PATHOLOGY OF FUNGAL INFECTION

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COLONIZATION AND DISEASES

• There are over 100,000 fungal species
• About 150 species are pathogenic of human
• Most of mycoses are contacted by exposure to environmental sources.
• A few, such as actinomycosis and candidiasis, are endogenous.
Ability of fungi to cause disease depends on

- Virulence
- Dose
- Route of infection
- Immunologic status of the host
IMMUNOCOMPROMISED HOSTS

- Chemotherapy
- Irradiation
- Immunosuppressive agents
- Hyperalimentation
- Broad-spectrum antibiotics
- Malignancies
- Burns
- Organ transplants
- Mucosal disruption

- Metabolic diseases
- Malnutrition
- Immune deficiency syndrome
- Abdominal, cardiac surgery
- Repeated intravenous injection
- Hematologic dysfunction
- Reduction of flora
- Immigration
Category of fungal colonization and disease development

• Most fungal infections are mild and self-infection caused by fungi that primarily colonize the superficial and subcutaneous layers of skin.
  • Superficial mycoses
  • Cutaneous mycosis
  • Subcutaneous mycoses

• Mucosal surfaces discourage colonization by organisms that cause pulmonary infections and spread to many organ systems.
  • Systemic mycoses
SUPERFICIAL MYCOSES

• The superficial mycoses is limited to keratinized tissues of the epidermis, hair, and nails.

• Superficial fungal infections may be passed from:
  • Person to person (anthropophilic)
  • Animal to humans (zoophilic)
  • Soil to humans (geophilic)
SUPERFICIAL MYCOSES

• The main superficial mycoses are the dermatophyte infections, tinea versicolor, and superficial candidiasis.

• Rare superficial infections include tinea nigra, and black or white piedra.

• In some articles: tinea vericolor, nigra, piedra are superficial mycoses and dermatophytoses are cutaneous mycoses.
Pityriasis versicolor

- **Organism:** *Malassezia furfur*

Symptoms/Signs: hypo/hyperpigmented macules on skin surface
Pityriasis versicolor

ID: Spaghetti and meatballs appearance of organisms in skin scrapings
Dermatophytoses

- Known as ringworm or tinea
- Caused by a group of organisms capable of invading keratinized tissue such as stratum corneum, nail, or hair
- *Trichophyton, Microsporum, and Epidermophyton*
- The clinical features of dermatophyte infections are best considered in relation to the site involved.
Tinea Corporis
Synonym: body ringworm

• Dermatophytoses of glabrous (relatively hairless) skin, except the palms, soles, and groin
• Annular plaque with a raised edge and central clearing
• The classic presentation is an annular lesion with scale across the entire erythematous border.
• The border is often vesicular and advances centrifugally.
Tinea Cruris
Synonym: ringworm of the groin, “jock itch”

• Dermatophytosis of the groin, genitalia, pubic area, perineal, and perianal skin
Tinea Pedis

Synonym: Athlete's foot, ringworm of the foot

• The most common presentation of tinea pedis, the *chronic intertriginous type*, begins as scaling, erosion, and erythema of the interdigital and subdigital skin of the feet.

• Papulosquamous pattern ("moccasin-like")

• Vesicular or vesiculobullous tinea pedis
Tinea Capitis

Synonym: scalp ringworm

- Tinea capitis is the fungal infection of the scalp and associated hair due to dermatophytes.

- Overcrowding, poor hygiene and protein malnutrition favor the occurrence of this disease.

- *Trichophyton tonsurans* is responsible in most cases.

- Cases caused by *Microsporum canis* occur sporadically and are acquired from puppies and kittens.

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*Note that a single organism may have more than one presentation.*
Tinea Capitis

- Endothrix infection: sporulation is within the hair shaft, replacing the intrapilary keratin and leaving the cortex intact, scaling is less pronounced.
- The hair is very fragile and breaks at the surface of the scalp, leaving behind a tiny black dot.
Tinea Capitis

- Ectothrix infection: *M. canis* causes an ectothrix infection where spores form on the outside of the hair shaft in the perifollicular stratum corneum, spreading around and into the hair shaft before descending into the follicle to penetrate the cortex of the hair.
- The scalp hair breaks above the skin surface. Scaling, itching, and loss of hair occur.
Tinea favosa: is usually considered a variety of tinea capitis

- Favus is characterized by the occurrence of dense masses of mycelium and epithelial debris forming yellowish cup-shaped crusts called scutula.
- The scutulum develops at the surface of a hair follicle with the shaft in the center of the raised lesion.
- After a period of years, atrophy of the skin occurs leaving a cicatricial alopecia and scarring.
Tinea barbe
Synonym: Ringworm of the beard, tinea sycosis

- Colonization of the bearded areas of the face and neck, hence being restricted to adult males.
Onychomycosis

• Any infection of the nail caused by dermatophyte fungi, nondermatophyte fungi, or yeasts.

