24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Fungal Diseases in Normal and Abnormal Hosts

John E. Bennett, MD
Bethesda, Maryland

7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

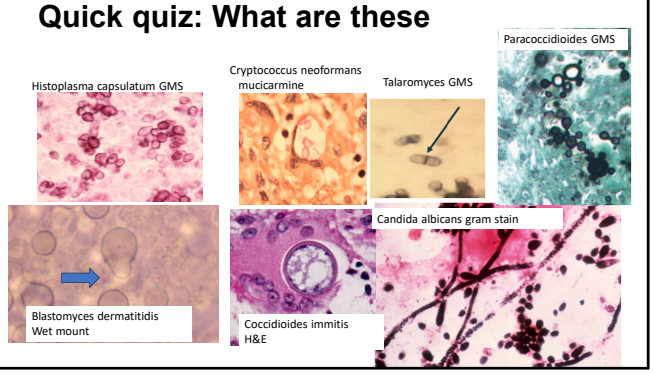
- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

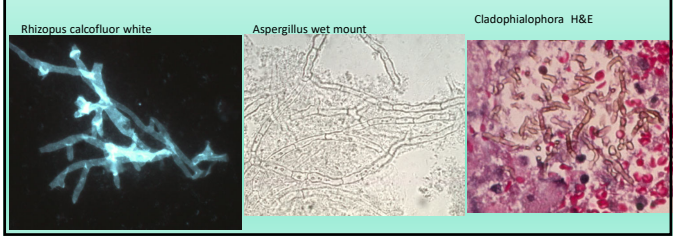
Mycology 101

- Yeasts reproduce by budding
  - All Candida have pseudohyphae in tissue except C.glabrata
  - Crypto has capsule, stains with mucicarmine
- Dimorphic fungi are round cells in tissue, hyphae in culture
  - Histoplasma, Coccidioides, Blastomyces, Sporothrix , Paracoccidioides
- Molds have hyphae in tissue and culture
  - Septate: Aspergillus, Fusarium, Scedosporium, others
  - Rare or no septae (Mucorales): Rhizopus, Mucor, Cunninghamella, others
  - Dark-walled fungi: many cause infection of skin, paranasal sinus, brain
    - Phaeohyphomycosis

Quick quiz: What are these



Quick Quiz: What are these?



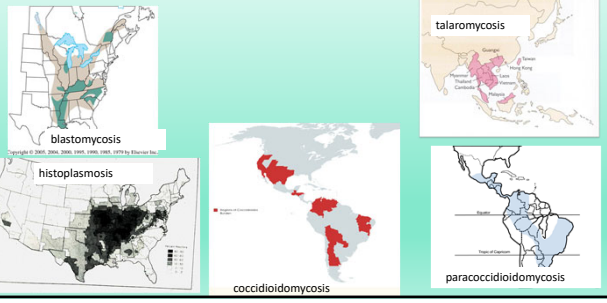
ENDEMIC MYCOSES

- Geographically restricted
- Dimorphic (yeast in tissue,hyphae in culture)
- Infection by inhaling spores in nature
- No person to person transmission
- Cluster of cases with fever, cough after soil exposure
  - No secondary cases
  - Desert dust=cocci. Rich earth, bat guano=histo
    - Streams, rivers=blasto

24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

What are these endemic mycoses?



CASE 1

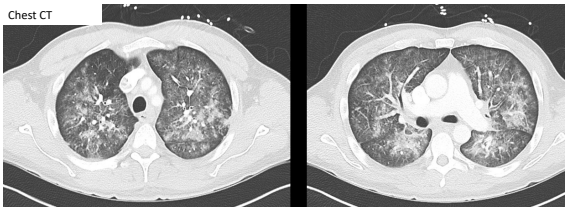
(COURTESY OF SHANAN IMMEL, MD)

