Histoplasmosis

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Disclosure

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- Astellas – consulting fees

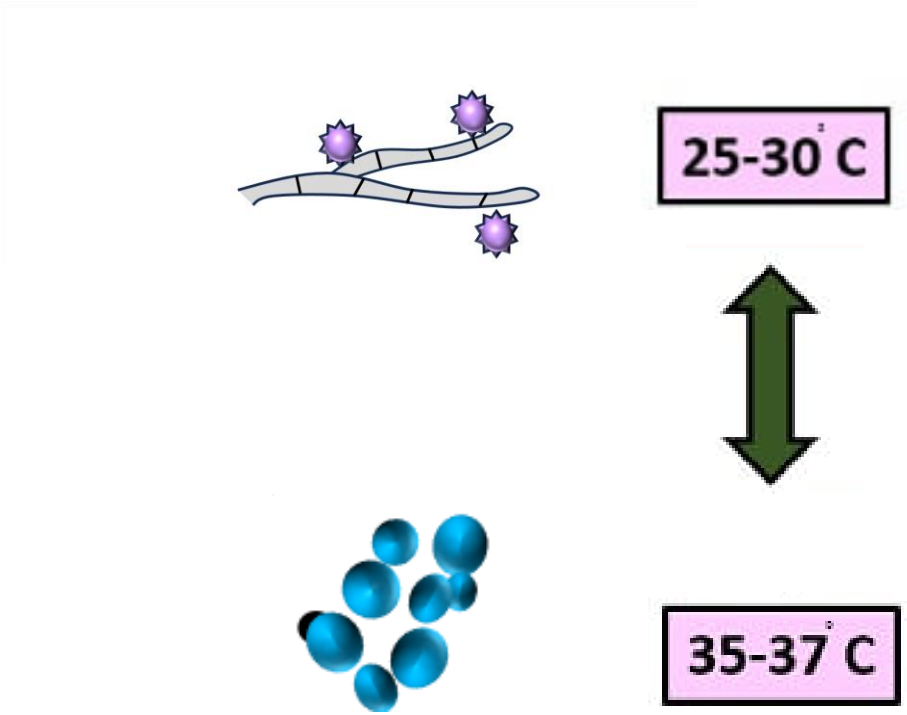
Introduction

Why is important to talk about histoplasmosis?

- Most prevalent endemic mycosis in US
- Invasive fungal infection that often presents as pneumonia
- Affects both immunocompetent and immunocompromised pts
- Often cannot be distinguished from other causes of respiratory illness based on clinical presentation alone
- >50% patients with histoplasmosis are misdiagnosed and receive inappropriate treatment
- Endemic disease, but …
  - travel and climate → may present outside endemic area

Microbiology

- *Histoplasma capsulatum* var. *capsulatum* (near-worldwide distribution)
- *Histoplasma capsulatum* var. *duboisii* (in Africa)

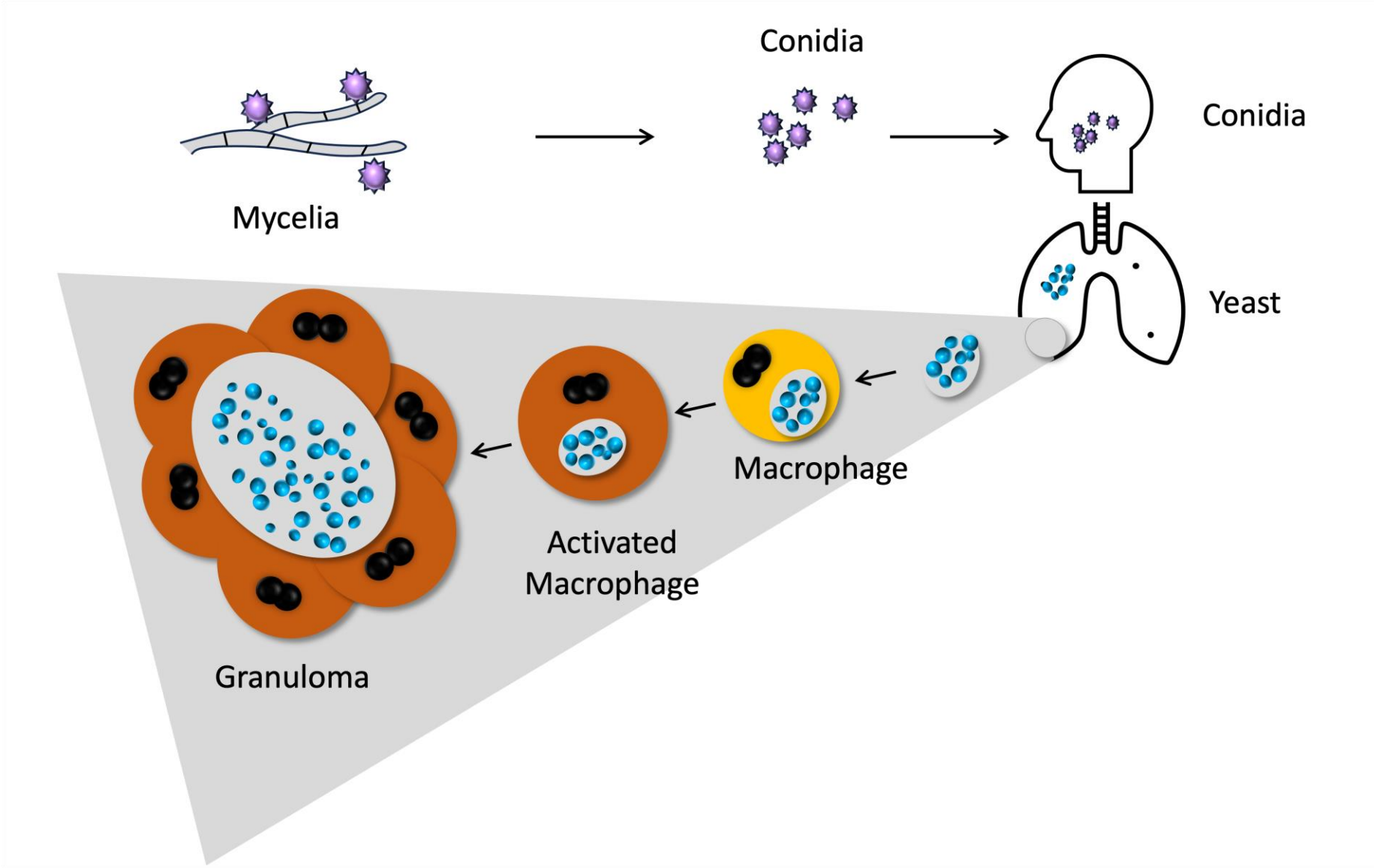


Dimorphic fungi:

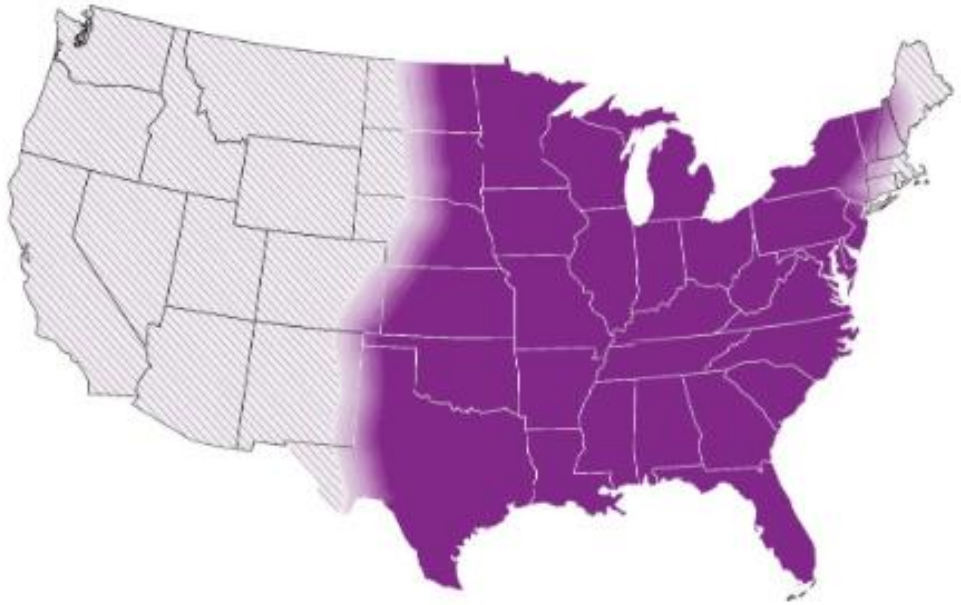
- mold in the environment
- yeast at body temp