• *Tinea unguium* refers strictly to dermatophyte infection of the nail plate.
Onychomycosis

ANATOMY OF THE NAIL UNIT
Onychomycosis

- Distal subungual onychomycosis
  - Infection begins with invasion of the hyponychium
  - Onycholysis (separation of the nail plate from the nail bed) and thickening of subungual area
Onychomycosis

- White superficial onychomycosis
  - Infection begins at the superficial layer of the nail plate invading progressively deeper layers
  - Initially “white islands” are seen on the external nail plates
Onychomycosis

- Proximal subungual onychomycosis
  - Infection by invasion of the proximal nail fold → penetration into the newly forming nail plate
  - Subungual hyperkeratosis, leukonychia, proximal onycholysis, and destruction of the nail unit
Onychomycosis

- Total dystrophic onychomycosis
  - Hyphae are seen lying between the nail laminae with a predilection for the ventral nail and nail bed
PATTERNS OF FUNGAL NAIL DISEASE

Distal and lateral subungual onychomycosis
Infection confined to sides and distal end of nail; surface normal but brown discoloration

Superficial white onychomycosis
Infection on surface of nail plate; white appearance

Proximal subungual onychomycosis
Infection confined to the proximal end of nail

Total dystrophic onychomycosis
Infection of full thickness of the entire nail; nail appears thickened, crumbling, mis-shapen
Tinea nigra

- Rare superficial fungal infection, caused by *Hortaea werneckii*
- Tinea nigra palmaris and tinea nigra plantaris
- Central and South America, Africa, Asia, and North America
- Direct inoculation onto the skin from contact with decaying vegetation, wood, or soil
Tinea nigra

• Brown to black, well-defined border, nonscaly macules (resemble silver nitrate stain)
• Macule: unique or multiple, rounded or irregular shapes, size 1 mm-1.5 cm
Tinea nigra

• Histopathology
  • Hyperkeratosis
  • Separation of corneal layer by branched hyphae (1.5 - 5 µm in diameter); only in the stratum corneum
  • Dimorphic dematiaceous fungi, elongated budding cells, 3x10 µm, in clusters or along the length of dark hyphae
  • Inflammation is usually absent
Black piedra

- **Organism:** *Piedraia hortai*
- **Symptoms/Signs:** black nodule on hair
- **Black nodule on hair shaft composed of spore sacs and spores**
White piedra

• Organism: *Trichosporum beigelii*

• Symptoms/signs: cream-colored nodules on hair shaft

• Morphology: white nodule on hair shaft composed of mycelia that fragment into arthrospores
SUBCUTANEOUS MYCOSES

• Environmental sources such as soil or plant debris
• Infections caused by these organisms: traumatic injury
• Infections involving the dermis, subcutaneous tissues, muscle, and fascia, tend to be chronic
• Rarely spread systemically
Chromoblastomycosis

• Dematiaceous fungi
• *Fonsecaea pedrosoi* and *Cladosporium carrionii*
• Infection follows implantation through superficial injury.
• Nodular or verrucoid, ulcerated, or crusted skin lesions on exposed areas of skin, particularly on the lower extremities.
Chromoblastomycosis

- Hyperkeratous pseudoepitheliomatous hyperplasia and keratolytic microabscesses in the epidermis
Chromoblastomycosis

- The characteristic spherical or polyhedral, dark brown, thick-walled sclerotic bodies (muriform cells) often divided by a cross wall can be seen in skin scrapings or biopsy where they are found in neutrophil abscesses or giant cells.
Chromoblastomycosis

• Copper-colored spherical yeast called Medlar bodies (sclerotic bodies) in tissue
Mycetoma (Madura foot)

- Tumorous lesions of subcutaneous tissue and bone
- Caused by *Actinomycetes* and fungi producing granules
- Infection occurs after localized minor trauma on skin.
- Lymphohematogenous spreading rarely occurs.
Mycetoma (Madura foot)

