

17 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

IDBR
INFECTIOUS
DISEASE
BOARD REVIEW

AUGUST 20-24
2022

Fungal Disease in Normal and Abnormal Hosts

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Bethesda, Maryland

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Disclosures of Financial Relationships with Relevant Commercial Interests



- None

For those not easily offended.....
I offer you the basics!!

WHAT IS A FUNGUS??



The basics: FUNGI ARE YEASTS OR MOLDS
OR BOTH: YEAST IN THE BODY AND MOLD IN CULTURE (DIMORPHIC)

YEAST (SIZE OF LYMPHOCYTE)	MOLD (longer, WIDER THAN BACTERIA)
DAUGHTER CELL BUD	HYPHA SPORES (CONIDIA)
	
Smooth colony (Cryptococcus)	Fuzzy colony (Aspergillus)

Moving on to the Advanced Course:
Good sources of board exam questions

- Recognize clinical features and host factors for
 - Histoplasmosis
 - Cryptococcosis
 - Coccidioidomycosis
 - Blastomycosis
 - Candidiasis
 - Aspergilliosis
 - Mucormycosis
 - Fusariosis
- Know exposures and endemic areas of histoplasmosis, coccidioidomycosis, and maybe paracoccidioidomycosis

Case 1

- 42 yr WF with Crohn's disease taking adalimumab is admitted to a Chicago hospital because of 6 weeks of low grade fever, pancytopenia and a 10 pound weight loss. Hydrocortisone 200 mg daily was begun for low serum cortisol not responding to Cortrosyn stimulation. Admission studies found her long standing anemia has worsened, with a hematocrit of 25%, platelet count 30,000, WBC 2,500 with a normal differential, alkaline phosphatase 250, ALT 120, AST 89 and creatinine 2.0 Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture. This infection came from:
 - a. Her intestinal tract
 - b. Human (coughing)
 - c. Pigeon droppings
 - d. Soil
 - e. Contaminated food

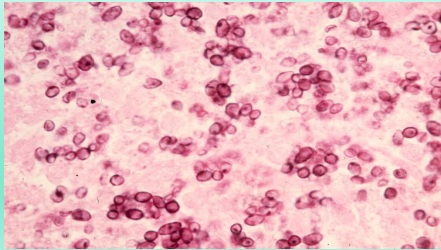
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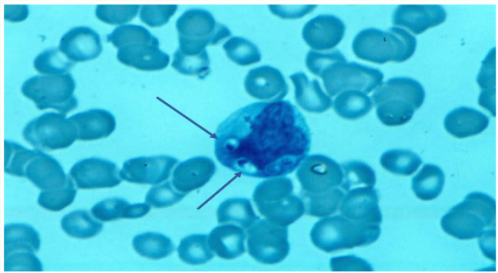
Histoplasma capsulatum

- Central USA highest exposure. Rich moist earth. Subclinical common.
- Disseminated infection mostly immunosuppressed, variable clinical presentation. Fatal in untreated
- Subacute or chronic. Fever. Cytopenias. Addison's. Endocarditis. Mucosal lesions in mouth, larynx, bowel. Miliary lung lesions.
- Diagnosis: antigen in serum, urine or CSF, pathology, culture is slow.
- Rx: amphi if severe. Itraconazole.

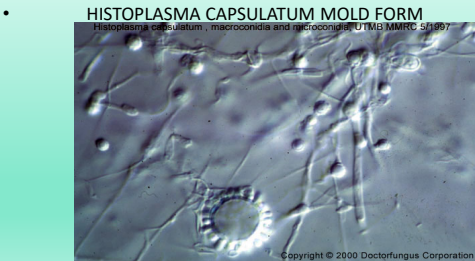
HISTOPLASMA CAPSULATUM in tissue, GMS (silver) stain



HISTOPLASMA CAPSULATUM YEASTS IN MONOCYTE



Histoplasma capsulatum growing at room temperature

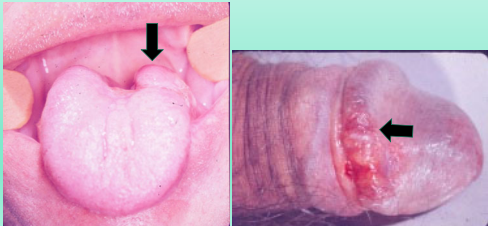


Gingival Ulcer



¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA



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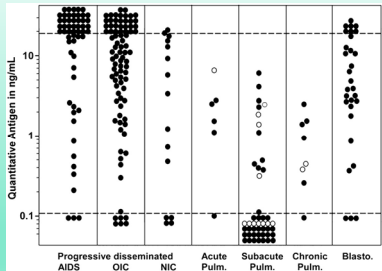
HISTOPLASMA IS A CAUSE OF "CULTURE NEGATIVE" ENDOCARDITIS (PERFORATED AORTIC VALVE)



MILIARY LUNG LESION IN DISSEMINATED HISTOPLASMOSIS (LOOKS LIKE PCP ON IMAGING)



Results for cases of proven and probable histoplasmosis and proven blastomycosis.