Examples: *Histoplasma*, *Blastomyces*, *Coccidioides*

Life cycle of *Histoplasma*



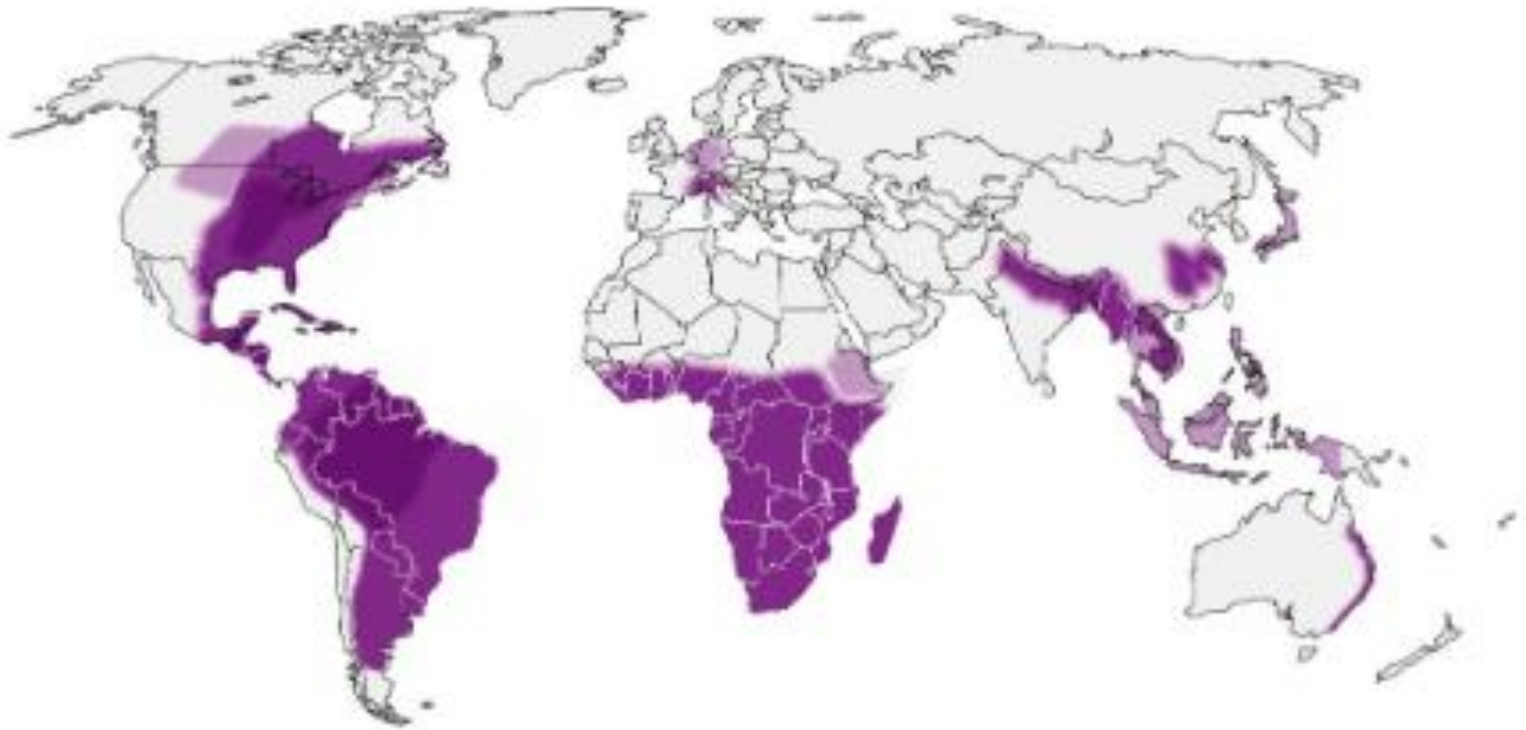
Epidemiology – endemicity



- Ohio and Mississippi River valleys
  - 60-90% exposed during their lifetime
  - Highest rates of dz occur in the Midwest
    - 6.1 vs. 3.4 cases /100,000 population (>65yo)

https://www.cdc.gov/fungal/cdc-and-fungal/histoplasmosis.html

Epidemiology - endemicity



Central and South America, Africa, Asia, and Australia

https://www.cdc.gov/fungal/cdc-and-fungal/histoplasmosis.html

Risk factors, people at risk

- Living in endemic areas
  - Exposure to soil that contains bird or bat droppings

- Disseminated histoplasmosis is more likely to occur in
  - immunosuppressed persons
    - HIV/AIDS, organ transplant, or use of immunosuppressive medications
  - Infants
  - > 55 years
  - Heavy exposure

Significant Exposures

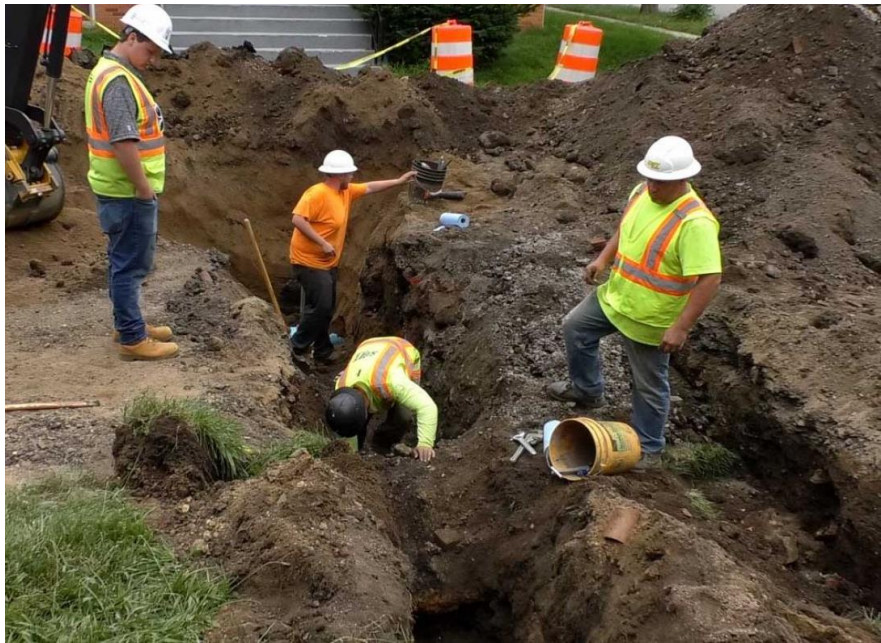
- Excavation, construction, demolition, remodeling, with cutting and gathering, exploring caves, cleaning structures that are encrusted by bird or bat guano

Significant Exposures

- It is thought that the bird and the bird and bat droopins, increase the nitrogen content of the soil which favors growth of histoplasma

Outbreaks

- Outbreaks may occasionally occur in the setting of:
  - construction,
  - renovation,
  - exploring caves,
  - tilling soil,
  - cleaning up bird roosting sites



Transmission

- Acquired via inhalation of airborne microconidia
- Primary cutaneous histoplasmosis and solid organ donor-derived histoplasmosis are extremely uncommon
- No person-to-person transmission / not contagious
- Dogs and cats can get histoplasmosis
  - They do not transmit the dz

Clinical Presentation

- Clinical presentation typically depends on the inoculum of the exposure and the immunological status of the patient

- Most infections are asymptomatic or self limited
- Symptoms include:
  - Fever, malaise, cough, headache, chest pain, chills, and myalgias

Clinical Presentation

- Symptomatic Dz
  - Pulmonary Infection
  - Severe and progressive disseminated infection

Pulmonary Histoplasmosis (PH)

- Acute Symptomatic PH
- Acute Diffuse PH
- Chronic PH (pt with underlying lung dz)
- Bronchiectasis
- Mediastinal granuloma/lymphadenitis
- Fibrosing Mediastinitis

(less frequent → pericarditis)

Suspect pulmonary histoplasmosis if…

- Pneumonia with mediastinal or hilar lymphadenopathy
- Mediastinal or hilar masses
- Pulmonary nodule
- Cavitary lung disease
- Pericarditis with mediastinal lymphadenopathy
- Pulmonary manifestations with arthritis or arthralgia plus erythema nodosum
- Dysphagia caused by esophageal narrowing
- Superior vena cava syndrome or obstruction of other mediastinal structures

Severe / disseminated Dz

- Severity of illness depends on host immunity and the intensity of the exposure.
- Immunosuppressed persons are at risk for developing disseminated histoplasmosis
  - T- cell immunity is key in controlling dz
  - IL-2, IFN-gamma and TNF alpha key

  SOT
  TNF alpha inhibitors (infliximab, etanercept adalimumab, etc
  HIV (AIDS, no ART)
  HD steroids
  Extremes of age
  Pregnancy?

