CRYPTOCOCCOSIS

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CRYPTOCOCCOSIS

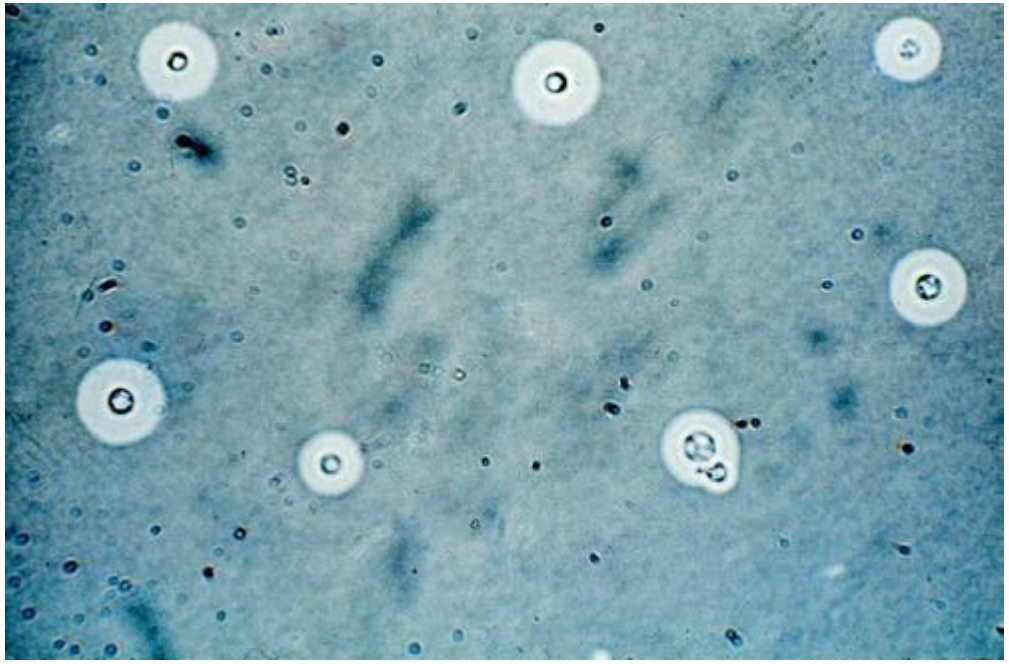
- A systemic mycosis caused by the encapsulated yeast *Cryptococcus neoformans* , an organism found in soil and often associated with pigeon droppings.
- Infection involves most frequently the lungs or central nervous system and less frequently the blood, skin, skeletal system, and prostate.
- Because the incidence of cryptococcosis is greatly increased in immunocompromised patients, especially among patients with AIDS or organ transplant recipients, cryptococcosis is considered an opportunistic fungal infection.

