CRYPTOCOCCOSIS

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MBBS

Presentation Layout

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Clinical Case

- DOA 27/01/16 DOD 17/02/16
- 31 year old female, newly diagnosed RVI with CD4 20 (05/01/16)
- Present with 2/52 hx of confusion, headache, vomiting, photophobia, neck stiffness, dysphagia, cough, SOB and diarrhea.
- No previous TB contacts (nor prior Rx) but reported unintentional weight loss, fever and night sweats.
- Current medications included Atripla and CTX 960mg.

Examination Findings

- Generally ill looking, GCS 14/15, fairly cachexic, with conjuctivial and palmar pallor.
- Ulcer noted on the mouth with oral thrush along the tongue.
- CNS; marked sensitivity to light, with reactive pupils and positive meningeal signs. No neurological deficit.
- RESP, ABD and CVS unremarkable.

Lab Investigations

- CSF Analysis: opening pressure 48 cmH_2O. Glucose 0.16, yeast cells 2+, WBC< $2/mm^3$. (INDIA INK NOT DONE).
- FBC: WBC 6.86, Hb 7.1, MCV 79.1, plt 243
- RFT: Na^+ 127 ,K^+ 3.3, Cr 69, urea 4,4
- LFT: ALT 15.1, AST 49.5, ALP 44, GGT 33, albumin 33.9, D Bil 2.4

So what is the diagnosis??

Diagnosis

- Advanced HIV infection.
- Cryptococcal Meningitis (Possible Bacterial Meningitis).
- Esophageal Candidiasis.
- Microcytic Anemia.
- Hyponatremia (Possible SIADH or GE induced).

Background Information

- Cryptococcosis refers to an infection caused by fungi belong to the Cryptococci genus.
- Two species are know to cause serious in infections in human begins namely *Cryptococcus neoformans* and *Cryptococcus gattii* .

Microbiology

- **Taxonomy** — *C. neoformans* and *C. gattii* are basidiomycetous, encapsulated yeasts, than can be sub classified into four serotypes (A, B, C, or D) between the two species.
- **Life cycle** — Involves asexual and sexual forms. The asexual form exists as yeast and reproduces by budding. These haploid, unicellular yeasts are the only forms of *C. neoformans* and *C. gattii* that have been recovered from human infections.

Mycology

- *C. neoformans* has been found in temperate climates, in soil samples from around the world in areas frequented by birds, especially pigeons and chickens.
- This fungus has also been isolated from roosting sites of pigeons and in association with rotting vegetation.
- The role of pigeon guano in the pathogenesis of human infections is obscure. A history of intense pigeon exposure is only rarely elicited from patients with cryptococcosis.
- **Outbreaks of the disease have never been traced to pigeon roosting areas.**

Mycology Cont'd

- Until recently, *C gattii* was found principally in tropical and subtropical climates.
- *C gattii* is not associated with birds but grows in the litter around certain species of eucalyptus trees (i.e, *Eucalyptus camaldulensis, Eucalyptus tereticornis*).

Epidemiology

The vast majority of patients with cryptococcosis are infected with *C neoformans*.

They are usually immunocompromised due to one of the following conditions (listed in order of decreasing frequency):

- AIDS (CD4 cell count <100 cells/microL).
- Prolonged treatment with glucocorticoids.
- Organ transplantation.
- Malignancy (most notably leukemias & lymphomas)
- Sarcoidosis.

