Medical Mycology

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Introduction

Mycology is the study of fungi, which are eukaryotic organisms that evolved in tandem with the animal kingdom However, unlike animals, most fungi are non motile and possess a rigid cell wall. Unlike plants, fungi are nonphotosynthetic Approximately 80,000 species of fungi have been described, but fewer than 400 are medically important, and less than 50 species cause more than 90% of the fungal infections of humans and other animals. Rather, most species of fungi are beneficial to humankind. They reside in nature and are essential in breaking down and recycling organic matter Some fungi greatly enhance our quality of life by contributing to the production of food and spirits, including cheese bread, and beer. Other fungi have served medicine by providing useful bioactive secondary metabolites such as antibiotics g, penicillin) .and immunosuppressive drugs (eg, cyclosporine)

Fungi have been exploited by geneticists and molecular biologists as model systems for the investigation of a variet y of eukaryotic processes, including molecular and cellular biology and development. Overall, fungi exert their greatest economic impact as phytopathogens; the agricultural industry sustains huge crop losses every year as a result of fungal diseases of rice, corn, grains, and other plants Like all eukaryotes, each fungal cell has at least one nucleus with a nuclear membrane, and secretory apparatus. Most ،endoplasmic reticulum, mitochondria fungi are obligate or facultative aerobes. They are chemotrophic, secreting enzymes that degrade a wide variety of organic substrates into soluble nutrients which are then passively absorbed or taken into the cell by active transport Fungal infections are mycoses .

Most pathogenic fungi are exogenous, their natural habitats being water, soil, and organic debris. The mycoses with the highest incidence candidiasis and dermatophytosis—are caused by fungi that are part of the normal human microbiotal and highly adapted to survival on the human host. For convenience, mycoses may be classified as superficial, cutaneous, subcutaneous, or systemic, invading the internal organs (Table- 1). The systemic mycoses may be caused by endemic fungi, which are usually primary pathogens, or by ubiquitous, oft en secondary opportunistic pathogens. Grouping mycoses in these categories reflects their most common portal of entry and initial site of involvement. However, there is considerable over lap since systemic mycoses oft en exhibit subcutaneous manifestations and vice versa. Most patients who develop opportunistic infections have serious underlying diseases and compromised host defenses. But primary systemic mycoses also occur in such patients, and the opportunists oft en infect immune competent individuals. During infection, most patients develop significant cellular and humoral immune responses to the fungal antigens .As medical advances have significantly prolonged the survival of patients with cancer, AIDS, and hematopoietic stem cell or solid organ transplants, the incidence of opportunistic mycoses has increased dramatically. Pathogenic fungi do not produce potent toxins, and the mechanisms of fungal pathogenicity are complex and polygenic. Most mycoses are difficult As medical advances have significantly prolonged the survival of patients with cancer, AIDS, and hematopoietic stem cell or solid organ transplants, the incidence of opportunistic mycoses has increased dramatically. Pathogenic fungi do not produce potent toxins, and the mechanisms of fungal pathogenicity are complex and polygenic. Most mycoses are difficult to treat.

Because fungi are eukaryotes they share numerous homologous genes, gene products, and pathways with their human hosts Consequently, there are few unique targets for chemotherapy and effective antibiotics. Fortunately, there is growing interest in medically significant fungi and in the search for virulence factors and potential therapeutic targets.

GENERAL PROPERTIES AND CLASSIFICATION OF FUNGI

Fungi grow in two basic forms, as yeasts and molds (or moulds). Growth in the mold form occurs by the production to treat. Because fungi are eukaryotes, they share numerous homologous genes, gene products, and pathways with their human hosts. Consequently, there are few unique targets for chemotherapy and effective antibiotics. Fortunately, there is growing interest in medically significant fungi and in the search for virulence factors and potential therapeutic targets of multicellular filamentous colonies. These colonies consist of branching cylindrical tubules called hyphae, varying in diameter from 2 to 10 µm. The mass of .intertwined hyphae that accumulates during active growth is a ycelium

Some hyphae are divided into cells by cross-walls or septa, which typically form at regular intervals during hyphal growth. However, members of the Order Mucor less produce hyphae that are rarely septated. Vegetative or substrate hyphae penetrate the supporting medium, anchor the colony, and absorb nutrients. In contrast, aerial hyphae project above the surface of the mycelium and usually bear the reproductive structures of the mold. When a mold is isolated from a clinical specimen, its growth rate, macroscopic appearance, and microscopic morphology are usually sufficient to determine its genus and species. The most helpful phenotypic features are the ontogeny and morphology of the asexual reproductive spores, or conidia. Yeasts are single cells, usually spherical to ellipsoid in shape and varying in diameter from 3 to 15 µm. Most yeasts reproduce by budding. Some species produce buds that characteristically fail to detach and become elongated continuation of the budding process then produces a chain of elongated yeast cells called pseudohyphae.