- Divide to Eumycotic mycetoma and actinomycotic mycetoma
- Foot and leg are common sites of infection.
Mycetoma (Madura foot)

• Subcutaneous swelling → sinus tracts open on skin → grain with plasma oozing
• The infection is chronic and destroys the underlying structures.
• Local lymph node invasion may occur.
Mycetoma (Madura foot)

- Granule formation is typical.
- The granules are composed of hyaline, septate, branching hyphae.
- Chlamydoconidia may be formed.
- Granules are found in purulent foci surrounded by fibrosis and a mononuclear cell inflammatory response.
Mycetoma (Madura foot)

- **Histopathology**
  - Masses of aggregated hyphae (granules) in purulent foci surrounded by fibrosis and a mononuclear cell inflammatory response
Mycetoma (Madura foot)

- Splendore-Hoepli phenomenon
  - The deposition of amorphous, eosinophilic, hyaline material around pathogenic organisms, as the result of a local antigen-antibody reaction.
Sporotrichosis

- Dimorphic fungus; *Sporothrix schenckii*
- Tropical and subtropical region
- Isolated from soil, and plant debris such as thorns, timber, hay and straw
- Entry via an abrasion
Sporotrichosis

- Distal extremities
- The fixed type: solitary cutaneous ulcer or nodule
  - Raised, nodular, erythematous lesion
  - Vary in size from tiny punctate lesions to 2–4 cm in diameter
- Lymphocutaneous disease: skin lesions progress to cause lymphangitis and regional lymphadenopathy
Sporotrichosis

• Histopathology
  • Granulomatous inflammation with central areas of acute suppuration
  • Demonstration of the organism in tissue may be difficult
Sporotrichosis

- Periodic acid-Schiff (PAS) staining
  - Cigar-shaped yeast forms
  - Subglobose to ovoid, 3-5 µm in diameter
  - Occasional hyphal forms and stellate eosinophilic material called asteroid bodies
  - Globose to ovoid, basophilic cells, 3-5 µm in diameter with radiating eosinophilic rays up to 10 µm in diameter (Asteroid bodies)
SYSTEMIC MYCOSES

• Invasive infections of the internal organs with the organism gaining
• Entry by the lungs, gastrointestinal tract or through intravenous lines, spread systemically
• Systemic mycoses are subdivided into two groups
  • Endemic mycoses
  • Opportunistic mycoses
SYSTEMIC MYCOSES

• Opportunistic mycoses: fungi with low pathogenic potential and produce disease only under unusual situations
  • Changes in the normal intestinal flora
  • Alteration of the host’s immune system by underlying endocrine disorders
  • Debilitation of the host by the use of therapeutic measures (e.g., cytotoxins, x-ray irradiation, steroids, and other immunosuppressive drugs).
  • Transplantation of organs
ASSOCIATION BETWEEN OPPORTUNISTIC INFECTIONS AND CD4+-LYMPHOCYTE COUNT

CD4+-lymphocyte count (cells/µl)

400
- Herpes zoster

300
- Tuberculosis
- Oral candidiasis

200
- Pneumocystis carinii pneumonia
- Esophageal candidiasis
- Mucocutaneous herpes

100
- Toxoplasmosis, cryptococcosis, coccidioidomycosis
- Mycobacterium avium complex, cytomegalovirus

50
- Cryptosporidiosis, PML

Time
Histoplasmosis

- Dimorphic fungi, *Histoplasma capsulatum*
- Endemic in North and South America, and tropical areas
- Soil contaminated with bird droppings or excrements of bats is the common natural habitat
- The infection is acquired through inhalation of *Histoplasma capsulatum* microconidia
Histoplasmosis

• Pathogenesis
  • Healthy individuals are affected
  • Chronic cavitary histoplasmosis: most commonly observed in individuals with underlying pulmonary disease
  • Conidia are inhaled and germinate into yeast in the tissues or when old foci of infection reactivate
  • Cellular immunity: key role in defense against *H. capsulatum*
Histoplasmosis

• Asymptomatic infection
  • Following low-level exposure
  • Pulmonary illness: subacute and mild, or asymptomatic
• In endemic areas, 50-80% of adults infected with *H. capsulatum*, most asymptomatic but (+) skin test
Histoplasmosis