PREVIEW QUESTION

- Formerly healthy 48M with 3 months of chronic fevers, cough, 25 lb weight loss, night sweats, presented with acute worsening on dyspnea and was found to have a high fever and diffuse lung infiltrates bilaterally. Office worker in Md. No travel.Wife healthy.
- Vitals: 39.3C, HR 97, RR 29, BP 97/54, O2: 88% on room air
- Crackle all over lung, spleen tip felt.
- WBC: 5,300, HgB 10.1 Plt 119,000, ALP 218, ALT 43, AST54, lactate 2.5, ferritin 2418, triglycerides 250. HIV neg.
- Intubation, pressors, ceftriaxone, voriconazole

PREVIEW QUESTION

Chest CT

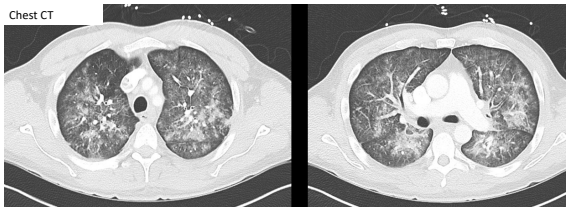


The preferred diagnostic procedure:

A. Bronchoscopy
B. Transthoracic needle lung biopsy
C. VATS lung biopsy
D. Serum antigen
E. Bone marrow

PREVIEW QUESTION

Chest CT



The preferred diagnostic procedure:

A. Bronchoscopy
B. Transthoracic needle lung biopsy
C. VATS lung biopsy
D. Serum antigen *
E. Bone marrow

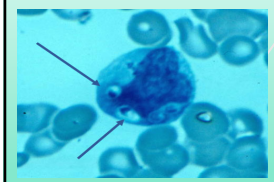
Recognizing mycoses on the board exam

Histoplasma capsulatum complex

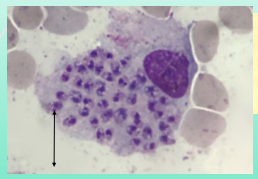
- Case clusters of acute pneumonia two weeks after soil exposure (rare: bat caves)
- Immunosuppressed patient with febrile disseminated disease
  - Cytopenias
  - Miliary lung infiltrate can look like PJP, miliary TB
  - Mucosal lesions resemble squamous carcinoma
  - Adrenal insufficiency
  - Can mimic HLH (hemophagocytic lymphohistiocytosis) or miliary TB
  - HIV patients can have IRIS after starting ARV
- Urine or serum antigen good diagnostic test
- Biopsy: small budding yeast, mold on culture
- Rx: ampho then itraconazole for disseminated
- Histoplasma duboisii (African histoplasmosis)
  - Skin and bone lesions

QUICK QUIZ: WHAT IS THE DISEASE ASSOCIATTED WITH THESE INTRACELLLAR PARTICLES?

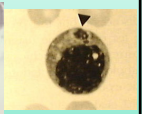
HISTOPLASMOSIS



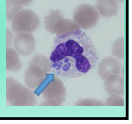
LEISHMANIASIS



EHRLICHIOSIS



ANAPLASMOSIS

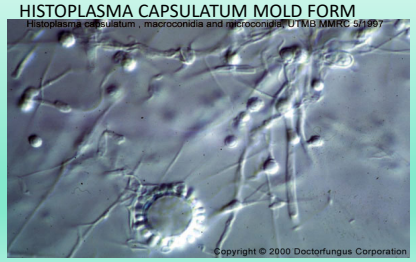


24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

Histoplasma capsulatum growing at room temperature

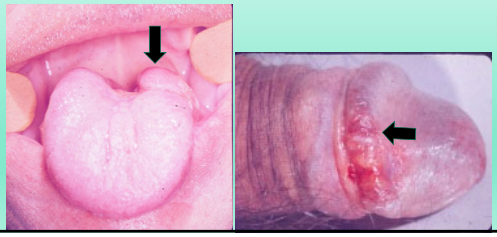
- HISTOPLASMA CAPSULATUM MOLD FORM



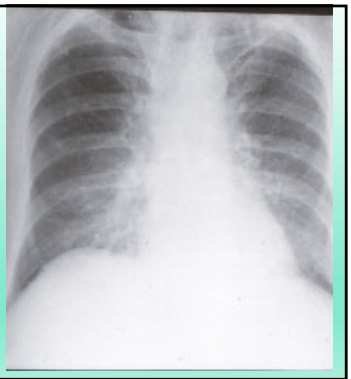
Gingival Ulcer

¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS
MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA