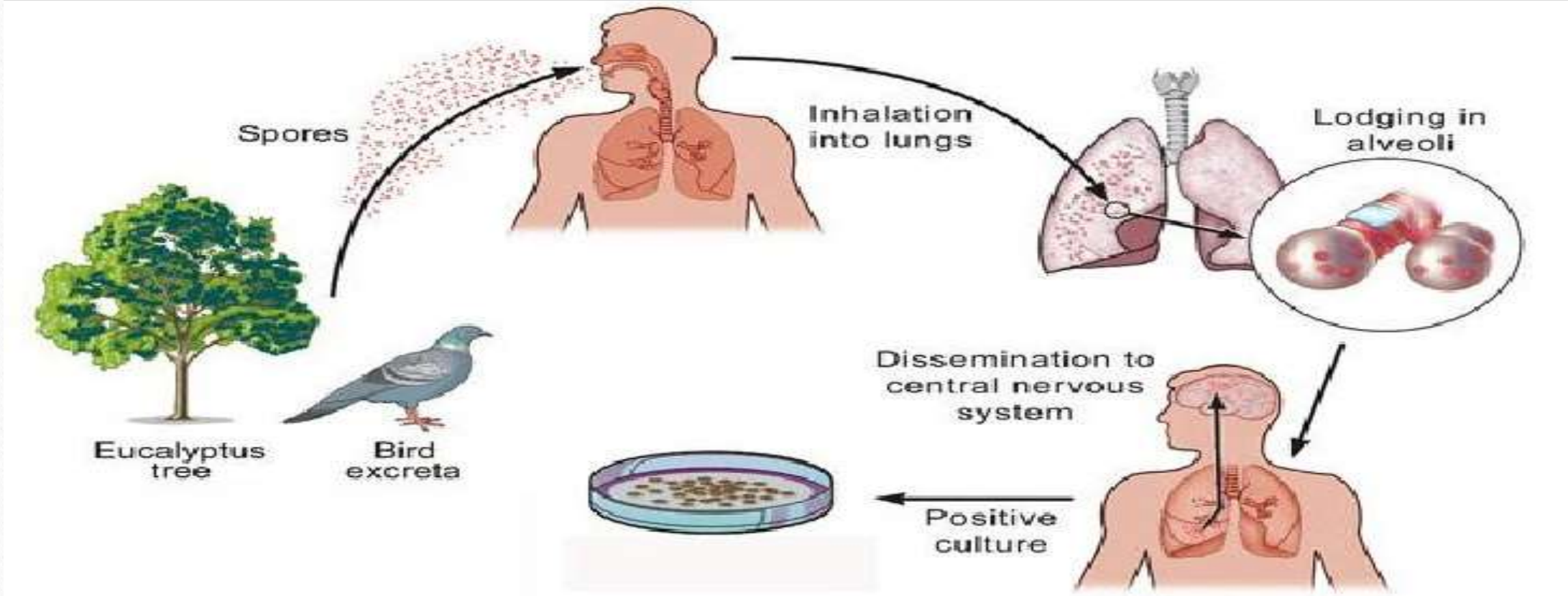
Pathogenesis

- The organism is primarily transmitted via the respiratory route, but not directly from human to human.
- The yeast spores are deposited into the pulmonary alveoli and evade phagocytic efforts by macrophages.
- Encapsulated organisms are more resistant to phagocytosis. The cryptococcal polysaccharide capsule has antiphagocytic properties and may be immunosuppressive. These properties of the capsule block recognition of the yeast and inhibit leukocyte migration into the area of fungal replication.

Pathogenesis Cont'd

- *C neoformans* infection is usually characterized by little or no necrosis or organ dysfunction until late in the disease. Organ damage may be accelerated in persons with heavy infections.
- The characteristic lesion of *C neoformans* consists of a cystic cluster of yeast with no well-defined inflammatory response (no granuloma).
- The organism disseminates hematogenously and has a propensity to localize to the central nervous system (CNS).
- In addition to invading the lung and CNS, cryptococci also invade the skin, bone, and genitourinary tract, but meninges appear to be the preferred site.

LIFE CYCLE OF C.NEOFROMANS



Why Meningeal Propensity?

- CSF is a favorable growth medium for the organism as it lacks the factors present in serum that inhibit cryptococcal growth (i.e. low complement activity).
- Dopamine levels in the CNS may promote cryptococcal virulence by serving as a substrate for melanin production by the organism (an import capsule component).