• Primary pulmonary histoplasmosis
  • Inhaled a large infecting dose
  • Develop a symptomatic illness 12–21 days after exposure
  • Diffuse pulmonary involvement, fever, headache, myalgia, cough and chest pain
Histoplasmosis

- CXR: diffuse reticulonodular infiltrates suggesting pneumonitis,
- Severe and recovery slow but recover without treatment
- Leave multiple scattered pulmonary calcifications
Histoplasmosis

• Chronic pulmonary histoplasmosis
  • Males and smokers, underlying pulmonary emphysema
  • Chronic cough, dyspnea, chest pain, fatigue, fevers and fibrotic apical infiltrates
• CXR: cavitations on chest radiographs
• Progressive illness: coin lesions, cavity enlargement, new cavities, tissue necrosis and fibrosis
• Dx: isolation of *H. capsulatum* from respiratory secretions
Histoplasmosis

• Disseminated histoplasmosis
  • Immune deficiency
  • An acute, rapidly fatal course with diffuse reticuloendothelial involvement: infants and others who are severely immunosuppressed
• Chronic course, more focal organ distribution: non-immunocompromised children and adults
• Shock, respiratory distress, hepatic and renal failure, and coagulopathy
Histoplasmosis

- Hepatomegaly or splenomegaly (50%) and lymphadenopathy (~33%)
- Meningitis or focal brain lesions, 10–20% of cases
- Other common sites: oral mucosa, skin and adrenal glands, 5–10% of cases
- CXR: abnormal (70%); diffuse interstitial or reticulonodular infiltrates
Histoplasma
Histoplasmosis

• Histopathology
  • In immunocompetent hosts → granulomatous inflammation with epithelioid cell and multinucleated giant cells
  • Granulomas resemble those seen in tuberculosis
  • In immunocompromised hosts → yeast-like cells in phagocytes
Cryptococcosis

- The infections produced by the encapsulated yeast *Cryptococcus neoformans*.
- Soil contaminated with pigeon droppings or eucalyptus trees and decaying wood.
- The polysaccharide capsule and phenol oxidase enzyme of *Cryptococcus neoformans* are its major virulence factors.
Cryptococcosis

- Immune deficiencies of the T-cell lineages.
  - AIDS now represent the most common risk factor
- Less commonly, organ transplant recipients or cancer patients, especially lymphoreticular malignancies receiving chemotherapeutics may develop cryptococcosis.
- Treatment with corticosteroids agents is an important association.
Cryptococcosis

• Pulmonary cryptococcosis
  • Portal of entry: lung (inhalation), then spreads to involve other organs
  • Acute or subacute respiratory disease: fever and cough and scattered
  • CXR: areas of pulmonary infiltration
Cryptococcosis

- Disseminated cryptococcosis
  - The most common ➔ meningoencephalitis
  - Subacute or chronic
  - May present with signs of acute meningism.
    - Pyrexia, headache, and mental changes such as confusion or drowsiness
  - Blurring of vision and papilledema
    - Due to increased intracranial pressure
Cryptococcosis

- Cryptococci may disseminate to other sites including liver and spleen, kidney, skin, or bone.
- The cerebrospinal fluid shows excessive numbers of lymphocytes, but sometimes polymorphonuclear leukocytes.
- Characteristically, the glucose concentration falls and protein rises.
- Cryptococci can be seen in some cases in an India ink preparation, which is used to highlight the capsule.
Cryptococcosis

• Histopathology
  • Initially a myxoid degeneration with the area of inflammation assuming a gelatinous appearance.
  • Large numbers of round yeast cells
  • The blastoconidia are attached by a narrow neck.
  • The capsules stain pink by the mucicarmine technique (mucin stain).
Aspergillosis

• Agents
  • *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *Aspergillus spp.*

• Hyphae in tissue sections. The hyphae are uniform, narrow, tubular and regular septate.

• Branching is regular progressive and dichotomous (acute angle)
Aspergillosis

• *Aspergillus* is a filamentous fungus found in nature.
• Commonly isolated from soil, plant debris, and indoor air environment.
• Immunosuppression is the main factor of infection
• Local involvement to dissemination.
Aspergillosis

- Aspergilloma
  - Mass of fungus
  - Usually associated with Aspergilli.
  - Mild symptom, cough or hemoptysis
Aspergillosis

• The symptoms are varies due to the host immune

• Symptoms in patient allergy to *Aspergillus*
  • Allergic bronchopulmonary aspergillosis
    • Mucoid impaction of proximal bronchi
  • Chronic eosinophilic pneumonia
  • Bronchocentric granulomatosis with asthma
  • Microgranulomatous hypersensitivity pneumonitis.
Aspergillosis

- Chronic necrotizing pulmonary aspergillosis
  - Infection of *Aspergillus* with local invasion and tissue destruction
  - Usually found in immunocompromised host with noncavitary lung disease.