ORGANISM

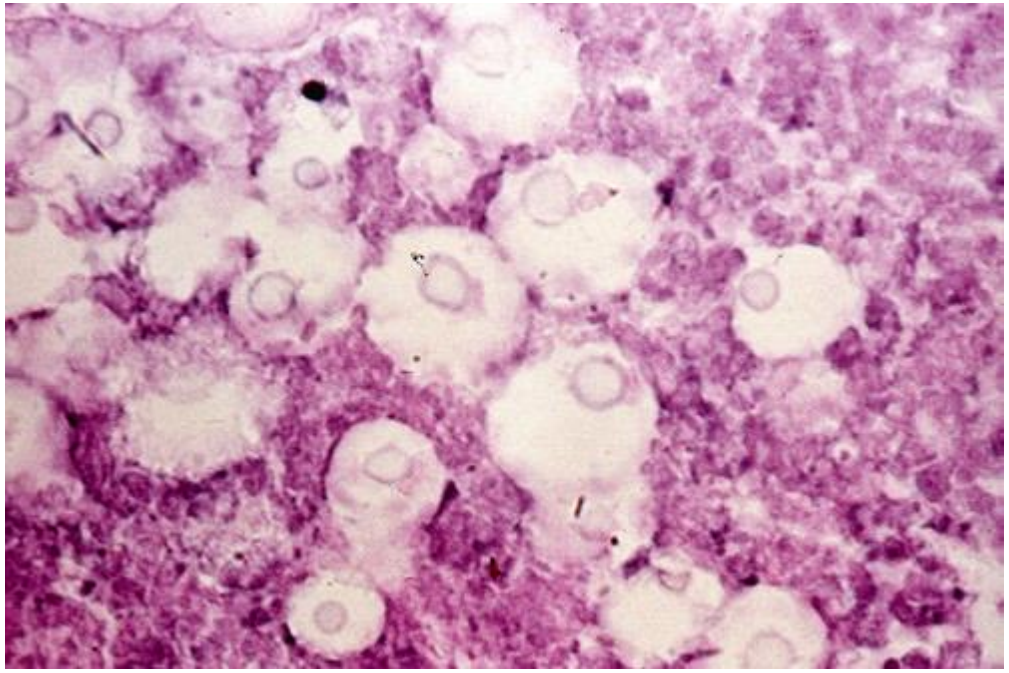
- *Cryptococcus neoformans* is a round or oval encapsulated yeast, measuring approximatly 4_6 um in diameter in clinical specimens, and having a capsule ranging in size from 1 to >30 um.
- *Cryptococcus neoformans* is grouped into serotypes A, B, C, D, and AD hybrids based on antigenic determinants on the polysaccharide capsule, with serotype A most common.

- *Cryptococcus neoformans* var. *neoformans* : serotype A, D and AD.
- *Cryptococcus neoformans* var. *gattii* : serotype B and C.

- *C. neoformans* produced white to cream- colored, smooth, mucoid colonies when grown on solid culture media such as blood agar or Sabouraud's dextrose agar.
- The amount of mucoidness of the colonies is related to the thickness of the capsule.
- Growth of Cryptococcus usually occurs in 36_72 h and is typically slower than that of Candida or Saccharomyces species under the same condition.
- The pathogenic *C. neoformans* grows at 37C.
- A distinguishing feature of *C. neoformans* is the ability to produce melanin.



India ink preparation showing Cryptococcus neoformans in cerebrospinal fluid. Note budding yeast form and distinct outline of cell walls and surrounding capsules



Mucicarmine stain of brain parenchyma showing numerous densely packed encapsulated cryptococci. Note variable size of capsules

PATHOGENESIS

- Once *C. neoformans* is inhaled colonization of the airways occurs before subsequent spread and establishment of respiratory infection.

- The incidence of infection is very low, suggesting that most people mount an appropriate host response when exposed to the organism.

- Cryptococcus, after it enters the body of a susceptible host, can produce latent infection or acute disease.

- Development of disease appears to depend on inoculum of inhaled organism, virulence of the organism, and interaction with the host's cellular immune response.

- After inhalation of the organism, the first line of defense is the alveolar macrophage, followed by recruitment of other inflammatory cells via chemokines and cytokines such as IL-12, IL-18, and monocyte chemotactic protein, in addition to complement-mediated phagocytosis.

- In vitro, alveolar macrophages are able to bind and phagocytize *C. neoformans* in the presence of human serum containing opsonins such as C3.

- Macrophages from patients with HIV infection tend to be impaired or defective in both oxidative-dependent and oxidative-independent killing of *C. neoformans* .

- The role of humoral immunity in protection against cryptococcal infections is controversial, but increasing data indicate that this facet of the immune response may play an important role.

- Antibodies to capsular constituents facilitate clearance of cryptococcal antigen, enhancing antibody-dependent cell-mediated killing and increasing antifungal activity of leukocytes and natural killer cells.

- In addition, an anti-beta-glucan monoclonal antibody has been shown to inhibit growth and capsule formation of *C. neoformans.*

- Among several factors of virulence and pathogenicity for *C. neoformans* and *C. gattii*, the best characterized include the:

- polysaccharide capsule.
- thermotolerance (ability to grow at 37°C).
- melanin pigment production.
- mannitol production.
- soluble extracellular constituents.