Clinical presentation

- Timing from exposure to presentation is variable
- Fever, fatigue, night sweats, diarrhea
- Respiratory symptoms may be present
- Symptoms vary depending on organs affected
  - LN
  - GI – (diarrhea, esophagitis, bleeding, etc)
  - Lungs (cough, SOB)
  - CNS (AMS, headaches)
  - Skin (ulcers, papules, nodules, etc)
  - Adrenal (electrolyte abn, hypotension, hypoglycemia)
  - Heart (endocarditis)

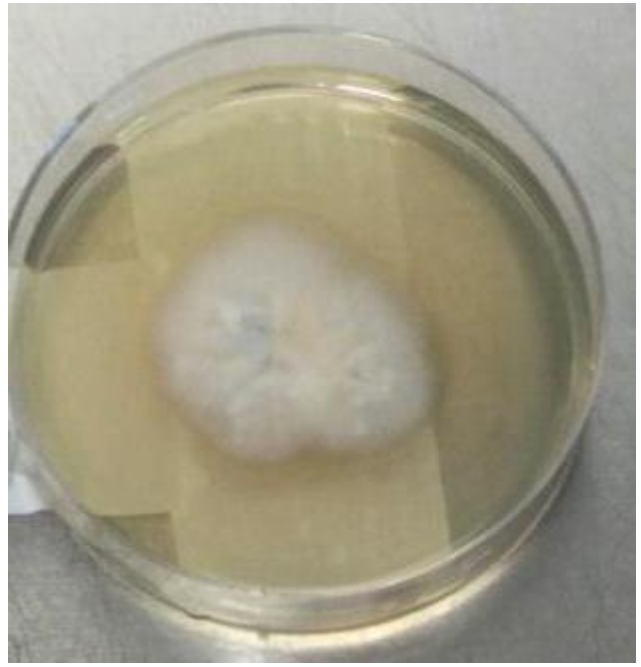
Laboratory abnormalities

- Anemia
- Leukopenia
- Thrombocytopenia
- Transaminases elevation (AP and Bil as well)
- LDH elevation
- Ferritin elevation

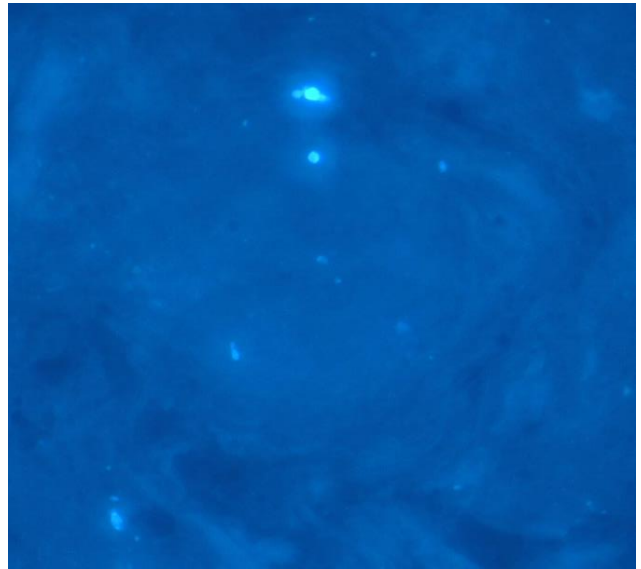
Culture based testing

- Culture: can be performed on tissue, blood, and other body fluids (BAL, others)
  - may take up to 6 weeks to become positive
  - highly specific

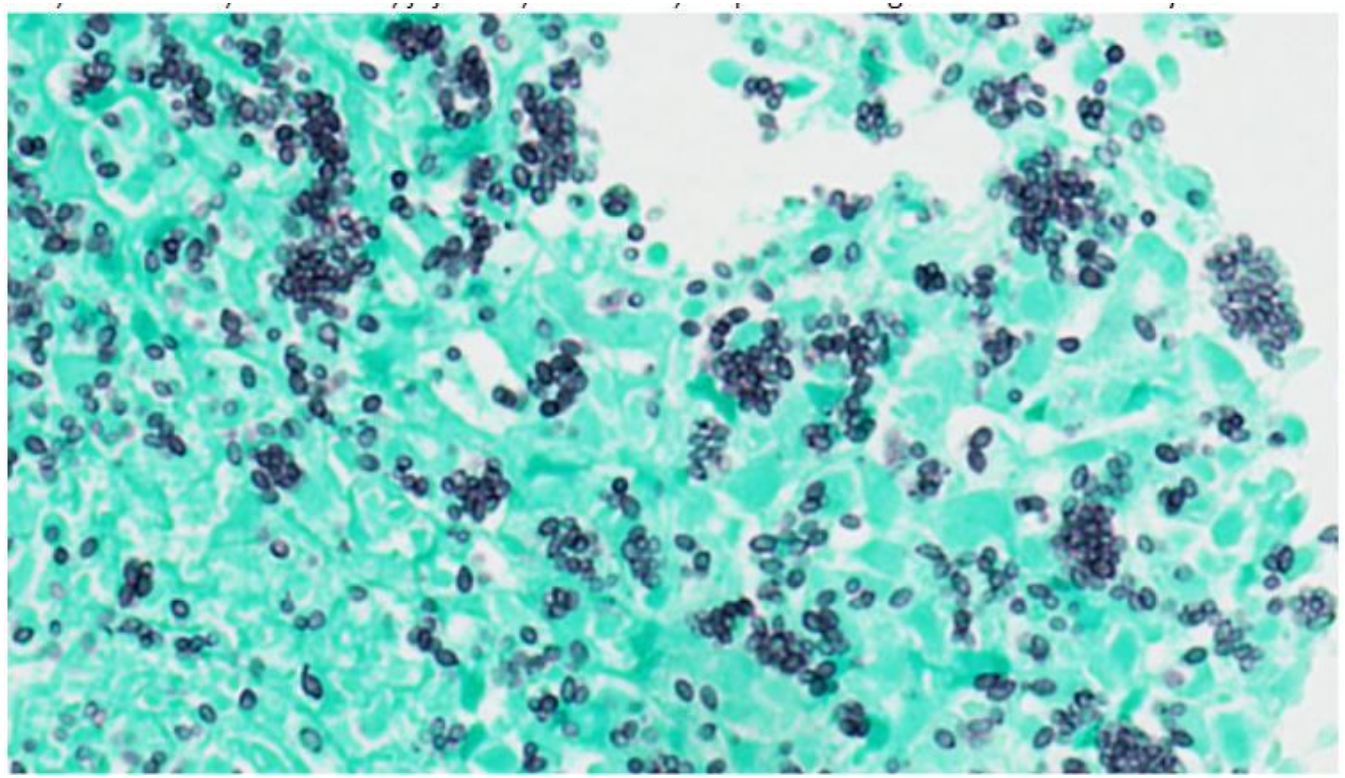
- Direct microscopy/smear
  - Calcofluor fluorescent stain
    - low sensitivity, but highly specific quick



Modified from https://www.intechopen.com/chapters/72531



Histoplasmosis – histopathology



Diagnosis

Antigen detection

Enzyme immunoassay (EIA)