- Invasive pulmonary aspergillosis
  - Severe, opportunistic infection occurs in severe immunocompromised patients
  - Invasion of fungus into blood vessels → thrombus
Aspergillosis

• Histopathology
  • Hyaline, septate, dichotomously branched hyphae of uniform diameter are observed.
  • In cavitary lesions, conidial heads are occasionally observed.
  • Purulent, necrotizing inflammation is present.
Aspergillosis

• Invasive aspergillosis
  • In severely compromised individuals
  • *A. flavus*, may invade tissue.
  • The initial site is normally lung, but extrapulmonary dissemination may occur, particularly to brain, kidney, liver, and skin.
Zygomycosis

• Mucormycosis
• The angiotropic (blood vessel-invading) infection produced by the various Zygomycetes.
• Mucorales, Mortierellales, and Entomophthorales.
• Absidia corymbifera, Rhizomucor pusillus, and Rhizopus arrhizus.
Zygomycosis

• Predisposing causes: neutropenia, diabetes mellitus, and burns.

• In the compromised host it may lead to paranasal destruction, necrotic lung or skin lesions, and disseminated disease.
Zygomycosis

• Clinical forms include
  • Rhinocerebral Mucormycosis
    • Fever and unilateral facial pain.
    • Facial swelling with nasal obstruction and proptosis.
    • There may be invasion into the orbit leading to blindness, into the brain, and the palate.
Zygomycosis

- Invasive pulmonary mucormycosis
  - Frequently in patients with acute leukemia and lymphoma
  - Invade vessels, caused infarct and hematogenous spreading.
Zygomycosis

- Gastrointestinal mucormycosis
- Secondary infection of preexisting ulcers
- May be a manifestation of disseminated infection.
- Stomach, colon and small bowel are usual sites of infection.
Zygomycosis

• Cutaneous mucormycosis
• Can be a manifestation of disseminated infection
• Primary infection in burned patients, surgical wound with contaminated elastic bandages
Zygomycosis

• Disseminated mucormycosis
• Involve almost any organ, most frequently lungs, CNS, spleen, kidneys, heart, and GI tract.
• Septic thrombosis of coronary arteries produces mycotic myocardial infarction.
Zygomycosis

- Histopathology
  - Acute suppurative inflammation predominates with focal areas of granulomatous inflammation.
  - Broad, thin-walled, hyaline, often aseptate or sparsely septate hyphae
  - The contours of the hyphae are typically non-parallel and branches are irregular
SYSTEMIC ZYGOMYCOSIS
Penicilliosis

• Filamentous fungi
• With only one exception (*Penicillium marneffei*), which is thermally dimorphic
• Soil, decaying vegetation, and the air.
• Immunocompromised hosts.
Penicilliosis

• *Penicilliosis marneffei* infection
  • One of the most opportunistic infection in AIDS patient in Chiang Mai, Thailand.
  • Endemic fungus in Southeast Asia
  • Can be found in chemotherapeutic patient
ENDEMIC AREAS FOR PENICILLIOSIS

- Area endemic for penicilliosis

- Countries: Burma, Vietnam, Laos, Thailand, Cambodia, China
Penicilliosis

• Inhalation of the fungus → pulmonary infection → dissemination

• The lymphatic system, liver, spleen and bones are usually involved.
Penicilliosis

• The skin lesions are dome shape papules with central necrosis
Penicilliosis

- Histopathology
  - Pathologic features: necrotizing granulomas and microabscess formation
  - Rapid diagnosis: touch smears and Wright stain of bone marrow aspirates or other tissue biopsies
Penicilliosis

- Clusters of small round pathogens phagocytized by macrophages are observed inside the macrophages.
- Globose, ovoid and elongated yeast-like cells measuring 2-3 x 2-6 μm seen within macrophages and free in infected tissues.
Penicilliosis

- Extracellular sausage-shaped cells up to 8-13 μm long may rarely be seen
- Central septation of the multiplying cells is characteristic of *P. marneffei* (differentiating it from *H. capsulatum*, which divides by budding)