Clinical CNS Presentation

- Meningoencephalitis is the most frequently encountered manifestation of cryptococcosis.
- Headache, Confusion, Lethargy, Obtundation or Coma
- Normal or mildly elevated temperature
- Nausea and vomiting (with increased intracranial pressure)
- Fever and stiff neck (with an aggressive inflammatory response; less common)
- Blurred vision, photophobia, and diplopia
- Hearing defects, seizures, ataxia, aphasia, and choreoathetoid movements

Pulmonary Presentation

Pulmonary cryptococcosis in immunocompetent patients are as follows:

- Cough (54%), cough with scant mucoid sputum (32%) or pleuritic chest pain (46%)
- Low-grade fever, dyspnea, weight loss, and malaise (less common)
- HIV-infected patients with pulmonary cryptococcosis may present with the following:
- Fever (84%). Cough (63%), Dyspnea (50%)
- Headache (41%), Weight loss (47%)
- Other possible findings in pulmonary infection are as follows:
- Pleuritic pain, Hemoptysis
- Acute respiratory distress syndrome (ARDS)

Other Sites Affected

The next most commonly involved organs in disseminated cryptococcosis include the skin, the prostate, and the medullary cavity of bones.

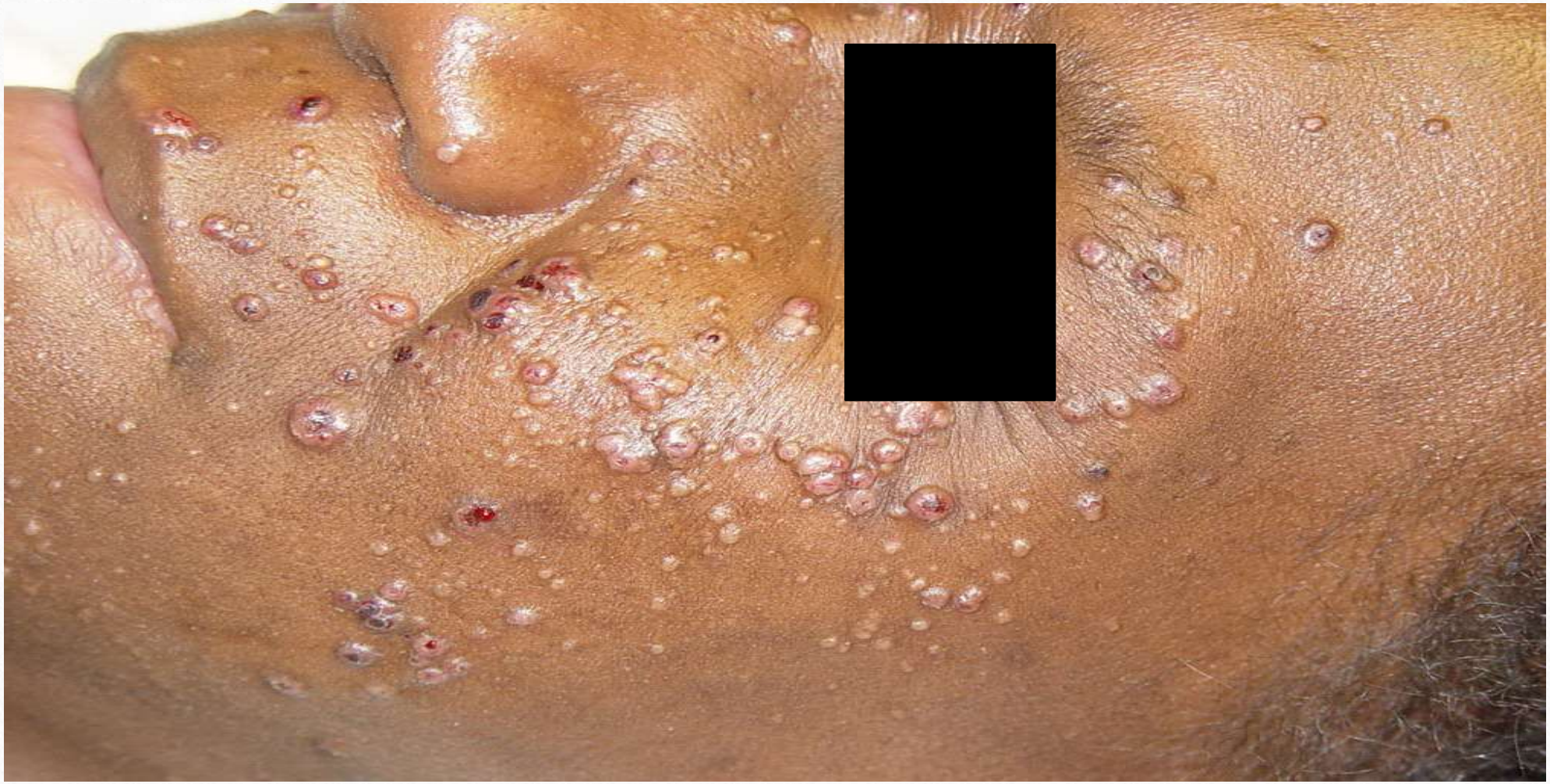
Cutaneous manifestations (10-15% of cases) are as follows:

- Papules, pustules, nodules, ulcers, or draining sinuses.
- Umbilicated papules in patients with AIDS.
- Cellulitis with necrotizing vasculitis in organ transplant recipients.

Other less common forms of cryptococcosis include the following:

- Optic neuritis or endophthalmitis, Myocarditis, Chorioretinitis, Hepatitis.
- Peritonitis, Renal abscess, Myositis. Adrenal involvement.

Cutaneous Cryptococcosis



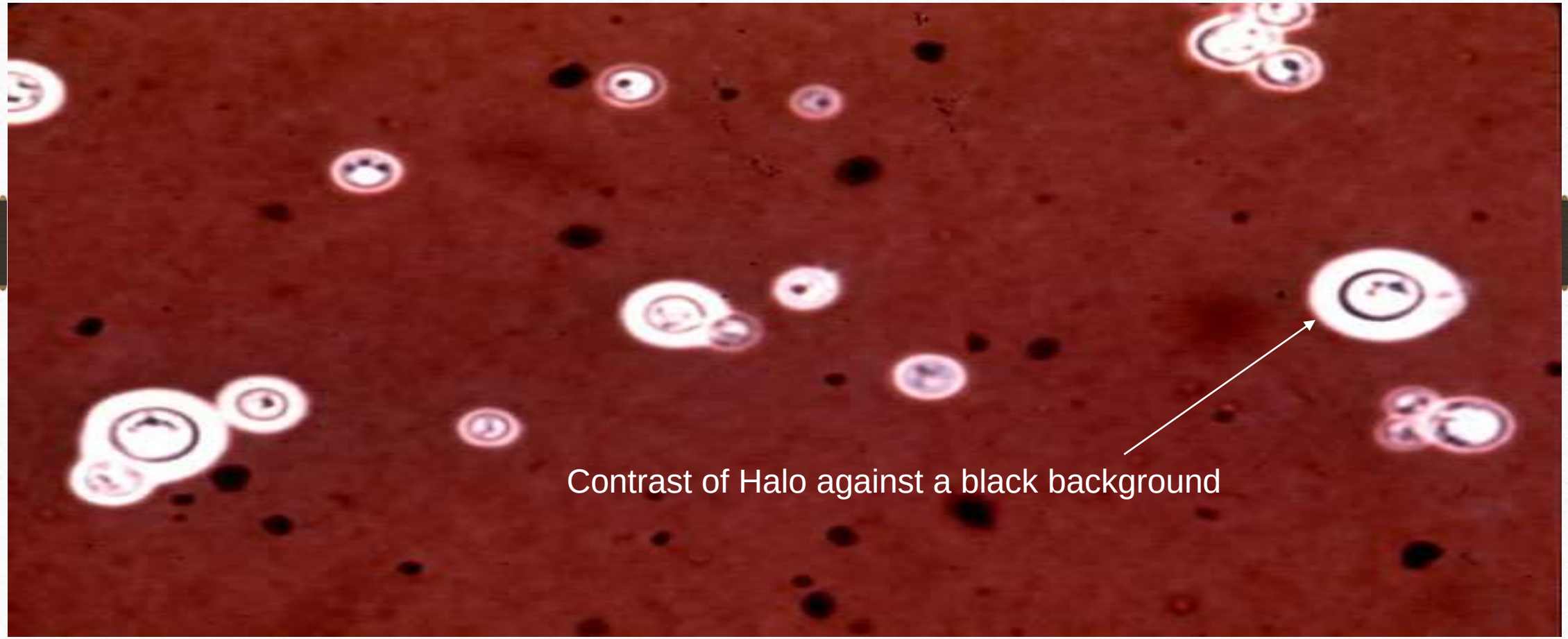
Preliminary Investigation (CSF analysis)

