Systemic Mycoses

Introduction

Systemic mycoses are caused by fungi of soil, which are inherently virulent and cause disease in healthy humans. The systemic mycoses include coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, blastomycosis, and cryptococcosis.

Coccidioidomycosis

Coccidioidomycosis caused by *Coccidioides immitis* was first recognized as a distinct disease entity in 1892. *C. immitis* is a dimorphic fungus, which occurs as a mold in soil and in culture at 25°C and as a spherule in tissue and in culture at 37°C. The spherule is oval with a thick, double refractile wall that is filled with endospores. Each endospore, measuring 2–5 m in diameter gives rise to a new spherule. *C. immitis* grows in mycelial form in the soil of endemic areas. Subsequently, the hyphal cells either develop into barrelshaped structures or shrink and die, producing the characteristic arthroconidia. The arthroconidia are the infective stage of the fungus. When the soil is disrupted, the arthroconidia become air-borne and if inhaled by a susceptible host, initiate the infection.

The arthrospore inside the pulmonary acinus gives off its outer layer, swells, and develops to a spherical structure called the spherule. The spherule is the parasitic stage of the organism, which reproduces by a process known asendosporulation.

Rupture of the spherule leads to release of endospores, each of which matures into spherules and the cycle is repeated. If the organism is cultured, it re-enters the mycelial phase with hyphae formation.

The spherule is the characteristic tissue form of the organism. Resistance of the spherule to eradication by host defenses is the main factor in the pathogenesis of disease. Spherules cause progressive suppuration and tissue necrosis.

More than half of the cases are asymptomatic. In symptomatic cases, *C. immitis* causes a primary pulmonary disease and disseminated disease. Pulmonary

infection is the most frequent presentation in symptomatic patients. In disseminated disease, virtually every tissue of the body including central nervous system (CNS), skin, and bones is involved. The condition is uncommon, but is highly fatal. *C. immitis* has a distribution restricted primarily to areas of the Western hemisphere. Laboratory diagnosis of coccidioidomycosis is made by demonstration of spherules containing endospores in (a) sputum, or smears from the lesion stained by calcofluor white and (b) in biopsy material stained by hematoxylin and eosin, silver, or periodic acid-Schiff stains. Culture is the most definitive method for diagnosis. The fungus grows well on Sabouraud's dextrose agar (SDA) and other media producing white and cottony colony within 5 days. Identification of colonial morphology is not adequate, because other fungi show similar mycelial forms. Therefore, demonstration of typical arthroconidia is useful to identify the organism. However, arthroconidia are infectious, hence pose a significant risk to laboratory personnel. Serodiagnosis of coccidioidomycosis is based on the demonstration of antibodies to coccidioidal antigens in patient's serum.DNA probe is a recent method used for accurate identification of the fungus.

Amphotericin B is the drug of choice for treatment of the condition. Fluconazole can be used for the treatment of mild to moderate disease and, occasionally, for the treatment of life-threatening disease in patients in whom amphotericin B is contraindicated for use. It is used as the drug of choice for long-term therapy of meningeal infection.

Cryptococcosis

Cryptococcosis, also called European blastomycosis, is an acute to chronic disease caused by an encapsulated yeast, *C. neofor*mans. Cryptococcosis is the most common life-threatening fungal disease in patients with AIDS. It is the only systemic mycosis frequently documented from India.

Morphology

■ *C. neoformans* is a true yeast.

■ It is an oval and budding cyst and measures 3–6 m in diameter. The yeast may be single or may have a single budding daughter cell.

■ Within the host and in certain culture media, the yeast is surrounded by a wide polysaccharide capsule. The polysaccharide capsule is composed of mannose, xylose, and glucuronic acid. This fungus forms a narrow-based bud in

contrast to that of *B. dermatitidis*, which forms a broad-based bud. Rarely, pseudohyphae develop.

■ *C. neoformans* on SDA medium forms smooth, convex, cream-colored colonies at 20–37°C. Lactophenol cotton blue (LPCB) wet mount of the colony shows budding yeast cells.

C. neoformans has two varieties: *C. neoformans var neoformans* and *C. neoformans var gattii*. Based on antigenic specificity of the capsular polysaccharide, the species has been classified into four serotypes. These are serotypes A and D (*C. neoformans var neoformans*) and serotypes B and C (*C. neoformans var gattii*).

Pathogenesis and Immunity

The immune status of the host is the crucial factor in pathogenesis of cryptococcosis. *C. neoformans* usually causes most serious infections in patients with impaired CMI. These include:

■ patients with AIDS,

■ patients undergoing corticosteroid treatment,

■ patients undergoing organ transplantation,

■ patients with reticuloendothelial malignancy, and

■ patients with sarcoidosis.

C. neoformans is primarily transmitted by inhalation (Fig.1). Following inhalation, the yeasts are deposited into the pulmonary alveoli, in which they survive before they are phagocytosed by alveolar macrophages. Glucosylceramide synthase has been identified as an essential factor in the survival of *C. neoformans* in pulmonary alveoli.

Cryptococcal polysaccharide capsule has antiphagocytic properties. Hence, unencapsulated yeast are readily phagocytosed and destroyed than the encapsulated organisms, which are more resistant to phagocytosis. The antiphagocytic properties of the capsule prevent recognition of the yeast by phagocytes and inhibit leukocyte migration into the area of fungal replication.