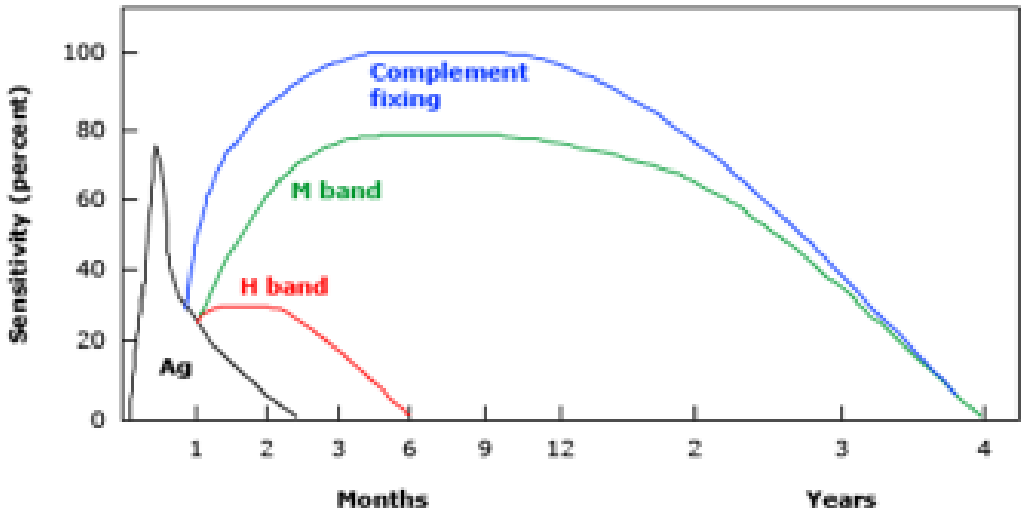
- typically, on urine and/or serum
- can be done on cerebrospinal fluid (CSF) or bronchoalveolar lavage fluid (BAL)

Antibody detection assays

- Immunodiffusion targets *Histoplasma* proteins M (a catalase) and H (a β-glucosidase) – takes 4-6 weeks to develop (IgG)
  - H band (persists 1-2 years)
  - M band (can persist up to 3 years after the infection has resolved)
  - (when both are present, likely more recent infection)
  - Sens 72-95%; spc 100%

- Complement Fixation (CF): antibodies may take up to 6 weeks to develop.
  - Detects ag-ab complex
  - ≥1:32 or a 4-fold rise indicate active infection
  - Sens 80-95%; spec 80%

Overview of serology and antigen tests in acute pulmonary histoplasmosis



Histoplasma capsulatum antigen (Ag) can be detected in patients with acute pulmonary histoplasmosis and is found more commonly in patients with severe clinical manifestations. Detection of high titers of complement fixing antibodies to the yeast or mycelia antigen precedes detection of M or H bands by immunodiffusion in most patients. However, antibodies rarely appear before the fourth week of infection and often do not reach maximal titers until the second or third month of infection.

Courtesy of Joseph Wheat, MD.

Test	Sensitivity	Specificity	Population Studied
Antibody Tests			
EIA antibody[8]	98%	97% (high cross-reactivity with *Blastomyces*)	Immunocompromised & healthy populations
Complement fixation (CF) antibody[9]	72%–95%	70%–80%	Adult populations
Immunodiffusion (ID) antibody[9]	70%–95%	100%	Adult populations
Antigen tests			
EIA Urine antigen[7]	79%	99%	Adult population, people living with HIV
EIA Serum antigen[7]	82%	97%	Adult population, people living with HIV
Other tests			
Culture[10]	15%–85%	100%	Acute or subacute, disseminated disease
Microscopy/histopathology[10]	9%–43%	100%	Acute or subacute, disseminated disease

https://www.cdc.gov/fungal/cdc-and-fungal/histoplasmosis.html

CASE 1

- 61 y.o. male
- heart transplantation in June of 2020 @Duke U
- August 2020 - CMV viremia, pulmonary aspergillosis
- Presents in June 2023
- Patient and wife are full time RVers, they were here in Michigan visiting family, reported he was having generalized fatigue and body aches and fevers for about 2 weeks
- he contacted Duke's heart transplant providers who recommended evaluation at the University of Michigan
- At presentation he was febrile, otherwise HDS hemodynamically stable, with ongoing diarrhea

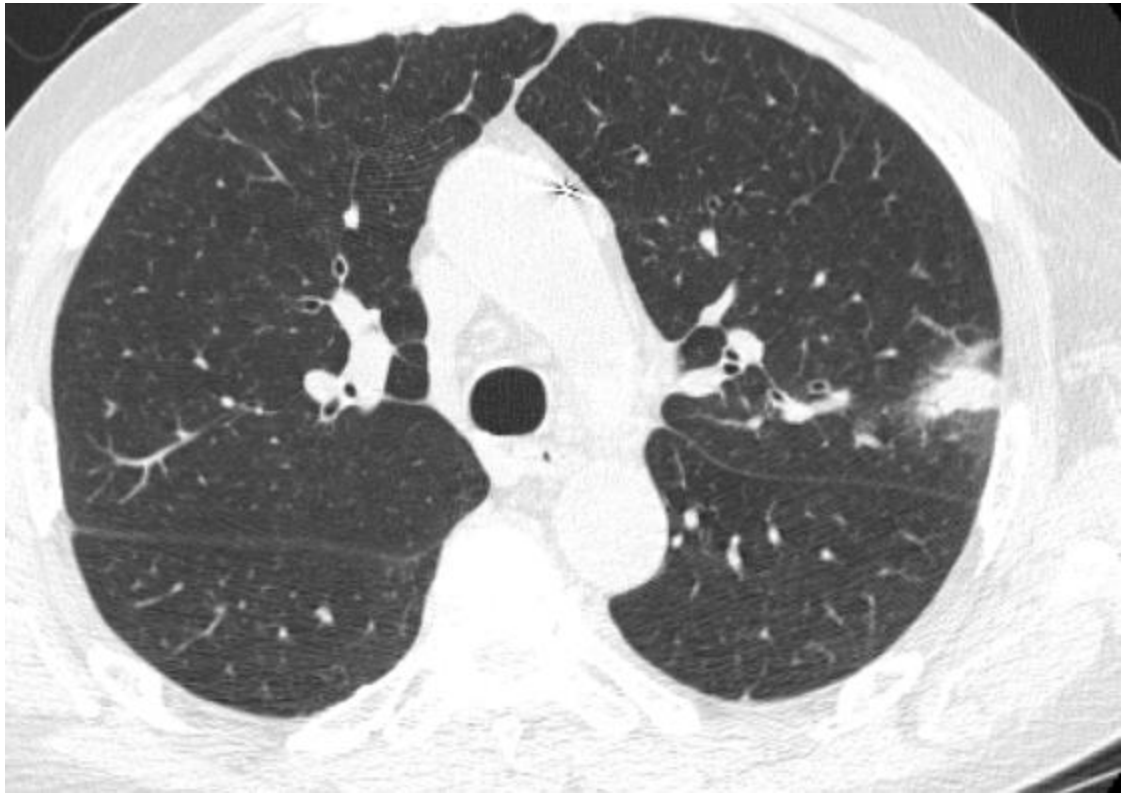
CASE 1 Labs

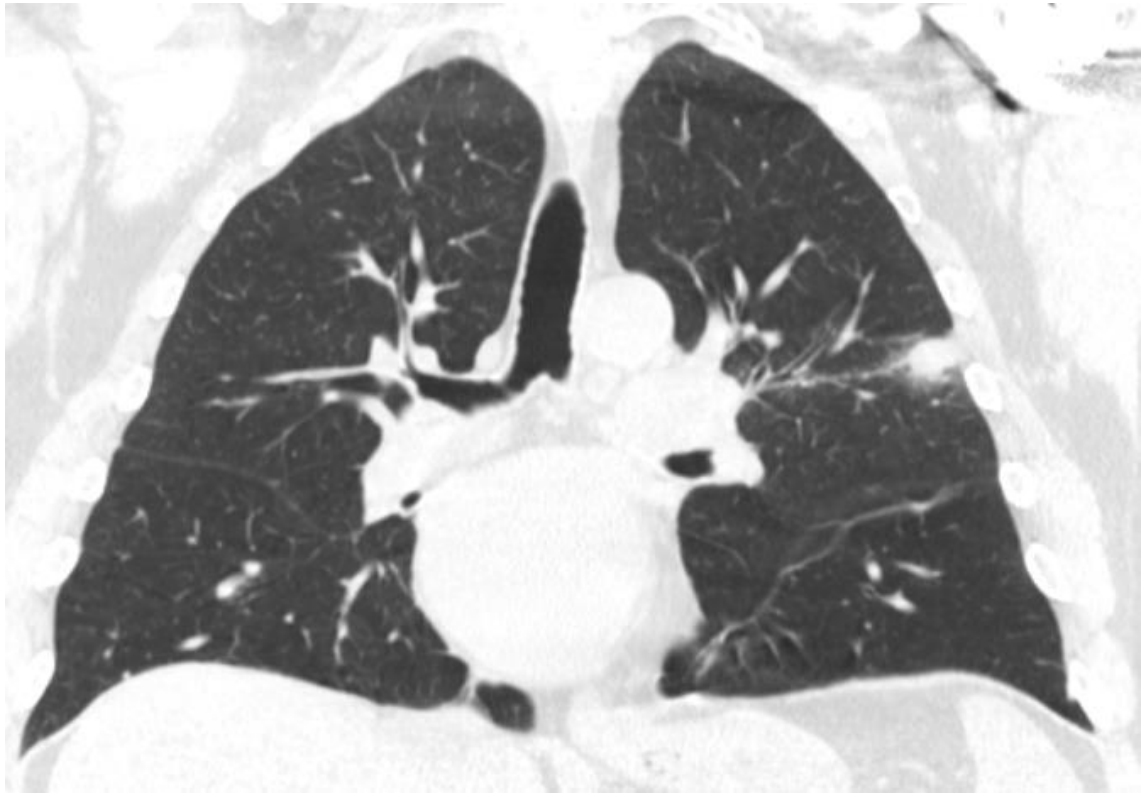
- WBC 2.8 (ALC 300)
- HB 12
- PLT 88
- Create 2.51
- AST /ALT 51/49