- The polysaccharide capsule of *C. neoformans* is composed of a backbone of a-1,3-d-mannopyranose units with single residues of b-d-xylopyranosyl and b-d-glucuronopyranosyl, and referred to as glucuronoxylomannan (GXM).
- The capsule appears to be the key virulence factor for *C. neoformans*; acapsular mutants are typically avirulent, whereas encapsulated isolates have varying degrees of virulence.
- Encapsulated *C. neoformans* cells are not phagocytized or killed by neutrophils, monocytes, or macrophages to the same degree as acapsular mutants.
- In addition, highly encapsulated strains are less able to stimulate T-cell proliferation, and do not enhance the production of cytokines as well as poorly encapsulated or acapsular strains.

- Melanin production also appears to be an important virulence factor of *C. neoformans*, based on in vitro and animal in vivo systems.

- Melanin is deposited in the inner cell wall of *C. neoformans*, and may resist oxidation or reactive nitrogen intermediates produced by phagocytes.

- Another virulence mechanism of Cryptococcus is its ability to survive within either alkaline or acidic environment of the phagolysosome of phagocytic cells, or bloodstream, thereby allowing it to survive and disseminate.

CLINICAL MANIFESTATIONS

Pulmonary Infection:

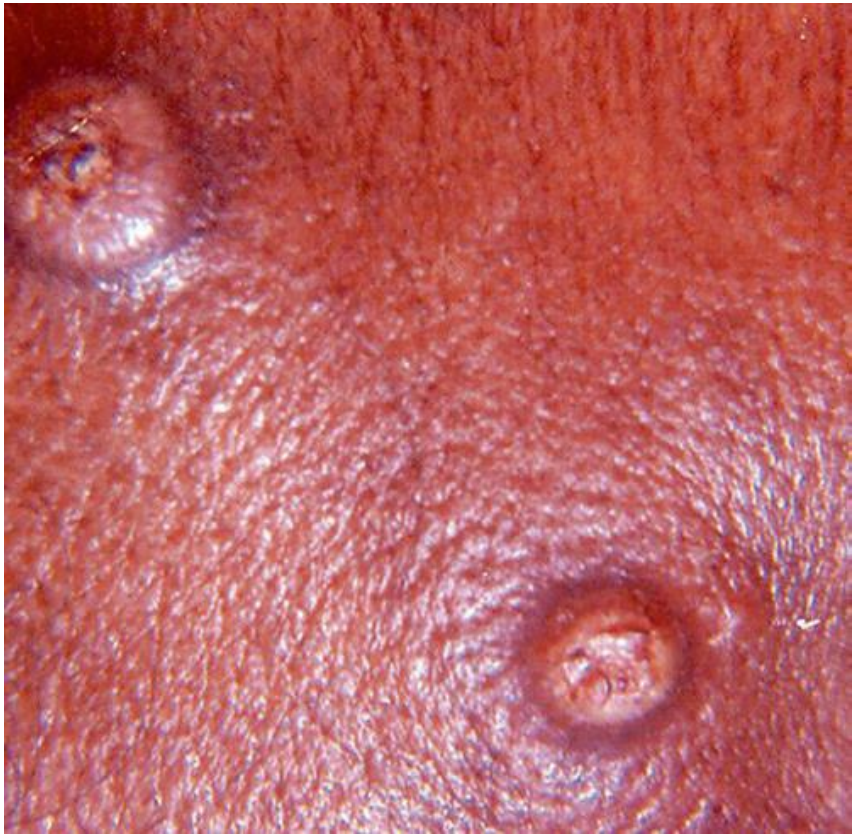
- Pulmonary cryptococcal involvement can manifest in a variety of ways, ranging from asymptomatic airway colonization or infection to fulminant respiratory failure with acute respiratory distress syndrome (ARDS).
- Most patients are asymptomatic, or will have only mild-to-moderate symptoms such as dyspnea, cough, malaise, pleuritic chest pain, night sweats or, rarely, hemoptysis.
- Constitutional symptoms, such as fever, night sweats, and weight loss are less common in HIV-negative patients unless extrapulmonary disease is also present.