Yeast colonies are usually soft, opaque, 1–3 mm in size, and cream-colored Because the colonies and microscopic morphology of any yeasts are quite similar, yeast species are identified on the basis of physiologic tests and a few key morphologic differences Some species of fungi are dimorphic and capable of growth as a yeast or mold depending on environmental conditions Fungi have an essential rigid cell wall that determines their shape and protects them from osmotic and

environmental stress. Cell walls are composed largely of carbohydrate layers—long chains of polysaccharides—as well as glycoproteins and lipids. Some sugar polymers are found in the cell walls of many fungi, such as chitin (an unbranched polymer of β-1,4-linked N-acetylglucosamine); glucans, which are glucose polymers (eg, β-1,3-glucan and β-1,6-glucan); and mannans, polymers of mannose (eg, α-1,6-mannose). In addition other polysaccharides may be unique to specific fungal species. During infection, fungal cell walls exert important pathobiologic properties. The surface components of the cell wall mediate attachment of the fungus to host cells. Specific fungal cell wall moieties bind to pattern recognition receptors on host cell membranes, such as certain toll-like receptors to stimulate innate immune responses. Cell wall glucans and other polysaccharides may activate the complement cascade and provoke an inflammatory reaction. Most of these polysaccharides are poorly degraded by the host and can be detected with special histologic stains. Cell walls also release immunodominant antigens that may elicit cellular immune responses and diagnostic antibodies. In addition, some yeasts and molds have melanized cell walls, which impart a brown or black pigment to the fungal colony. Such fungi are dematiaceous Several studies have shown that melanin protects these fungi from host defenses and is associated with virulence .The life cycles of fungi are remarkably versatile. Depending on the fungal species, the predominant nuclear chromosomal count may be haploid or diploid. Some species exist entirely by clonal growth or asexual reproduction, and barring spontaneous mutations, every cell will be a genetic clone.

Other species are capable of sexual reproduction, which may or may not require genetically different partners for mating and meiosis. Asexual as well as sexual reproduction can result in the production of spores, which enhance fungal survival. Spores are usually dormant, readily dispersed, more resistant to adverse conditions, and germinate to form vegetative cells when conditions for growth are favorable. Spores derived from asexual or sexual reproduction are termed anamorphic or teleomorphic

states, respectively. Like vegetative cells, asexual spores are mitotic progeny (ie, mitospores). The medical fungi produce two major types of

asexual spores, conidia, which are produced by most pathogenic fungi, and, in the Order Mucorales sporangiospores (see below and Glossary). Informative features of spores include their ontogeny (some molds produce complex conidiogenic structures) as well as their morphology

In some fungi, vegetative cells may transform into conidia (eg arthroconidia, chlamydospores). In others, conidia are produced

by a conidiogenous cell, such as a phialide, which itself may be attached to a specialized hypha called a conidiophore Sporangiospores result from mitotic replication and spore production within a sac-like structure .called a sporangium, which is supported by a sporangiophore

Taxonomy

Earlier classifications of fungi into phyla were based largely on henotypic data, and this approach has been supplanted by molecular systematics, which more accurately reflect phylogenetic relationships, At the basal level, there is some ambiguity about the divergence of fungi and animals

and their extant ancesters. The lower fungi were assigned to the Phylum Zygomycota, but this phylum, which was shown to be polyphyletic, has been replaced by the Phylum Glomerulomycota and four subphyla, two of which contain the Orders of zoopathogenic molds, the Mucorales and

the Entomophthorales.However, the two largest phyla Ascomycota and Basidiomycota, are well supported by phylogenetic analyses. Phylum Ascomycota (or ascomycetes includes more than 60% of the known size, shape, texture, color, and unicellularity or) fungi and about 85% multi cellularity of the human pathogens.