Hage C A et al. Clin Infect Dis. 2011;53:448-454

Clinical Infectious Diseases

REVIEW:

DISSEMINATED HISTOPLASMOSIS

TNF ALPHA INHIBITORS, AIDS, CORTICOSTEROIDS, IMMUNOSUPPRESSION
NEUTROPENIA DOESN'T PREDISPOSE

SOURCE: INHALATION OF ORGANIC SOIL ENRICHED WITH BIRD DROPPINGS

CLINICAL FEATURES: ONSET SUBACUTE OR INDOLENT

PANCYTOPENIA, ORAL LESIONS, MILIARY LUNG LESIONS, ADDISON'S,
BLOOD CULTURE-NEGATIVE ENDOCARDITIS. HLH-LIKE SYNDROME

DIAGNOSIS

YEAST IN BLOOD SMEAR OR BIOPSY. GROWS AS MOLD. (DIMORPHIC)

ROUTINE CULTURES NEGATIVE. FUNGAL CULTURES OFTEN NEGATIVE.

URINE OR SERUM ANTIGEN BEST (CROSS REACTS WITH BLASTOMYCOSIS)

TREATMENT:

AMPHOTERICIN FOLLOWED BY ITRACONAZOLE

FATAL IF UNTREATED

Case 2

44 yr previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache. Cranial MRI was normal. Lumbar CSF had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512. Liposomal amphotericin B was begun at 5.0 mg/kg IV daily. On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

Case 2

The most important next step in this patient is which of the following:

- A. start flucytosine
- B. start fluconazole
- C. Start acetazolamide (Diamox)
- D. Begin daily lumbar punctures
- E. Start dexamethasone

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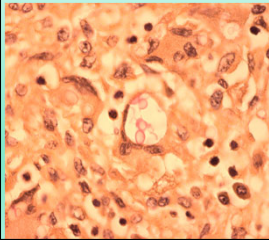
Cryptococcosis

- Encapsulated yeast inhaled from sources in nature. *C. neoformans*, worldwide, pigeon droppings., *C. gattii*: S. California, Vancouver Island, overseas, certain trees
- *C. neoformans*: corticosteroids, AIDS, normal. *C. gattii* more often normal patient. Similar diseases.
- Symptoms: indolent onset. Usually present in CNS as headache, altered mentation
- Diagnosis: antigen in serum, CSF. Yeasts on biopsy or smear. Fungal culture good.
- Rx: ampho +/- flucytosine then fluconazole. Maintenance in HIV
- Start ARV after 2-10 wks of antifungal Rx in HIV naïve patients.
- Daily lumbar punctures for pts with opening pressure of at least 25cm and symptoms
- Pregnancy: use ampho until delivery (5FC is category C, azoles all teratogenic)

More on Cryptococcosis and IRIS

- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDs or prednisone

Cryptococcal lung lesions usually asymptomatic
Skin lesions can resemble molluscum contagiosum
Mucicarmine often stains crypto pink.

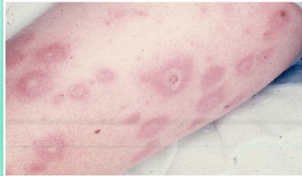


Cryptococcosis review

- Serum antigen good screen in susceptible hosts but can miss early case. LP needed if serum antigen positive. Brain MRI insensitive. CSF antigen sensitive, specific
- Relieve high intracranial pressure to prevent blindness, death
- Start with ampho with fluconazole later. Start with fluconazole if lung only and otherwise healthy
- Wait to start ARV to delay possible IRIS
- Echinocandins not effective

Case 3

35 yr male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.



Case 3

The most likely fungus is which of the following:

- A. *Scedosporium apiospermum* (*Pseudallescheria boydii*)
- B. *Lomentospora* (*Scedosporium*) *prolificans*
- C. *Apophysomyces elegans*
- D. *Fusarium multifforme*
- E. *Alternaria alternata*

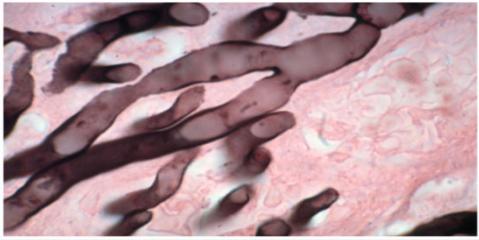
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Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Blood culture grows mold in a third to half the patients
RX: response poor in severe neutropenia
PMN transfusions?
Fusarium solani: ampho?
Other *Fusarium* species : Voriconazole?