Central Nervous System Infection:

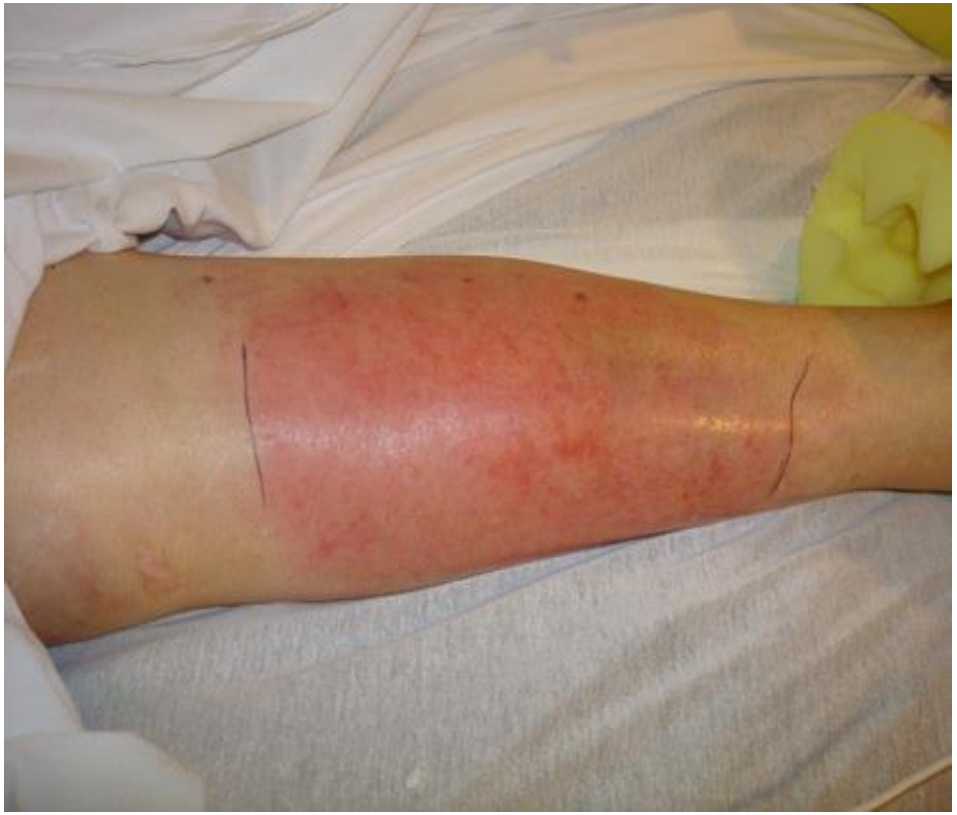
- The most common clinical manifestation of cryptococcosis is CNS infection, manifested typically as meningitis, which can be subacute or chronic.
- A wide range of symptoms and signs can be seen with CNS cryptococcosis, but complaints are often mild or nonspecific and include headache, nausea and vomiting, and malaise.
- In some instances, patients are even asymptomatic.
- Fever is typically low-grade, and is more likely to be present in HIV-infected patients. Unlike in bacterial meningitis, meningismus is uncommon.
- Cranial nerve dysfunction may occur in up to 30% of patients, and may result from increased intracranial pressure, cryptococcal invasion of cranial nerves, or brain parenchymal lesions (cryptococcomas).
- The most common symptoms and signs of cranial nerve involvement include decreased visual acuity, blindness, diplopia, hearing loss, and facial weakness. Seizures, often a reflection of increased intracranial pressure or focal mass lesions, tend to occur later in the course of disease.