	Normal Adult	Cryptococcal Meningitis	Bacterial Meningitis	Viral Meningitis	Tuberculosis
Appearance	Clear	Clear or cloudy	Clear, cloudy or purulent	Clear	Clear to opaque
Opening Pressure	10-20cmH_2O	Elevated	Elevated (>25cmH_2O)	Normal or Elevated	Elevated
WBC Count	0-5 cells/μL (< 2% PMN)	10-500 cells/μL	> 100 cells/μL (> 90% PMN)	10-10 000 cells/μL (early PMN then lymph)	50-500 cells/μL (early PMN then lymph)
Glucose Level	>60% of serum glucose	Low	Low	>60% of serum glucose	Low (<40% of serum glucose)
Protein Level	<45 mg/dL	Elevated	Elevated (> 50mg/dL)	Elevated (> 50mg/dL)	Elevated

India Ink Staining

- Since the burden of organisms is usually high in AIDS patients, an India ink preparation of the CSF will usually demonstrate typical round encapsulated yeast organisms consistent with cryptococcus in 60 to 80 percent of patients.
- India ink does this by outlining the organisms by negative contrast, identify the yeast cells in fluids or macerated tissue samples.
- The advantage of the India ink preparation is that a diagnosis of cryptococcal infection can be made rapidly while confirmatory testing is being performed (eg, CSF culture or antigen).

Microscopic Appearance Of Cryptococcus Species Stained With India Ink



Cryptococcal Antigen (CrAg)

- CrAg can be detected in serum and CSF through immunodiagnostic techniques, such as latex agglutination or ELISA.
- A positive CrAg in the CSF strongly supports the diagnosis of cryptococcal meningitis and is sufficient evidence to initiate treatment in patients.
- Sensitivity approaches 100% for CSF, ~95% for serum.
- **The lateral flow assay (LFA)** is an alternative approach to detecting CrAg. It is a simple dipstick test that is inexpensive to perform and can be used on urine, blood, serum, CSF, or plasma samples. The LFA compares favorably with he latex agglutination and ELISA, and is used in both resource limited and resource available areas.

Cryptococcal Culture

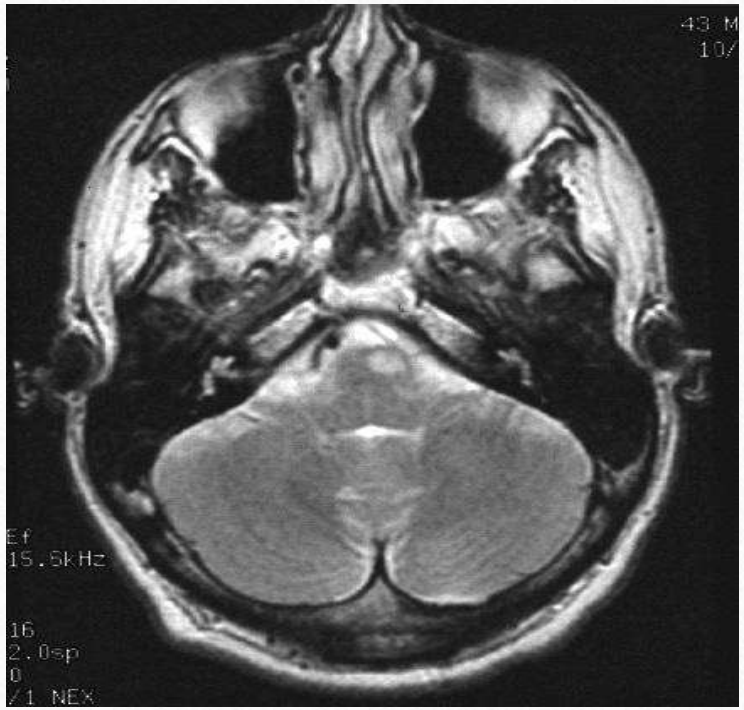
- Since CrAg detection does not allow identification of the species of *Cryptococcus*, culture is essential for definitive diagnosis.
- *C. neoformans* and *C. gattii* produce white mucoid colonies on a variety of agars that usually become visible to the naked eye within 48 hours. The identification of *C. neoformans* and . *gattii* in the clinical laboratory begins with isolation of a urease positive, encapsulated yeast.
- Further confirmation can be achieved with biochemical tests contained in commercial kits and by detection of the enzyme phenol oxidase, which is solely produced by *C. neoformans* and *C. gattii*.

