
Cryptococcosis*,**

Definition - a chronic, subacute or rarely acute pulmonary, systemic or meningitic infection caused by *Cryptococcus neoformans* - the encapsulated Blastomycetes anamorph of *Filobasidiella neoformans* - Basidiomycota

Syn of Cryptococcosis

Busse - Buschke's disease
European Blastomycosis
Pigeon's disease
(Pigeon breeders'disease)

*usually considered to be an opportunistic mycosis that often becomes systemic.

**remains the most common fatal infection involving the central nervous system in patients with AIDS

History

Busse (1894) & Buschke (1895)

first reported isolation of fungus from human disease (tibia of human female).

Sanfelice - described encapsulated yeast isolated from nature which caused infections in animals
- *Saccharomyces neoformans* (1895)

Vuillemin - determined fungus was not ascosporic. Therefore, imperfect and illegally assigned to *Saccharomyces*.
Renamed in 1901 B & B's fungus as *Cryptococcus hominis* (*hominis* illegal) & Sanfelice's as *C. neoformans*.

Kreger - Van Rij (1952) with Lodder

stabilized anamorph name as *C. neoformans* (Sanfelice) Vuillemin; based on work of Benham et al.

Benham et al (1950's) (also Lodder and Evans) determined:

- 1) only 1 species most likely
- 2) 4 serotypes - antigenic nature of capsular polysaccharides (GXM = glucuronoxylomannans); serotypes A,** B,+ C,+ D* (AD new, 2000, so now 5 serotypes)
- 3) blastomycosis & cryptococcosis were different diseases
- 4) serotypes A & D associated with pigeons

Howard, Kwon Chung, Bennett, etc. (1960's to 1990's)

** = var *grubii* A (95% US isolates); (post 1980's, mostly A with AIDS in US)

* = var *neoformans* D (other temperate regions)

+ = var *gattii* B (5% US isolates) & C (tropical & subtropical)

- established some correlations between serotypes & ecological & geographical distribution

Shadomy (1970) clamps & dolipores (see Kwon-Chung & Bennett, P. 432)

Kwon Chung (1975) *Filobasidiella* teleomorph

Ellis & Pfeiffer (1990) var *gattii*

sero B isolated from *Eucalyptus camaldulensis* in Australia and then U.S.

Heitman et al. (2001) Serotype AD strains are diploids and are heterozygous at the mating-type locus.

Kwon-Chung et al. (2002) proposes to make var. *gattii* separate species.

Importance of discovery of *C. neoformans* teleomorph

1. clarified many aspects of "unusual" biology of this form-species
2. clarified why serotypes might be geographically correlated and environmentally localized
3. appeared to clarify why pigeon handlers and breeders in particular seemed to have propensity for pulmonary disease prior to onset of cryptococcosis
4. suggested smaller size of basidiospores vs yeasts might also often initiate infections, although dried, dehydrated yeasts* usually thought to initiate infection to be phagocytized in lungs

*dried yeast are very much smaller than rapidly growing, hydrated yeasts.

Unique Features of the Mating-type and Mating Locus of *Filobasidiella (Cryptococcus) neoformans*

1. The morphological features of the sexual state of this species are unique, even as related to Basidiomycota (for example, conjugation tube are produce by *MATa* yeast but not *MATα* yeast; also *MATa* yeast but not *MATα* yeast can exhibit "haploid fruiting").
2. The mating-type loci are very large and contain mating-type specific pheromone response MAP kinase cascade genes, but also several additional genes not associated with fungal mating.
3. Some of the mating-type specific genes have specific functions peculiar to one strain but not the other.
4. Nuclear migration during mating is unidirectional from *MATα* to *MATa*, and mitochondrial inheritance is unidirectional from *MATa* to *MATα*.

Note: Virulence is more associated with *MATα* strains then with *MATa* strains no matter whether they are clinical or environmental isolets.

*These features may only pertain to serotypes A & D strains.

		Teleomorph		
<i>Filobasidiella neoformans</i> var. <i>neoformans</i>		Basidiomycota Phragmobasidiomycetes (?) teleomorph Class & Order controversial		
var. <i>bacillispora</i>		Tremellales or Filobasidiales ?		
<i>C. neoformans</i> *** (anamorph)		caffeic acid & phenol oxidase → brown colonies		
var		assimilation malate	color change CGB* or GCP	growth 37-39°C
<i>grubii</i> var. (2001) sero A <i>neoformans</i> (1975) sero D (sero *A & D) Temperate A, mainland U.S.		--	yellow	+
<i>gatti</i> (1989) (sero *B & C) Tropical & Subtrop. B & A, So. Cal.		+	blue* red**	_ or + very weak

*creatine, glucose, brom thymol blue agar

**glycine, cycloheximide, phenol red agar

*** capsulated yeast Blastomycetes (form-class)

Clinical Forms of Cryptococcosis

Primary Pulmonary vs Opportunistic*

1. **Pulmonary**
 - a. Primary forms in normal hosts rapidly resolved with minimal symptoms (often subclinical)
-probably initiated by inhaling basidiospores or dried yeasts in low numbers. No evidence exposure yields long-term immunity. Inhalation of larger numbers of yeasts or spores* may yield acute symptomatic infections with infrequent spread to other body sites (CNS)
 - b. chronic forms of pulmonary** infection w/o spread or slow spread yielding cutaneous or meningitic involvement
 - c. Treatment of chronic pulmonary cryptococcosis
Ampho B alone (or with 5FC)
surgical removal of lung lesions
fluconazole following failure with 5FC and/or Ampho B
other azoles*(Diflucan)
2. **Opportunistic forms^{+, ++}**
 - a. pulmonary
 - b. CNS (most diagnosed form)
 - c. cutaneous (rarely primary)
 - d. mucocutaneous
 - e. osseous
 - f. visceral

* All forms of active cryptococcoses must be treated to prevent more serious disease or death.