Fusarium hyphae. GMS stain



Case 4

- 47 WM executive referred from Baltimore because of severe headaches, diplopia, high fever of 1 wk's duration
- 4 wks PTA: Maui resort one week
- 3 wks PTA: ranch outside Tucson, Arizona 1 wk
- 2 wks PTA: back at work in Baltimore
- 1 wk: PTA: Headache began
- Exam: Temp 38.5 C. Looks ill. Photophobia, nuchal rigidity, right CN6 palsy
- CBC, Routine blood chemistries normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and serum RPR. MRI with contrast normal. Worsens during 2 wks of ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

CASE 4

The most helpful diagnostic test would be:

- A. CSF cytology
- B. Stool O&P
- C. Dietary history
- D. Fungal serology
- E. Leptospirosis serology

Coccidioidomycosis=Valley Fever

- Two species, one disease:
 - *C. immitis* and *C. posadasii*. Both serious lab hazards Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis
- Rx: fluconazole. Nonmeningeal: itraconazole

COCCIDIOIDOMYCOSIS DIAGNOSIS

SEROLOGY

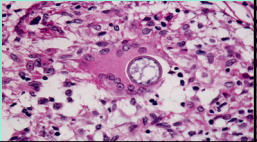
CSF CF serology useful. Serum CF >16 suggests dissemination, falls with Rx
Serum IgG by EIA converts to positive late, stays positive .
Serum antigen may be useful?

CULTURE

Routine cultures negative, fungal cultures positive. Lab hazard

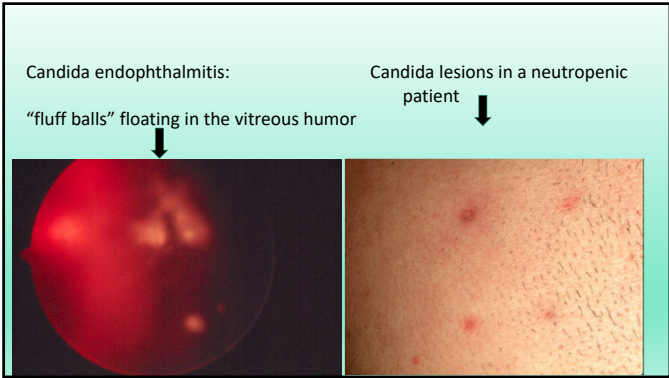
BIOPSY

Distinctive non-budding spherules



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Candidiasis: key points

- Fundoscopy for retinal lesions in candidemia patients.
 - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- Candida auris hospital outbreaks. Poor hygiene
- Fluconazole resistance in C. auris, C. krusei, C. glabrata
- Fungitell (1-3) beta-D-glucan positive in serum

Case 7
32 yr old male with allogeneic hematopoietic stem cell transplant recipient for AML, developed graft versus host disease, given high dose prednisone, discharged and re-admitted for fever not responding to antibacterial antibiotics. These two chest CT's, were taken at admission and a week later while he was responding to voriconazole. The most likely source of infection is:

a. Dirt from his garden
b. His oral flora
c. Contaminated food
d. Intravenous catheter

Aspergillus Pneumonia

Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis but mucormycosis gives same CT findings: halo sign early, crescent sign later

Septated hyphae invade blood vessels, infarct tissue.

Galactomannan useful in CSF, BAL, blood

False positives

False negatives with azole prophylaxis

Rx. voriconazole, isavuconazole, posaconazole, amphotericin B

Two CT's showing transient worsening of CT despite clinical improvement. Note halo sign.

ASPERGILLUS HYPHAE IN AN ARTERIOLE

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Mucormycosis mimics cavernous sinus thrombosis

CASE 8
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA

MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaia
- Broad, flexible nonseptate hyphae right angle branching
- Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
- Massive soft tissue trauma. IV drug abuse
- Hyphae invade blood vessels, causes infarction and necrosis. May form cavity if PMN's return.
- Negative beta d glucan, negative galactomannan
- Rx. Ampho B. Posaconazole f/u. Isavuconazole. Surgical debridement

Control diabetes

HALO SIGN IN A LEUKEMIC

MUCORMYCOSIS

BRAIN ABSCESS IN A HEROIN USER

CAVITY AFTER PMN RETURN

MUCORMYCOSIS
LOCAL EXTENSION FROM PARANASAL SINUS

Mucormycosis:
Vascular invasion

Thrombus in lung

Broad aseptate hyphae

Hyphae in artery

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MYCOSES WORTH MENTIONING

- SCEDOSPORIUM APIOSPERMUM: IMMUNOSUPPRESSED HOST
CLINICALLY RESEMBLING ASPERGILLOSIS . BRAIN ABSCESS AFTER NEAR
DROWNING IN POLLUTED WATER. AMPHOTERICIN B RESISTANT
- TRICHOSPORONOSIS: LIKE CANDIDIASIS BUT ECHINOCANDIN
RESISTANT
- PARACOCCIDIOIDOMYCOSIS: RURAL CENTRAL AND SOUTH AMERICA.
MAY APPEARS DECADES AFTER LEAVING ENDEMIC AREA.
- TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI). SOUTHEAST
ASIA, AIDS, DISSEMINATED INFECTION WITH SKIN LESIONS. YEAST IN
BIOPSY, MOLD IN CULTURE.

The end

Thanks!