-Basidiomycota (basidiomycete)

or the Order Mucorales of the Phylum GlomerulomycotaIn the diagnostic laboratory, the species of a clinical isolate can be identified by molecular or phenotypic methods (eg, signature DNA sequences, morphology of reproductive structures physiologic properties). Sexual reproduction may be helpful and typically occurs when mating-compatible strains of a species are stimulated by pheromones to

undergo plasmogamy, karyogamy nuclear fusion), and meiosis, resulting in the exchange of genetic information. Since clinical isolates almost always represent infection by a single clone, they reproduce asexually in the laboratory. Consequently, many pathogenic fungi were initially classified according to their asexual reproductive structures During the evolution to become successful pathogens, some fungi have apparently lost the ability to reproduce sexually. The following classification is highly abridged and only lists taxonomic groups that include major human pathogens A. Phylum Glomerulomycta, Order Mucorales Sexual reproduction results in a zygospore; asexual reproduction occurs via sporangia. Vegetative hyphae are sparsely septate Examples: Rhizopus, Lichtheimia, Mucor, CunninghamellaB.

Phylum scomycota(Ascomycetes)

Sexual reproduction involves a sac or ascus in which karyogamy

and meiosis occur, producing ascospores. Asexual reproduction is via conidia. Ascomycetous molds have septate hyphae. Examples: Most pathogenic yeasts (Saccharomyces Candida) and molds (Coccidioides, Blastomyces, Trichophyton

Phylum Basidiomycota (Basidomycetes)

Sexual reproduction results in dikaryotic hyphae and four progeny

basidiospores supported by a club-shaped basidium. Hyphae

have complex septa. Examples: Mushrooms, Cryptococcus.

GROWTH AND ISOLATION OF FUNG

Most fungi occur in nature and grow readily on simple sources of nitrogen and carbohydrate. The traditional mycological medium, Sabouraud's agar, which contains glucose and modified peptone (pH 7.0), has been used because it does not readily support the growth of bacteria. The morphologic characteristics of fungi used for identification have been described from growth on Sabouraud's agar. However,other media, such as inhibitory mold agar, have facilitated the recovery of fungi from clinical specimens. To culture medical fungi from non-sterile eg, gentamicin, chloramphenicol))specimens, antibacterial antibiotics and cycloheximide are added to the media to inhibit bacteria and saprobic molds respectively. The specimens used for isolation of fungi and other media used to isolate them.

Table 1 The Major Mycosis and Causative Fungi

Category	Mycosis	Causative Fungal Agents
Superficial	Pityriasis versicolor	*Malassezia* species
	Tinea nigra	*Hortaea werneckii*
	White piedra	*Trichosporon* species
	Black piedra	*Piedraia hortae*
Cutaneous	Dermatophytosis	*Microsporum* species, *Trichophyton* species, and *Epidermophyton floccosum*
	Candidiasis of skin, mucosa, or nails	*Candida albicans* and other *Candida* species
Subcutaneous	Sporotrichosis	*Sporothrix schenckii*
	Chromoblastomycosis	*Phialophora verrucosa, Fonsecaea pedrosoi,* and others
	Mycetoma	*Pseudallescheria boydii, Madurella mycetomatis,* and others
	Phaeohyphomycosis	*Exophiala, Bipolaris, Exserohilum,* and other dematiaceous molds
Endemic (primary, systemic)	Coccidioidomycosis	*Coccidioides posadasii* and *Coccidioides immitis*
	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatitidis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
Opportunistic	Systemic candidiasis	*Candida albicans* and many other *Candida* species
	Cryptococcosis	*Cryptococcus neoformans* and *Cryptococcus gattii*
	Aspergillosis	*Aspergillus fumigatus* and other *Aspergillus* species
	Hyalohyphomycosis	Species of *Fusarium, Paecilomyces, Trichosporon,* and other hyaline molds
	Phaeohyphomycosis	*Cladophialophora bantiana;* species of *Alternaria, Cladosporium, Bipolaris, Exserohilum* and numerous other dematiaceous molds
	Mucormycosis (zygomycosis)	Species of *Rhizopus, Lichtheimia, Cunninghamella,* and other zygomycetes
	Pneumocystis pneumonia	*Pneumocystis jiroveci*
	Penicilliosis	*Penicillium marneffei*

SUPERFICIAL MYCOSES

Pityriasis Versicolor

Pityriasis versicolor is a chronic mild superficial infection of the stratum corneum caused by Malassezia globosa, Malassezia restricta, and other members of the Malassezia furfur complex Invasion of the cornified skin and the host responses are both minimal. Discrete, serpentine, hyper-, or hypopigmented maculae occur on the skin, usually on the chest, upper back, arms or abdomen. The lesions are chronic and occur as macular patches of discolored skin that may enlarge and coalesce, but

scaling, inflammation, and irritation are minimal. Indeed, this common affliction is largely a cosmetic problem Malassezia species are lipophilic yeasts, and most require lipid in the medium for growth.