CASE 1 – Exposures

- Patient has been in Michigan, in the RV park x 3 months
- he works @ RV park, his duties include mowing the lawn, maintenance, stated he had been working on a ground pipe.
- Prior to Michigan, he had been in Arkansas where he was at a friend's house, helping him to build a barn - this work included cutting pine wood and mounting it in the walls and ceilings.
- He denies any sick contacts.
- No tobacco, THC or IVDA, no alcohol

CASE 1- CT chest





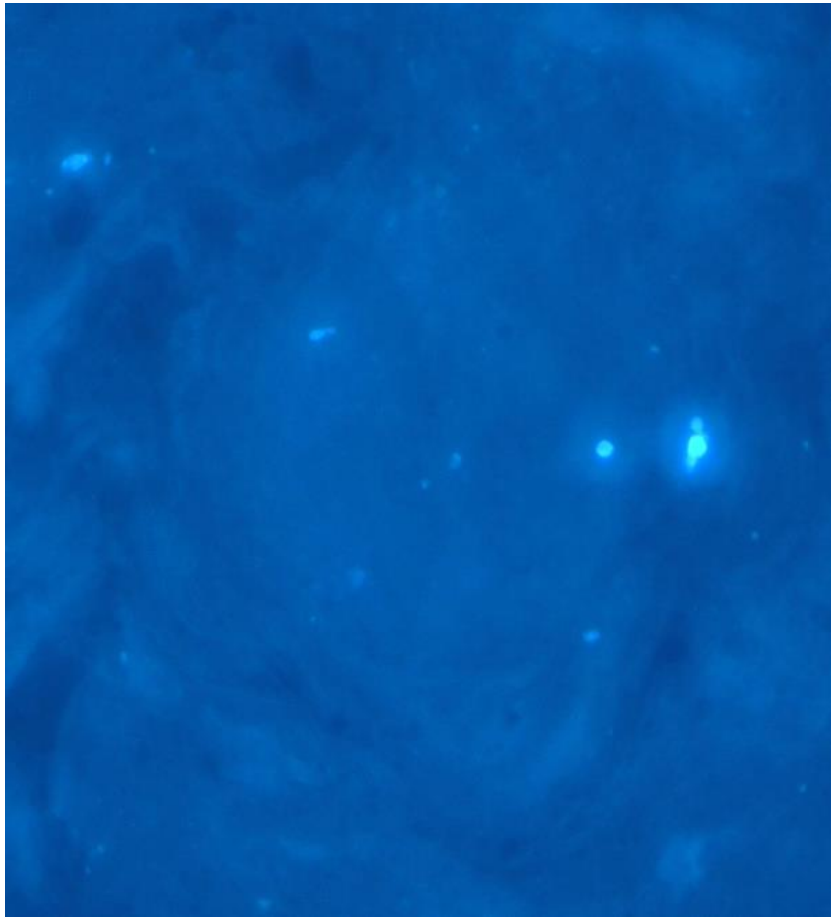
CT chest: New areas of nodular consolidation with surrounding GGOs in the RUL, with the larger more peripheral area of nodular consolidation measuring up to 16 mm with a smaller and more central area of nodular consolidation measuring 9 mm.

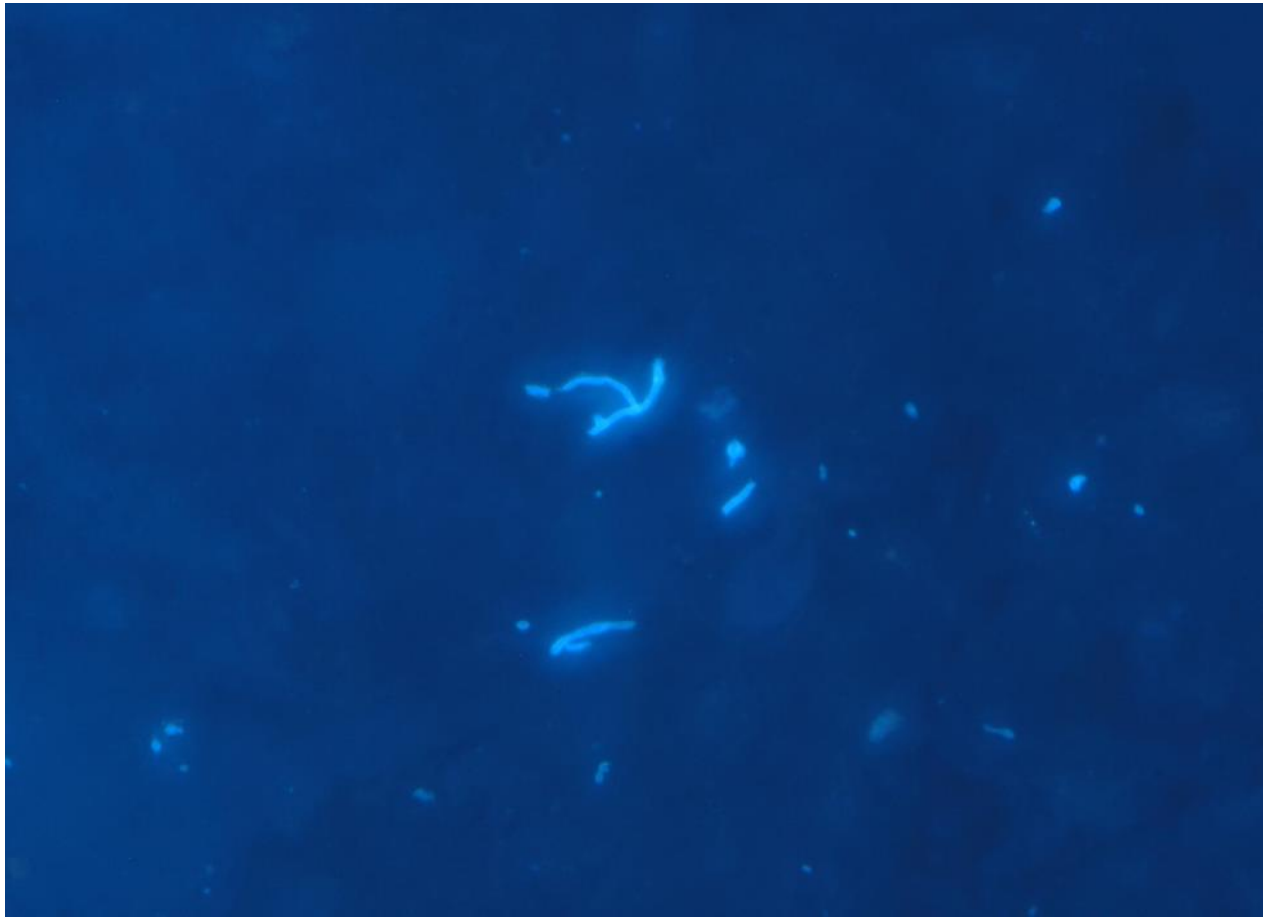
CASE 1 Testing

- BC neg
- Histoplasma ag urine >20 (above the limit of quatification)
- Histoplasma ag serum: 15.27
- Blastomyces ag urine ag ALQ
- Blastomyces ag serum: 9.85