MILIARY LUNG LESION IN DISSSEMINATED HISTOPLASMOSIS (LOOKS LIKE PJP ON IMAGING)



Case

PREVIEW QUESTION

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

PREVIEW QUESTION

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

24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

Case 2

PREVIEW QUESTION

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

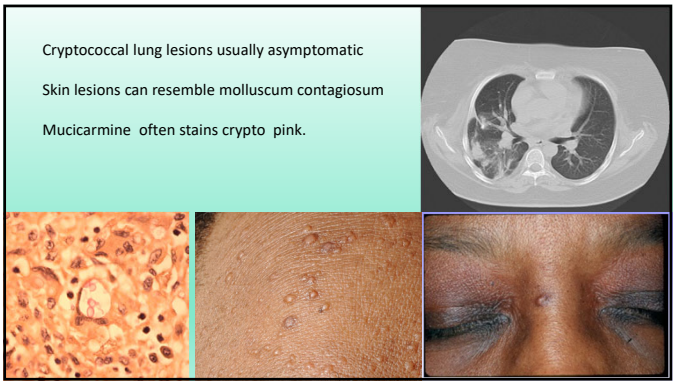
Crypto is a killer, not a currency

- Cryptococcus neoformans species complex:
  - Wordwide, pigeon guano,corticosteroids, transplants, HIV
- Cryptococcus gattii species complex
  - Pacific coast, trees, Australia, tropics, often previously healthy
  - Serum antibody to GM-CSF
- Chronic lymphocytic meningitis
  - Headache, confusion, cranial nerve palsies, +/- fever, vision loss
  - Rx ampho+flucytosine then fluconazole, relieve high opening pressure (LP's, shunt)
  - HIV ARV-naïve: consider delay ARV 2 weeks (IRIS)
  - Skin lesions (10%) like molluscum contagiosum
- Lung only: fluconazole alone (negative LP)
- Cryptococcal antigen in CSF, serum
  - Diagnosis, screening high risk patients

Cryptococcal lung lesions usually asymptomatic

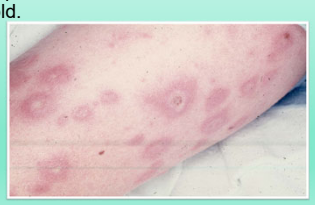
Skin lesions can resemble molluscum contagiosum

Mucicarmine often stains crypto pink.



Case 2

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 multiforme
E. Alternaria alternata

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 multiforme *
E. Alternaria alternata

24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Routine blood culture grows mold in a third to half the patients
RX: response to amph and vori poor in severe neutropenia. Experimental: PMN transfusion?, fosmanogepix (investigational)??
Note: fungal meningitis from F. solani, Mexico, epidural anesthesia.

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

CASE

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

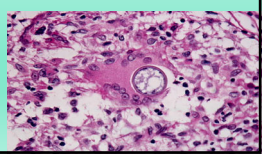
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards
  Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans,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

CULTURE
Routine cultures negative, fungal cultures positive. Lab hazard

BIOPSY
Distinctive non-budding spherules



24 – Fungal Disease in Normal and Abnormal Hosts

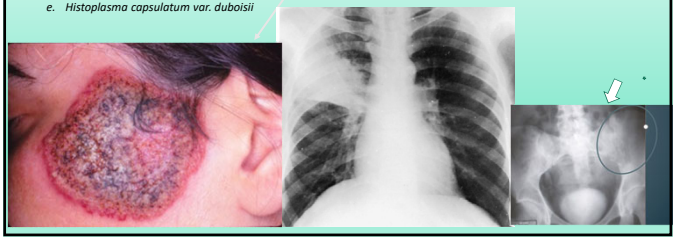
Speaker: John Bennett, MD

CASE 5

A previously healthy 52 yr old Wisconsin man presented with a leg lesion, painful elbow swelling and asymptomatic lung lesion on chest xray and lytic lesion on condyle of his humerus.