**often from long-term repeated exposure to relatively low doses of infecting agent (pigeon breeder's disease)

⁺probably all initiated by inhaling spores/yeasts (dried)

⁺⁺often associated with collagen diseases, also lupus erythematosus, sarcoidosis, neoplasias, bushing's syndrome & AIDS

Clinical Forms of Cryptococcosis (continued)

Opportunistic forms also initiated as pulmonary disease in compromised hosts.

Main type of disease known for about 1st 50 - 60 years of study of cryptococcosis.

Case ranges from 200 - 300/year of cerebral meningitis in U.S. to 15,000 subclinical cases in New York City/year.

1982 hospital release data estimates 1,200/year with ~200 deaths (pre-AIDS)

-mainly diagnosed as meningitis or CNS disease because pulmonary form difficult to diagnose.

1990 to present: *Cryptococcus neoformans* is currently the most commonly isolated pathogen from CSF in U.S.

The vast majority of persons with cryptococcal meningitis have AIDS. (Most common CNS fatal infection)

Majority of all cryptococcosis cases are AIDS related, although other populations (renal transplant recipients, diabetics, and those with hematologic malignancies) are at risk. (Today)

Before HAART about 5-10% of AIDS patients developed cryptococcal meningitis in U. S.; percentage may increase as survival is prolonged among AIDS patients (due to immunosuppression, use of antipneumocystis prophylaxis and antiretroviral therapy, etc.). Case rate prior to HAART 17-66 cases/1000 patients with AIDS vs 0.2 -0.9/100,000 without AIDS.

Today, 4th most commonly recognized cause of life-threatening infection in AIDS patients world-wide.

Relapses after successful treatment of cryptococcal meningitis among AIDS patients is common.

Successful retreatment among AIDS patients who relapse their cryptococcal meningitis is rare and most patients die from the cryptococcosis.

With cryptococcosis and AIDS, the concept of indefinite suppressive therapy has emerged as a viable strategy.

Fluconazole and Amphotericin B are relatively effective agents for prevention of relapse cryptococcal meningitis in AIDS patients (relapse rates: 12 of 78 with Amphotericin B versus 2 of 111 and 1 of 34 with fluconazole).

Itraconazole is also effective.

Risk Factors for Cryptococcosis*:

- HIV infection
- Chronic corticosteroid therapy
- Organ transplants
- Chronic leukemias and lymphomas
- Sarcoidosis

*Perfect, JR: Cryptococcosis. Infect. Dis. Clin. North Am 3:77-102, 1989.

Factors for Successful Treatment:

1. Prompt diagnosis
2. Intensive treatment with amphotericin B (6 to 10 weeks)/selected EBI fluconazole
3. A suppressive regimen for high-risk patients
4. Control of the underlying disease

Symptoms and Clinical Pictures

1. Pulmonary (Primary)
 - a. mostly asymptomatic
 - b. symptomatic
 - cough
 - low-grade fever
 - pleuritic pain
 - weight loss (some)
 - little productive sputum
 - nonlocalized lung lesions
 - resolution → few residual scars of past lesions
 - X-ray picture very variable
 - definitive identification of disease depends on isolation of organism and/or latex agglutination test for cryptococcal antigen or fluorescent antibody of biopsy
2. Cutaneous (primary - rare)
3. Opportunistic

CNS Cryptococcosis

1. most commonly diagnosed form of disease
2. before Ampho B, disease considered to be uniformly fatal (now ~ 6-10% & getting better even as related to AIDS)
3. main early presenting symptoms
 - headache
 - possibly slight fever
 - confusion
4. brain may have multiple or single lesions → cryptococcal granuloma
 - nausea -coma
 - vomiting -paralysis
 - mental changes -death

Cutaneous and Mucocutaneous

1. indicative of dissemination
2. pustular lesions or abscesses
3. represent about 5 to 15% of patients presenting with cryptococcosis today

Osseosis (bone involvement)

1. about 10 - 15% of cases
2. very difficult to diagnose
 - X-ray indication together with other evidence for disease (CT)

Visceral

1. any organ or tissue (CT)
2. extremely serious

Prostate

1. persistent focus in some patients after "successful" antifungal therapy

Detection of CNS Cryptococcosis

Spinal Tap

1. increased pressure due to fluid accumulation
2. clear fluid
3. cell count somewhat elevated
4. sugar is very low
5. organisms sparse or numerous -usually spun to concentrate and examined microscopically after staining with India ink for capsular yeast
6. L.A. test, IFA sometimes

Other CAT (computerized axial tomography) scans & MRI (magnetic resonance imaging) scans helpful, but generally only suggestive of brain/spinal cord problems.

Clinical Forms of Cryptococcosis

	Serodiagnosis
	Primary tool for diagnosis
1. Pulmonary	LA Test
2. CNS	
3. Cutaneous****	LA Test
4. Mucocutaneous	+
5. Osseous	IFA*
6. Visceral	TA**

* Latex agglutination test; 90-95% accurate for CNS; titers>1:8 indicative of active infection; detect polysaccharide antigens

** IFA; Indirect Fluorescent Antibody test

*** Tube Agglutination test; carried out with capsular polysaccharide antigens.

**** rarely primary