Skin Infection:

- Cryptococcal skin lesions are seen in up to 15% of patients with disseminated cryptococcosis, and are most common in HIV patients.
- Skin disease may manifest as a variety of cutaneous lesions, including pustules, papules, purpura, ulcers, cellulitis, superficial granulomas or plaques, abscesses, and sinus tracts.
- Cases of necrotizing cellulitis have also been described.
- In AIDS patients, umbilicated papules resembling molluscum contagiosum are present frequently.
- Cellulitis, characterized by prominent erythema and induration, is often present in patients receiving systemic corticosteroids or other immunosuppressive therapy.
- Cryptococcal skin lesions have resulted rarely from local inoculation, predominately due to laboratory accidents, but the majority of skin lesions result from disseminated infection.



Molluscum contagiosum–like umbilicated papules due to cryptococcosis in the skin of an AIDS patient

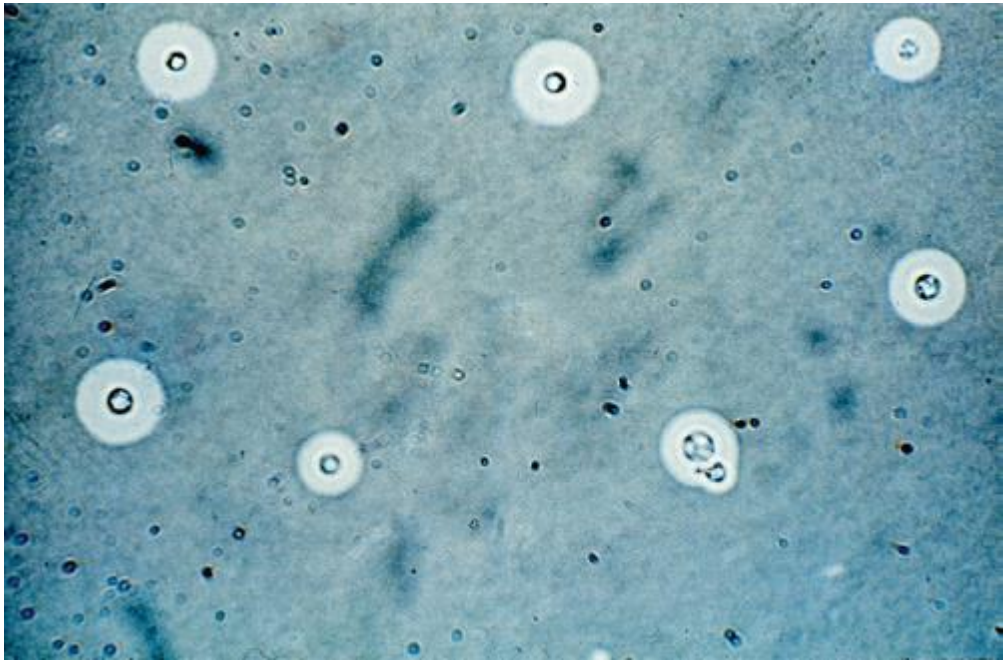


Cryptococcal cellulitis in a corticosteroid-treated lung transplant patient

DIAGNOSIS

The diagnosis of cryptococcosis can be made by using several methods.

- A definitive diagnosis is made by culture and identification of the organism from a sterile site. Clinical specimens can be examined with an India ink preparation, a rapid test which is performed by mixing an equal amount of CSF or other fluid and nigrosin or Pelikan India ink on a slide. After adding a coverslip and upon viewing, the polysaccharide capsule of Cryptococcus will exclude the ink particles and appear as a halo around the organism.



India ink preparation showing Cryptococcus neoformans in cerebrospinal fluid. Note budding yeast form and distinct outline of cell walls and surrounding capsules

- Presumptive diagnosis of cryptococcosis can also be made by wet preparations of clinical samples or with the use of Gram stain.
- However, with these methods, the appearance of cryptococci may be highly variable; therefore, culture should be used for confirmation. Although not specific for the cryptococcal cell wall, Calcofluor white staining may be useful, particularly if few yeast cells are present.

- The detection of cryptococcal polysaccharide antigen in CSF or serum is useful in patients with suspected cryptococcosis.
- After infection is established, cryptococcal polysaccharide becomes solubilized in fluids and can be detected by latex agglutination and quantified.
- In cryptococcal meningitis, antigen testing is highly sensitive and specific, and may be particularly useful if CSF cultures are negative.
- Cryptococcal antigen is found in CSF in >90% and in serum in >70% of patients with cryptococcal meningitis.