Imaging Studies

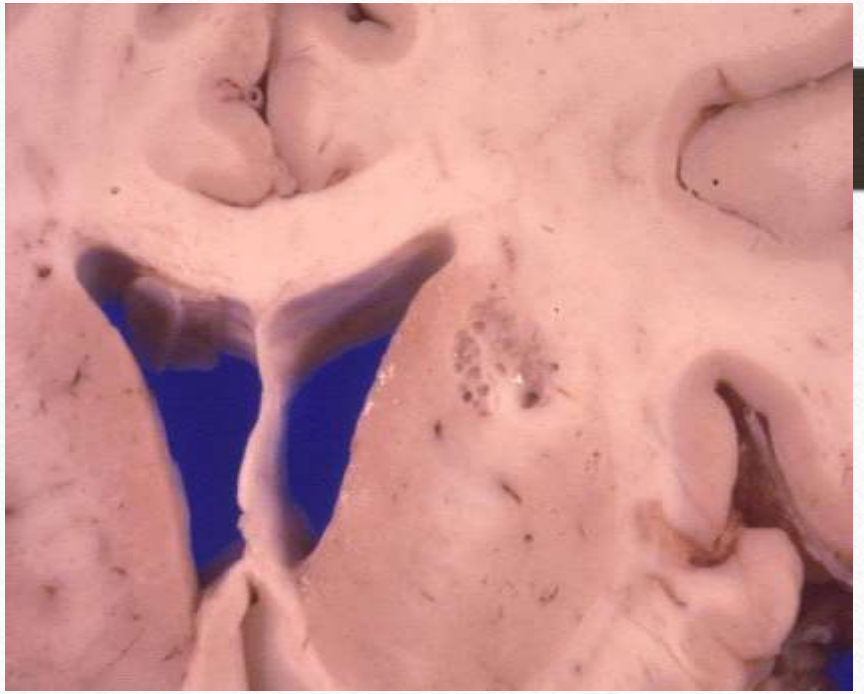
- Consider CT or MRI prior to LP in the setting of focal neurologic signs, papilledema, or impaired mentation.
- MRI is more effective than CT for identifying CNS cryptococcal lesions.
- On MRI 20-30% of patients show meningeal enhancement, parenchymal solid mass lesion without hemorrhage, atrophy, cerebral edema or hydrocephalus.
- If the imaging shows a cryptococcal mass lesion (ie, cryptococcoma), toxoplasmosis and lymphoma must be considered in the DDx brain biopsy may be indicated.
- NB *C. gattii* is significantly more likely than *C. neoformans* to cause cryptococcomas of the lungs and/or brain.

Cryptococcomas

Magnetic resonance imaging showing a cryptococcoma in the medulla



Coronal section of brain showing a cryptococcoma in the basal ganglia



Standard of Treatment in Botswana

First Line Therapy

- **Induction therapy:** at least 14 days IV **Amphothericin B** in D5W 0.7-1mg/kg/day OD + **Fluconazole** 800mg once daily.
- **Consolidation therapy:** For 8 weeks with PO **Fluconazole** 800mg OD.
- **Maintenance therapy:** (secondary prophylaxis) PO **Fluconazole** 200mg once daily until HAART increases CD4 count to > 200 for at least 6 months.