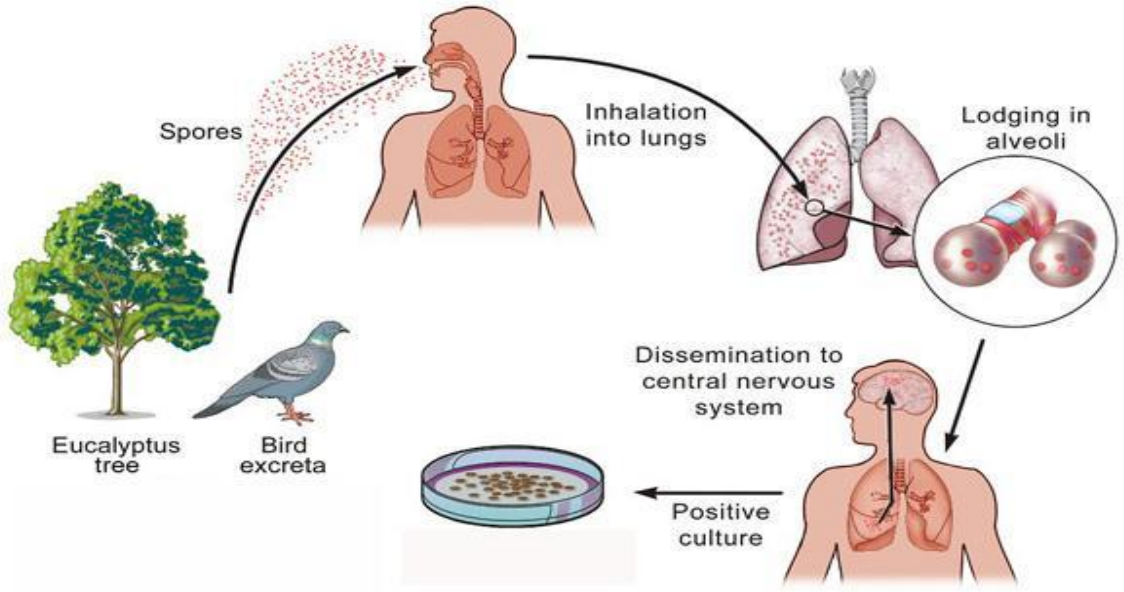

Fig. 1 Transmission of *cryptococcus neoformans.*

◗ Host immunity

The host immunity in cryptococcal infection is mediated by both cellular and humoral responses. CMI is mediated by natural killer cells and T lymphocytes can inhibit or kill cryptococci. An increase in helper T-cell activity, skin test conversion, and a reduction in the number of viable organisms in the tissues indicates a

successful host response against the fungus. Humoral immunity is mediated by anticryptococcal antibodies and soluble anticryptococcal factors. Both anticryptococcal antibodies and the complement play a crucial role in facilitating the macrophage- and lymphocyte-mediated immune response to the organism.

Clinical Syndromes

C. neoformans causes (a) pulmonary cryptococcosis in immunocompetent hosts and in immunocompromised hosts, (b) CNS cryptococcosis, and (c) disseminated

nonpulmonary non-CNS cryptococcosis.

◗ Pulmonary cryptococcosis

The clinical manifestations of pulmonary cryptococcosis are widely variable. Pulmonary disease varies from asymptomatic colonization of the respiratory tract to acute respiratory distress syndrome affecting immunocompromised hosts. It depends on the immune status of the host.

CNS cryptococcosis

Both the brain and meninges are involved in cryptococcal infection of the CNS infections. Meningitis and meningoencephalitis are the most common manifestations. These are usually subacute or chronic in nature. Without specific

therapy, the infection is invariably fatal. The patient dies due to the disease 2 weeks to several years after the symptom onset.

◗ Disseminated nonpulmonary non-CNS cryptococcosis

Disseminated cryptococcosis includes the skin, prostate, and medullary cavity of the bones, next only to the lungs and CNS, and it occurs most commonly in patients with AIDS and other immunosuppressed conditions.

Epidemiology

C. neoformans is distributed worldwide. The incidence of cryptococcosis is increasing and now it represents a major lifethreatening fungal infection in

patients with AIDS. Most cases of cryptococcosis are caused by serotypes A and D. *C. neoformans var gattii* is the most common variety that causes disease in immunocompetent patients. *C. neoformans var neoformans* is the most common variety that causes disease in immunocompromised patients, e.g., AIDS. C. neoformans is primarily transmitted by inhalation . Human-to-human transmission does not occur.

Laboratory Diagnosis

Laboratory diagnosis of cryptococcal infection is made by demonstration of the yeast in CSF, sputum, pus, and brain biopsy tissue by smear and culture. Methenamine silver or periodic acidSchiff stains are used to stain the tissue specimens for demonstration of the capsule of *C. neoformans*. Fixed tissue may also be stained with mucicarmine, which preferentially stains *C. neoformans*.

India ink preparation is commonly used to detect budding yeast cells in the CSF . The capsule appears as a clear halo around the yeast cells. By this method, cryptococci can be demonstrated in 25–50% of patients with cryptococcal meningitis. Gram-stained smear of the CSF shows Gram-positive yeast cells .The culture of centrifuged CSF specimens confirms diagnosis of the condition. This fungus is identified based Latex agglutination test (LAT) is a frequently used serological test to detect cryptococcal polysaccharide antigen in the serum or CSF for diagnosis of meningitis.

Treatment

Amphotericin B is the drug of choice for initial therapy in meningitis or other disseminated infections caused by *C. neoformans*. Amphotericin B may be used alone or in combination with flucytosine. The therapeutic goal for patients with cryptococcal disease not complicated by HIV infection is to achieve a permanent cure of the fungal infection. The therapeutic goal for patients with concomitant HIV infection without a CD4 count of greater than 100 cells/L is to control the acute infection, followed by lifelong suppression of *C. neoformans.*