CASE 1 - Calcofluor stain from blood culture

BAL smear and culture – (+) Histoplasma capsulatum





Treatment

- Indication to treat is determined by
  - Severity of dx
  - Host

- Mild to moderate acute pulmonary histoplasmosis will often resolve without treatment
- Severe acute pulmonary, chronic pulmonary, disseminated dz → need treatment

Treatment → ID consult

- Moderate and Chronic pulmonary → oral treatment (ITRACONAZOLE)

- Disseminated, and central nervous system (CNS) histoplasmosis → require IV lipid formulation amphotericin B for ~2 weeks (CNS typically requires 6 weeks of IV) followed by itraconazole step-down therapy (6-12 months)
- Limitations of L-AMB → renal toxicity and electrolyte abnormalities
- Itraconazole capsules → absorption improves with gastric acidity (avoid PPI, antiacids), can give with coca cola
- Itra liquid →well absorbed in empty stomach – but GI SA
- Posacoanzole is an option when pt cannot take Itra
- TDM – needed with itra and other azole drugs
- Less effective drugs: flu, vori, isavuconazole

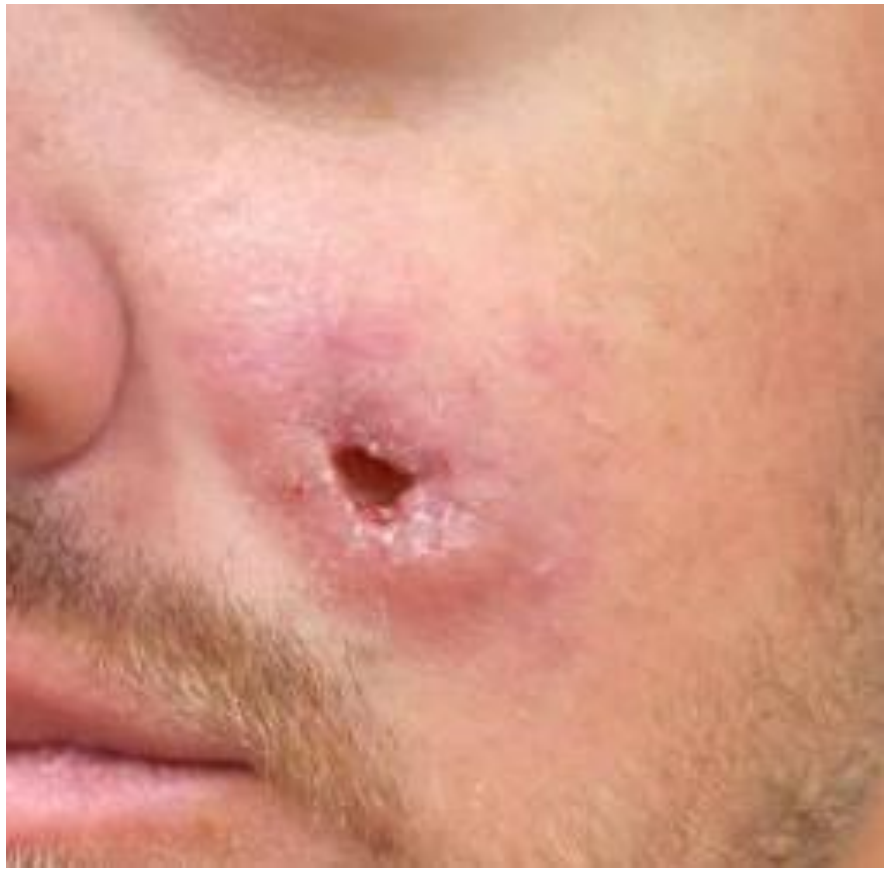
Treatment – Disseminated Histoplasmosis

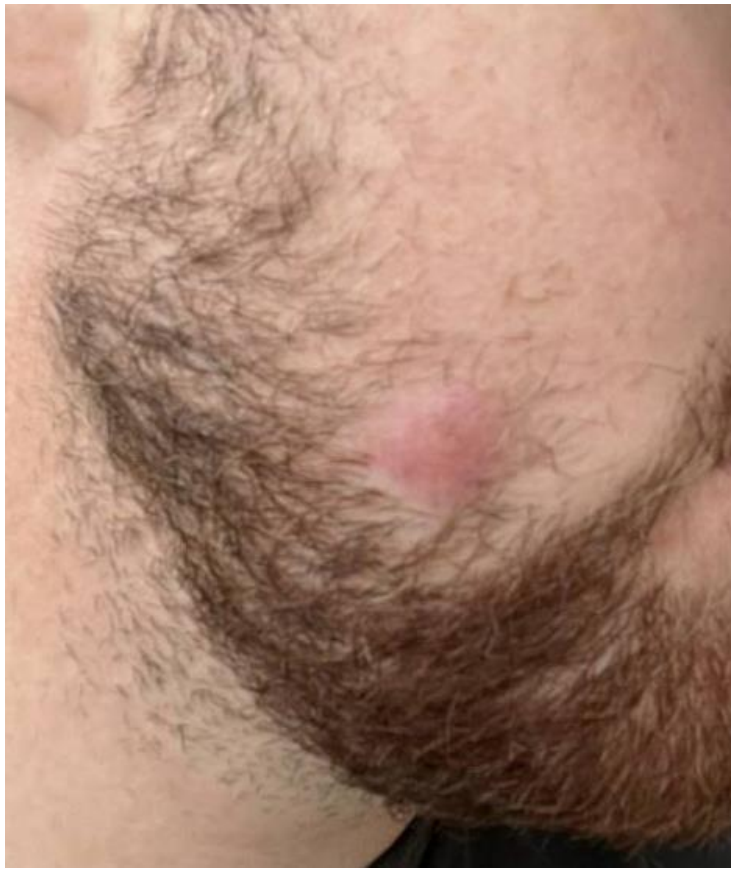
- IV liposomal amphotericin B 3-5 mg/kg/d (7-14 days)
- Stepdown
  - Itraconazole 200 mg po TID x 3
  - Then itraconazole 200 mg po BID 6-12 months

CASE 2

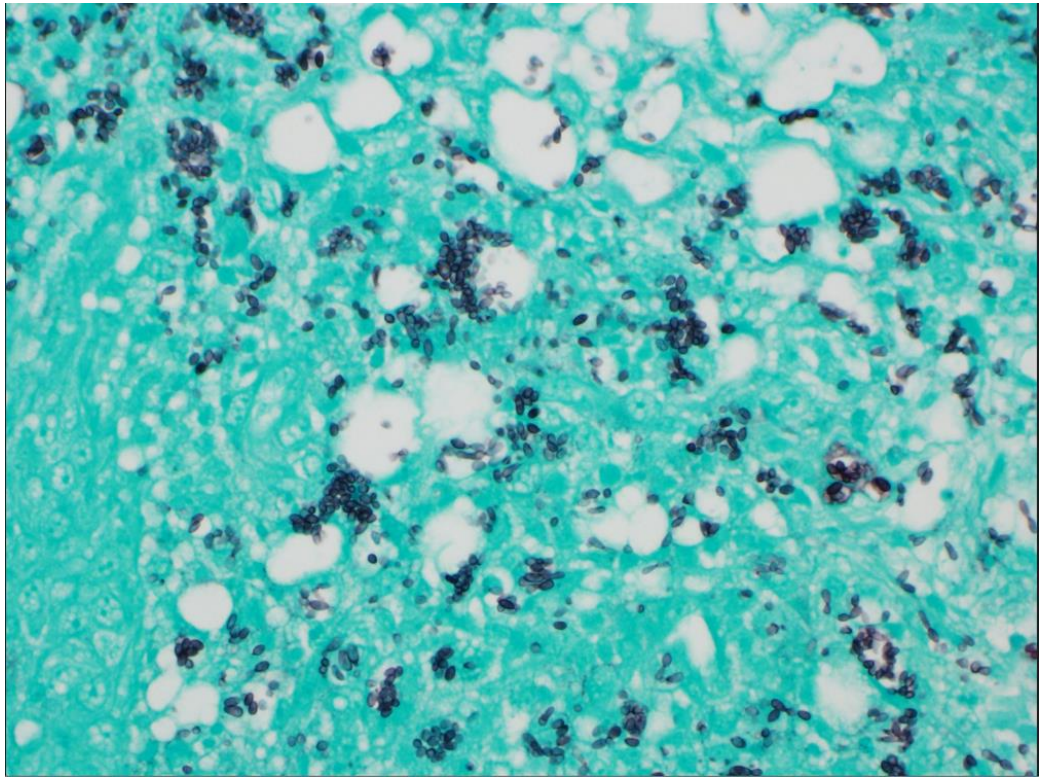
- 23 yo Male h/o Renal transplant
- Recently received HD solumedrol for graft rejection 5 months prior to presentation
- Pt reported ongoing fevers x 3 months
- He developed skin lesions which prompted ED evaluation