Botswana Treatment Cont'd

Alternative treatment Indicated if Ampho B unavailable, or not tolerated.

- **Induction Therapy**: PO **Fluconazole** 1200mg OD for 14 days (15 total doses).
- **Consolidation Therapy:** PO **Fluconazole** 800mg once daily for 8 weeks (60 total doses).
- **Maintenance Therapy**: PO **Fluconazole** 200mg OD for 6 months.

USA Guidelines

- **Initiation Therapy: Liposomal amphotericin B** 3 to 4 mg/kg IV OD or **amphotericin B lipid complex** 5 mg/kg IV OD + **Flucytosine** 100 mg/kg PO OD or QID for 14 days.
- **Consolidation Therapy: Fluconazole** 800 mg [6 to 12 mg/kg] PO OD for 8 weeks.
- **Maintenance Therapy: Fluconazole** 200mg PO OD for 6 to 12 months.

USA Alternatives

For circumstances in which no amphotericin formulations are tolerated or available,

Alternative 1.

- **Initiation Therapy:** Fluconazole 800 to 1200 mg PO OD + Flucytosine 100 mg/kg PO OD or QID may be administered for 2 to 10 weeks.

Alternative 2

- **Initiation Therapy:** 800 to 1200 mg PO OD for at least 10 weeks or until CSF culture results are negative.

Maintenance Therapy: Fluconazole 200 to 400 mg PO OD for 6 to 12months.

Honorable Mentions

- Flucytosine + Amphotericin B for the first 2 weeks of therapy provides greater early fungicidal activity than amphotericin B alone.
- In addition, the absence of flucytosine is associated with lack of CSF sterilization at week 2 and treatment failure.
- Combination therapy with amphotericin B plus flucytosine also results in lower mortality compared with amphotericin B monotherapy or combination therapy with amphotericin B + fluconazole.

Usual Adverse Reactions to Antifungals

• Amphotericin B	Fluconazole	Flucytosine
• Nausea, Chills, Fever, Headache • Hypokalemia, Hypomagnesemia • Pain (generalized), thrombophlebitis • Renal function abnormalities, Renal failure • Bone marrow suppression (Thrombocytopenia, Anaemia Agranulocytosis) • Maculopapular rash	• Headache, Vomiting, Nausea • Abdominal pain, Diarrhea Anaphylactic reactions, Angioedema • Cholestasis, Hepatitis, Transaminitis • Hypertriglyceridemia, Hypokalemia • Leukopenia, Thrombocytopenia • Rash, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis	• Nausea,Vomiting, Headache • Abdominal pain, Diarrhea • Hallucinations, Psychosis, Parkinsonism, Ataxia • Anaphylaxis, Photosensitivity, Pruritus, Urticaria • Hypoglycemia, Hypokalemia • Bone marrow suppression (Anemia, Leukopenia, Thrombocytopenia) • Elevated liver enzymes, Hepatitis • Peripheral neuropathy, Paresthesia • Elevated BUN and serum creatinine, Renal failure

Prevent and Monitor Amphotericin B complication

- Always **give Ampho B in D5W** to avoid drug precipitation; **Prehydrate with NS** 1L prior to each dose followed by continuous NS 100-150cc/h (40mEq KCl my be added)
- **Monitor renal functions and serum potassium** at least twice weekly (azotemia and hypokalemia develop in at least 50% of patients).
- **Discontinue** Ampho B if CrCl falls below 50ml/min and no other reversible cause of renal failure.

Management Of Raised ICP

- Subsequently repeat ICP evaluation for any clinical worsening.
- If opening pressure (OP) > 20 cmH_2O drain CSF until pressure = 15- 20 cmH_2O (to avoid risk of herniation repeat measurement after every 10ml removed and avoid reducing pressure by more than 50%) .
- Repeat LP drainage daily until opening pressure is consistently < 20 on 2 consecutive days.
- Mannitol and acetazolamide are not appropriate for control of elevated ICP in the setting of cryptococcal meningoencephalitis.
- There is no benefit to administration of glucocorticoids, except in the setting of immune reconstitution inflammatory syndrome (IRIS).

