytes are found throughout the world, the most prevalent strains and the most common sites of infection vary by region. Countries like India with their hot and humid climates and overcrowding predispose populations to skin diseases, including tinea infections.

Dermatophyte diseases recur at a high rate following treatment with an antifungal [Gupta AK, Cooper EA (2008)]. It is currently unknown whether this is due to insufficient clearing of the fungus during treatment and reemergence of disease, and thus an example of relapse, or if these represent new infections (Fig. 1.2).

Is it drug-resistant dermatophytes? Surprisingly, drug resistance among dermatophytes is rare. Two large clinical studies looking at drug susceptibility in dermatophytes did not find significant increases in the minimum inhibitory concentration of several antifungal drugs used to treat dermatophytes [Ghannoum M, et al.]. Cases of drug resistance have been documented, in the last few years from India specially to terbinafine.

Issues with dermatophytes research: Despite the prevalence of dermatophyte infections worldwide, a sophisticated understanding of how they cause disease is lacking [White TC]. The historic difficulties in working with dermatophytes have been

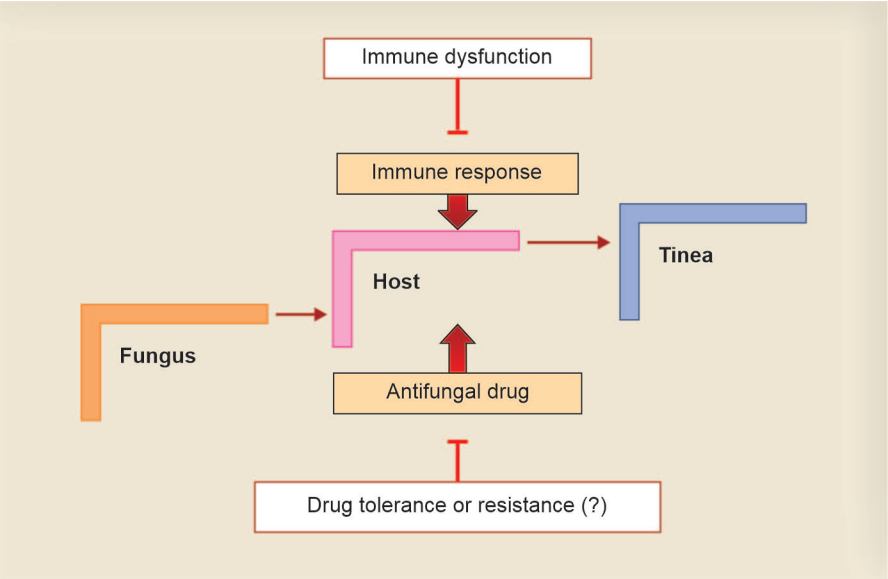

Fig. 1.2: A depiction of the role of host immunity and antifungal drug in the causation of tinea infection

twofold: technical difficulties due to poor virulence models and a lack of genetic tools, and an under-appreciation of the need to study these organisms.

Another reason is that many mycologists do not consider dermatophytes as important as other infectious diseases. Therefore, there are a limited number of researchers working on it, our own work has found resistance, with high MIC, to terbinafine. Surprisingly itraconazole should work consistently but there are cases of failure which might be due to quality issues with the pellet technology.

A deeper understanding of the pathogenesis (*see* Chapter 2) can make one appreciate that it is the host factors and particularly the fungi-immune interaction that can explain the recalcitrant dermatophyte infection in our country.

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