This is most likely which of the following:

a. Candida auris
b. Trichosporon cutaneum
c. Leishmania donovani
d. Blastomyces dermatitidis
e. Histoplasma capsulatum var. duboisii



CASE

A previously healthy 52 yr old Wisconsin woman presented with a faciallesion, painful elbow swelling and asymptomatic lung lesion on chest xray and lytic lesion in her pelfic bone

This is most likely which of the following:

a. Candida auris
b. Trichosporon cutaneum
c. Leishmania donovani
*d. Blastomyces dermatitidis **
e. Histoplasma capsulatum var. duboisii

Blastomyces dermatitidis , B. gilchristii

CENTRAL USA AND CANADA, MOLD IN NATURE
LARGE BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

NORMAL HOST

YEAST WITH BROAD BASED BUD, THICK WALL

ACUTE PNEUMONIA MAY SELF HEAL

INDOLENT, PROGRESSIVE PNEUMONIA
DISSEMINATES TO SKIN, BONE, MALE GU TRACT

OFTEN PRESENTS AS SKIN LESIONS

RX: ITRACONAZOLE, AMPHO B

Case 6 : What are these lesions in a febrile, recently neutropenic patient?

CASE 6

Which is the most likely

A. Babesia microti
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

CASE 6

Which is the most likely

A. Babesia microti
B. Candida tropicalis *
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

24 – Fungal Disease in Normal and Abnormal Hosts

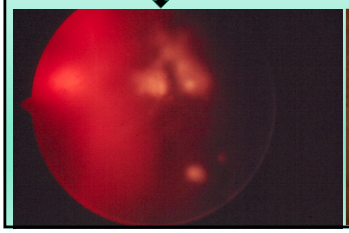
Speaker: John Bennett, MD

Candidiasis makes the sick get sicker

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

Candida endophthalmitis:

"fluff balls" floating in the vitreous humor

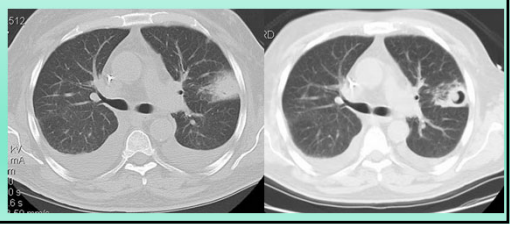


Candida lesions in a neutropenic patient

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:

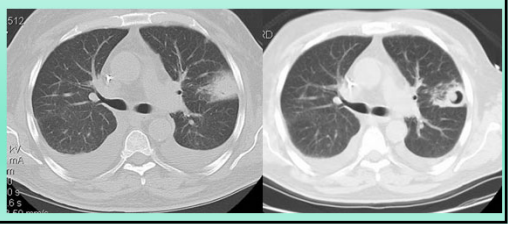
A. Dirt from his garden
B. His oral flora
C. Contaminated food
D. Intravenous catheter



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, halo sign early, crescent sign later

Septated hyphae invade blood vessels, infarct tissue.

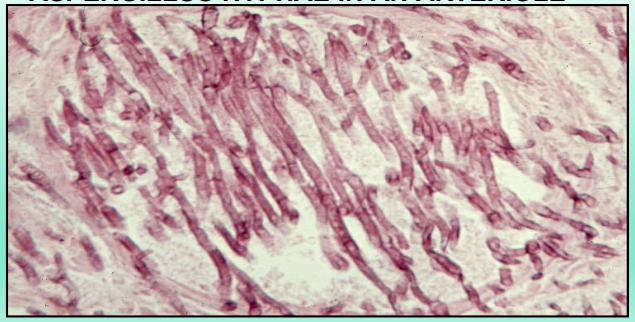
Galactomannan useful in CSF, BAL, blood

False positives

False negatives with azole prophylaxis

Rx. voriconazole, isavuconazole, posaconazole, ampho B

ASPERGILLUS HYPHAE IN AN ARTERIOLE



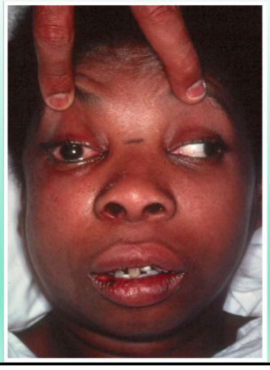
24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