CASE 2 - SKIN LESIONS

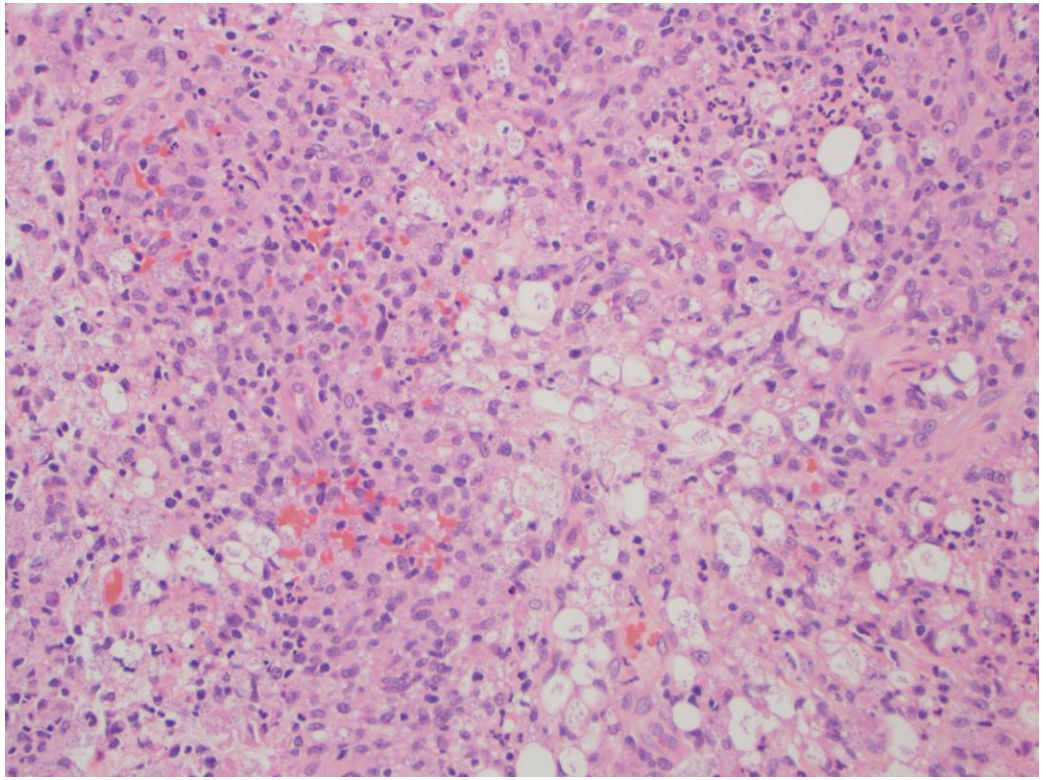




CASE 2 - SKIN BIOPSY

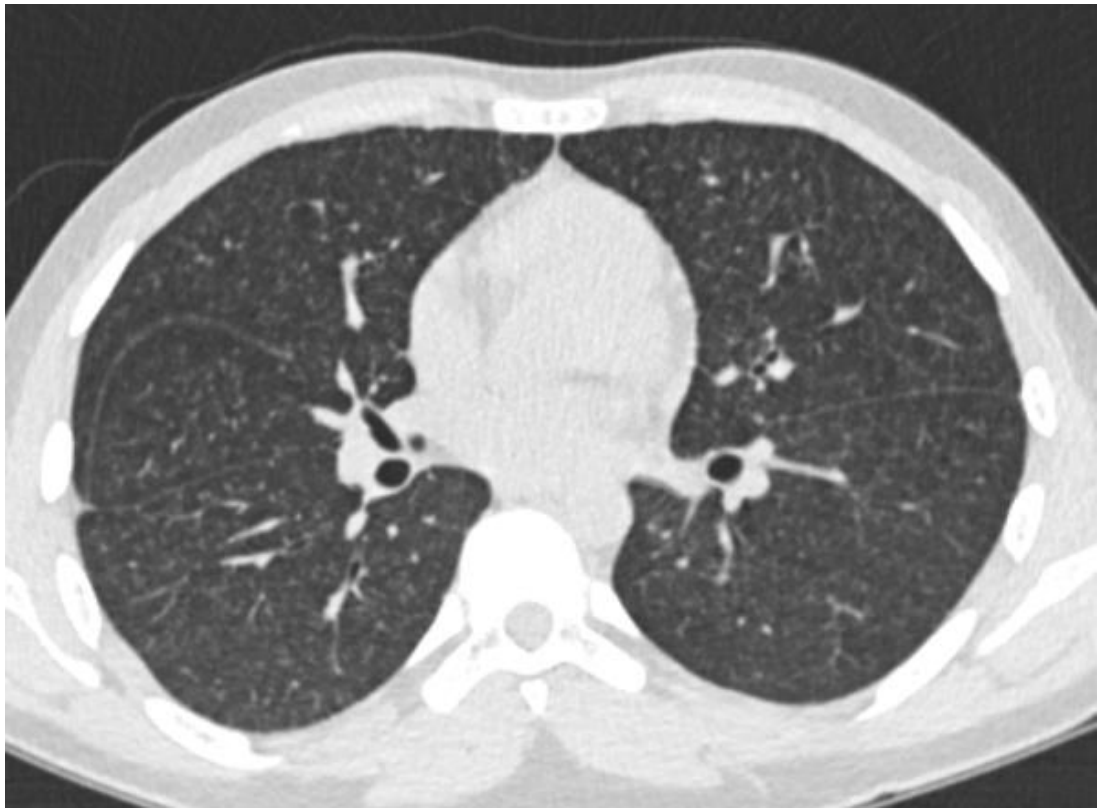


GMS

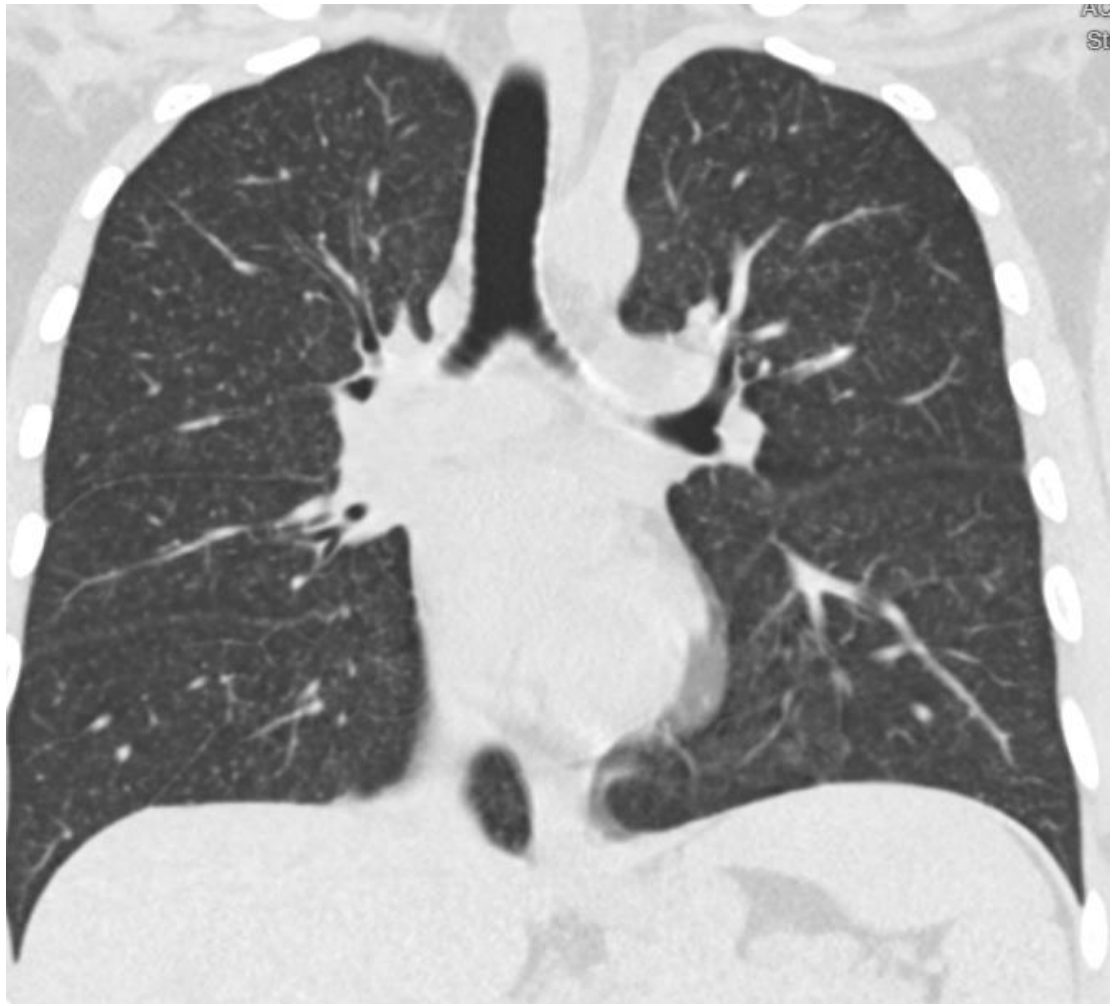


H&E

CASE 2- CT CHEST



1. Diffuse, bilateral centrilobular micronodules, involving all pulmonary lobes. Findings are overall significantly improved when compared to prior CT chest from 1/6/2022, which could represent improving infectious process; however, recurrence is also possible, in the appropriate clinical setting.



CASE 3

- 37 yo M h/o UC on remicade and IgA vasculitis who presented with BRBPR, c/f UC flare. ID is consulted now because of pulmonary nodules.
- Patient presented with concerns for UC flare which has been worsening for the past 3 weeks. Did not improve with prednisone 20-40mg. Describes significant BRBPR. States this UC flare is different than prior -- more focal to the rectum.

- In the hospital, patient started on IV steroids. Had flex sig that showed ulceration in the distal 13cm of rectum. CT enterography done 1/22 to further evaluate; this was noted to have significant increase in pulmonary nodules visualized previously at the lung bases. Dedicated lung CT was obtained 1/23 and showed innumerable pulmonary nodules. ID was consulted for infectious workup.

CASE 3

On history, the patient denies fevers. Has had drenching night sweats requiring clothing change for the last few weeks. About 20lbs weight loss.

Patient is originally from Marquette but lives in Northville. Works as project manager for a large engineering company. Enjoys fishing and spends a lot of time in state and national parks. No recent travel outside the area (has been to Canada). Went to Mexico in 2003 or so. No recent travel to NE Michigan. No known exposure to anyone with tuberculosis.