- Either routine bacteriologic or fungal media will facilitate culture of C. neoformans. Colonies are usually detected after 2–7 days of growth.

- For blood cultures, the lysis-centrifugation (isolator) technique appears to be the most sensitive method to identify C. neoformans.

- Use of canavanine-glycine-bromthymol blue (CGB) agar will help to distinguish C. gattii from other Cryptococcus species, as colonies of C. gattii will turn the agar blue, while other species do not elicit a color change.

TREATMENT

TREATMENT OF CRYPTOCOCCAL INFECTION IN THE HIV-NEGATIVE PATIENT

Pulmonary disease

A. Colonizationa

1. Observation in the immunocompetent patient

2. Fluconazole 400 mg daily for 6–12 months

B. Asymptomatic or minimally symptomatic disease

1. Fluconazole 200–400 mg/day for 6–12 months

Alternative: Close observation without therapy is a consideration

C. Mild-to-moderate disease

1. Fluconazole 200–400 mg/day for 6–12 months

Alternative: (1) Itraconazole 200–400 mg/day for 6–12 months

(2) Voriconazole 200 mg twice daily or posaconazole 400 mg twice daily for 6–12 months

D. Severe or progressive disease, or azole drug not an option Amphotericin B 0.5–1.0 mg/kg/day for a total dose of 1–2 g. This may be followed by oral fluconazole in selected patients

Alternative: (1) Regimens similar to those used for CNS disease, as described below

(2) Surgical resection in selected cases refractory to therapy

CNS disease

Amphotericin B 0.5–1.0 mg/kg/day plus flucytosine 100 mg/kg/day for 2–4 weeks followed by fluconazole 400 mg/day, for 8–10 weeks.

Amphotericin B, 0.5–1.0 mg/kg/day plus flucytosine 100 mg/kg/day for 6–10 weeks.

Note: Lipid formulations of amphotericin B (liposomal AmB 3–6 mg/kg/day or ABLC 5 mg/kg/day) may be substituted in patients with intolerance to amphotericin B deoxycholate).

Maintenance therapy

Fluconazole 200 mg/day for at least 6 months should be considered for patients with persistent immunosuppression, i.e., transplant recipients.

TREATMENT OF CRYPTOCOCCAL INFECTION IN THE HIV-INFECTED PATIENT

Pulmonary disease

A. Asymptomatic or mild-to-moderate disease

Fluconazole 400 mg/day for 6–12 months depending on immune reconstitutiona.

Alternatives: Itraconazole 400 mg/day 6–12 months depending on immune reconstitutiona.

Fluconazole 400 mg/day plus flucytosine 100 mg/kg/day for 10 weeks.

B. Severe, progressive disease

Regimens similar to those for CNS disease (see next)

CNS disease

Amphotericin B 0.7–1.0 mg/kg/day plus flucytosine 100 mg/kg/day for 2 weeks followed by fluconazole 400 mg/day for 8–12 weeks.

Alternative:

Itraconazole 400 mg/day may be substituted for fluconazole

Amphotericin B 0.7–1.0 mg/kg/day for 4–6 weeks.

Amphotericin B 0.7 mg/kg/day plus fluconazole 800 mg/day for ³8 weeks.

Note: Lipid formulations of amphotericin B (liposomal AmB 3–6 mg/kg/day or ABLC 5 mg/kg/day) may be substituted in patients with intolerance to amphotericin B deoxycholate).

Fluconazole 400 mg/day plus flucytosine 100 mg/kg/day for 10 weeks.

Fluconazole 800–1200 mg/day for 10–12 weeks.

Itraconazole 200 mg/day for 10–12 weeks.

Maintenance therapy:

Fluconazole 200 mg/day.

Alternatives: Amphotericin B 1 mg/kg/week.

Itraconazole 200–400 mg/day.

THANK YOU