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:

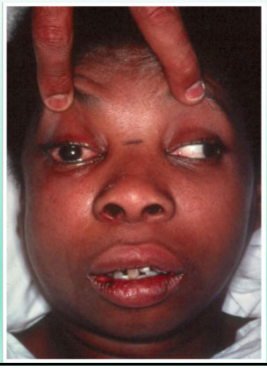
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA



CASE 8

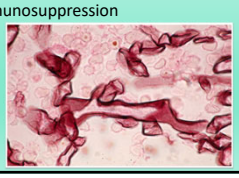
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:

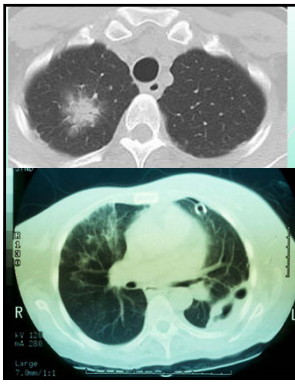
A. RHIZOPUS *
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA



MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae, right angle branching
- Rhinoorbital: poorly controlled DM2 or immunosuppression
- India: severe COVID + DM2+steroids
- Pulmonary: neutropenia, immunosuppression

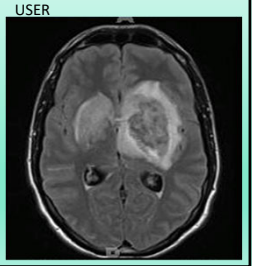




HALO SIGN IN A LEUKEMIC

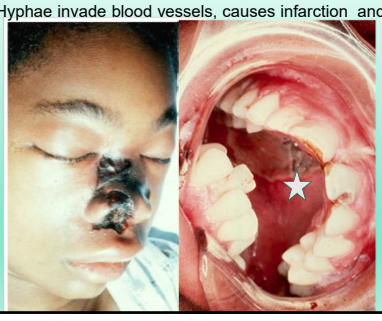
MUCORMYCOSIS

BRAIN ABSCESS IN A HEROIN USER



CAVITY AFTER PMN RETURN

Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
India: COVID-19+ corticosteroids+ poorly controlled diabetes mellitus
Hyphae invade blood vessels, causes infarction and necrosis.



-Rx. Ampho
Followup: Posaconazole o
Isavuconazole?

-Surgical debridement

-Control diabetes.

-Decrease immunosuppression.

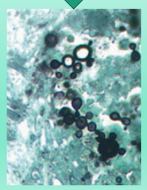
24 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

PARACOCCIDIOIDOMYCOSIS:
- RURAL CENTRAL AND SOUTH AMERICA.

-MAY APPEAR DECADES AFTER LEAVING ENDEMIC AREA.

MULTIPLE BUDS



TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI).

SOUTHEAST ASIA

MOSTLY AIDS

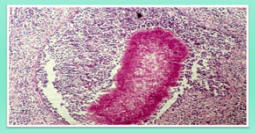
YEAST IN BIOPSY, MOLD IN CULTURE.
DIVIDES BY FISSION

DISSEMINATED INFECTION WITH SKIN LESIONS

MYCETOMA (Madura foot)

MINOR TRAUMA TO FOOT OR HAND
FIRM SWELLING PROGRESSES OVER YEARS
DRAING SINUSES

GRAINS IN PUS
FUNGI OR HIGHER BACTERA



MYCOSES WORTH MENTIONING

- SCEDOSPORIUM APIOSPERMUM: IMMUNOSUPPRESSED HOST CLINIALLY RESEMBLING ASPERGILLOSIS . BRAIN ABSCESS AFTER NEAR **DROWNING** IN POLLUTED WATER. ***AMPHOTERICIN B RESISTANT***
- TRICHOSPORONOSIS: LIKE CANDIDIASIS BUT ***ECHINOCANDIN RESISTANT***

THAT'S IT!

It' s all perfectly clear, isn't it?