The diagnosis is confirmed by direct microscopic examination of scrapings of infected skin treated with 10–20% potassium hydroxide (KOH) or stained with calcofluor white. Short unbranched hyphae and spherical cells are observed. The lesions also fluoresce under Wood's lamp. Pityriasis versicolor is treated with daily applications of selenium sulfide. Topical or oral azoles are also effective Rarely, Malassezia may cause an opportunistic fungemia in patients—usually infants—receiving total parenteral nutrition as a result of contamination of the lipid .emulsion

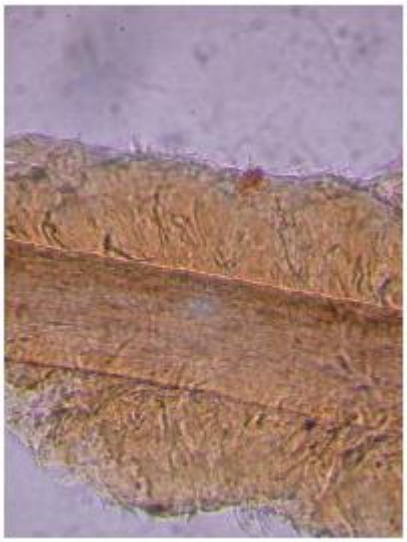
In most cases, the fungemia is transient and corrected byreplacing the fluid and intravenous catheter. Some individuals develop folliculitis due to Malassezia. Species of Malassezia are considered part of the cutaneous microbiota and can be isolated from normal skin and scalp. They have been implicated as a cause of or contributor to seborrheic dermatitis, or dandruff. This hypothesis is supported by the observation that many cases are alleviated by treatment with ketoconazole.

Tinea Nigra

Tinea nigra (or tinea nigra palmaris) is a superficial chronic and asymptomatic infection of the stratum corneum caused by the dematiaceous fungus Hortaea **(Exophiala) werneckii** This condition is more prevalent in warm coastal regions and among young women. The lesions appear as a dark (brown to black) discoloration, often on the palm. Microscopic examination of skin scrapings from the periphery of the lesion will reveal branched, septate hyphae and budding yeast cells with melanized cell walls. Tinea nigra will respond to treatment with keratolytic solutions, salicylic acid, or azole antifungal drugs.

Piedra

Black piedra is a nodular infection of the hair shaft caused by Piedraia hortae Fig. 1-A . White piedra, due to infection with **Trichosporon** species, presents as larger, softer, yellowish nodules on the hairs Fig 1 - B. Axillary, pubic, beard, and scalp hair may be infected. Treatment for both types consists of removal of the infected hair and application of a topical antifungal agent. Piedra is endemic in tropical countries.



A

B

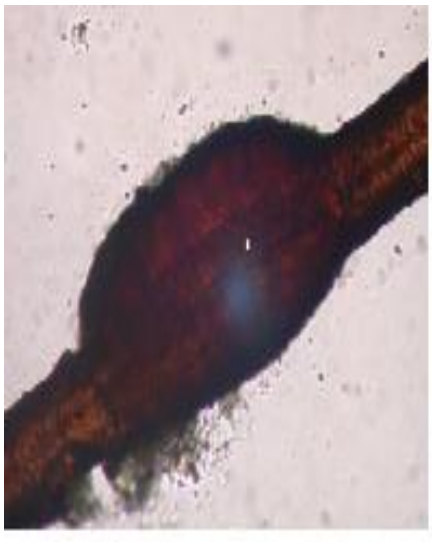


Fig -1 : Piedra. A: White piedra hair with nodule due to growth of Trichosporon.

B: Black piedra hair with a hard, black nodule, caused by growth of the dematiaceous mold, **Piedraia hortae.**