Has never had a positive PPD or a positive IGRA.

CASE 3

CT chest showed miliary pattern

Empiric therapy for miliary TB was started while further evaluations was pending, including Bronch was planned

F/U -

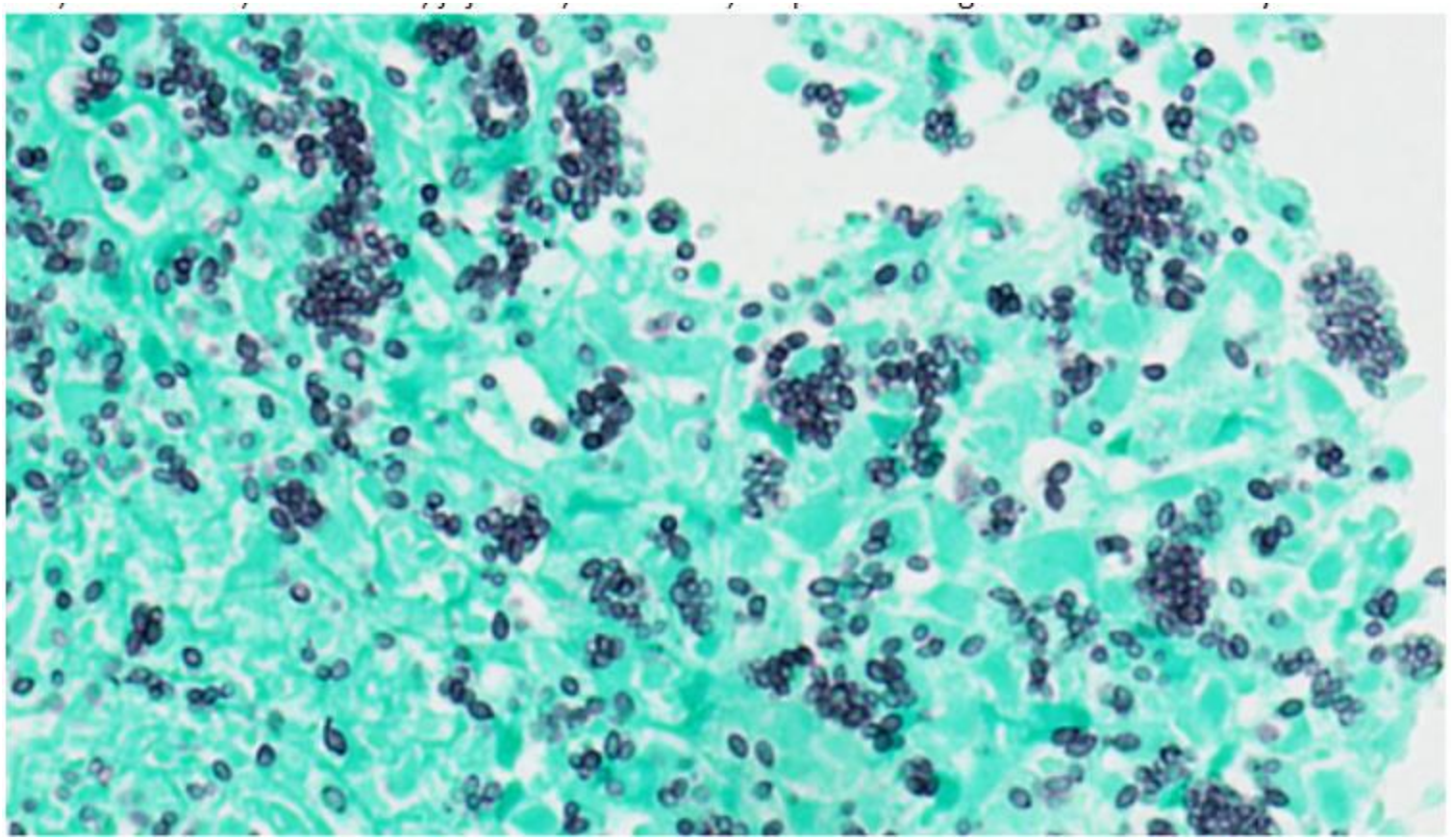
- urine Histo Ag + at 8.7
- bronchoscopy cancelled
- empiric RIPE stopped

CASE 3

- started amphotericin B liposomal
- discussed with primary team his need for therapy for UC but that TNF-a inhibitors were contraindicated in this situation

- TB QFN neg
- Histo urine Ag 8.61
- Histo serum Ag 2.9
- Blasto serum Ag 2.03
- Fungitell <31
- Rectal ulcer has intracellular yeast forms on pathology review

CASE 3 pathology



GMS

Outcome

- Sequelae
- Can include pericarditis, broncholythiasis, pulmonary nodules, mediastinal granuloma, or mediastinal fibrosis
- Progressive, chronic, or disseminated dz → symptoms may be present months or longer.

- Mortality
  - Overall is low (no data)
  - Higher in HIV-infected or IS persons with disseminated/severe dz

Summary

- Histoplasmosis can be indistinguishable from CAP
- Clinicians may consider testing for histoplasmosis in pts who have not improved with at least one course of empiric antibiotics, live in or have traveled to an endemic area, exposure to bird or bat droppings (e.g., entered cave, demolition/remediation of building with extensive droppings, have chest X-ray demonstrating new nodules or lymphadenopathy, or are linked to known histoplasmosis outbreak
- Not all cases of histoplasmosis need to be treated
- IDSA guidelines, CDC website and UpToDate are good resources to understand the disease and guide management
- Consult/Refer to Infectious Diseases Specialist