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Is the paradoxical worsening of an infectious process following restitution of immune function and occurs most commonly in HIV patients with initiation HAART.
- Distinguishing between IRIS, relapse or progression of cryptococcal infection, and other infections or complications can be difficult.
- Active cryptococcal infection have positive CSF cultures, whereas patients with IRIS have sterile CSF cultures.
- Recommendations are to treat through the IRIS (complete antifungal course).

IRIS Cont'd

- For increased ICP give oral glucocorticoids (prednisone 0.5 to 1 mg/kg once daily), to be tapered over 6 weeks.

When to initiate HAART?

- There is a 20% mortality with crypto-associated IRIS! ARV should be delayed until 5 weeks after starting initiation therapy and started only if patient has improved clinically and has consistent opening pressures < 20 cmH_2O.

Cerebral Cryptococcomas

- **Induction therapy** should consist of **amphotericin B deoxycholate** (0.7 to 1.0 mg) or **liposomal amphotericin B** (3 to 4 mg/kg IV OD)
- Plus **flucytosine** (100 mg/kg PO OD) for at least 6 weeks. Consolidation and maintenance therapy consists of **fluconazole** (400 to 800 mg PO OD) or 6 to 18months.
- The duration of therapy depends on the clinical and radiographic response.
- Some brain lesions persist radiographically for long periods and/or develop surrounding edema.

Cryptococcomas Cont'd

- Glucocorticoids may be administered in the setting of mass effect and surrounding edema, especially if there are neurologic deficits.
- Surgical removal may be necessary for large (≥3 cm) lesions and lesions with mass effect with substantial surrounding edema.
- Surgery may also be needed in the setting of optic nerve involvement and in cases unresponsive to prolonged or repeated induction antifungal therapy.
- Shunting is indicated for symptomatic hydrocephalus with dilated cerebral ventricles.

Persistent or Relapsed Infection

- **Persistent infection** refers to persistently positive CSF cultures after 4 weeks of appropriate antifungal therapy.
- **Relapse of infection** refers to resolution of infection followed by subsequent recurrence (as demonstrated by new symptoms of cultures of cryptoccoci).
- Most cases are attributable to inadequate primary therapy (dose and/or duration) or insufficient adherence to consolidation or maintenance fluconazole therapy.

Persistent or Relapsed Infection Factors

Risk factors for relapse include:

- Low initial CSF white blood cell counts
- Persistently low CSF glucose concentration after 4 weeks of therapy
- Treatment with prednisone (≥20 mg) or equivalent after completion of antifungal therapy

Treatment of Persistent or Relapsed Infection

- Repeat induction phase therapy should be reinstituted for a longer course (4 to 10 weeks) and a surveillance lumbar puncture should be performed after 2 weeks of therapy.
- The amphotericin B dose may be increased. (max dose).
- In azole exposed patients, increasing the dose of the azole alone is unlikely to be successful. Amphotericin B deoxycholate (1.0 mg/kg IV OD) should be administered until CSF is sterile.
- Pending in vitro susceptibility testing, salvage consolidation therapy with fluconazole (800 to 1200 mg PO OD) should be reinstituted.
- If all else fails consult a specialist.

Prognosis

CNS cryptococcosis is fatal unless treated, mortality rates of 6-14%. A minority of patients die within the first 6 weeks after diagnosis, despite treatment.

Predictors of poor prognosis are controversial, but they have included the following:

- High CSF cryptococcal antigen titer
- Minimal CSF pleocytosis
- Altered mental status at presentation
- Positive India Ink preparation
- Hyponatremia
- Positive cultures from extrameningeal sites

Primary Prophylaxis

- Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients who have CD4 counts <100 cells/μL.
- However, in the USA, primary prophylaxis in the absence of a positive serum cryptococcal antigen test is not recommended.
- There is lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance and increased burden of cost.

THANK YOU FOR YOUR ATTENTION

The Floor Now Belongs to the Audience

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