Citywide Case conference Paulisa H. Ward, MBBS June 25 2019

Queltzaltenango farm highlands Guatemala

## History of presenting illness

37 yo man from Guatemala complains of loss of appetite for 2 weeks

(end of winter- beginning of spring )

- No dysphagia or odynophagia
- No regurgitation of food
- No nausea or vomiting
- No altered bowels or change in frequency
- No abdominal pain or fullness

✓Associated weight loss- unknown amount over the same period

### Review of systems

- Constitutional: intermittent fever and diaphoresis
- HEENT: denied headache, diplopia, tinnitus, sore throat, neck stiffness
- CVS: denied chest pain, palpitations
- RESP: SOB- exertion and at rest, no cough
- ABD: no nausea or vomiting, no abd pain, constipation or diarrhea
- CNS/MSK: no muscle fasciculations, no weakness or paresthesias
- Skin: noted a rash on his chest and face for the past week- 1<sup>st</sup> episode
  nonpruritic, appeared simultaneously

### Other pertinent history

- PMH: HIV/AIDS diagnosed 2014 in Guatemala- last known CD4 76 cells/uL (3 years ago)
- No previous surgeries
- No medications currently- was taking TDF/FTC/EFV along with TMP/SMX and Fluconazole until 4 months ago
- No drug allergies
- Born in Guatemala, in the US for the past 2-3 years working as a landscaper and painter in PA
- No smoking, alcohol or illicit drug use, family resided in Guatemala

### Physical examination

- T 100.9 BP 117/61 RR 18 P 127 Sa02 95% on room air
- General- alert and oriented x3, mild conversational dyspnea, no adenopathy, not cyanotic
- HEENT- nc/at, anicteric, PERTL, mm moist, neck supple, no thrush, no tonsillar hypertrophy or exudate
- CVS- s1 and s2, no m/r/g
- RESP-coarse breath sounds in bibasilar fields no wheezing
- ABD-soft nontender, no organomegaly, bowel sounds present
- CNS- CN intact, no focal deficits peripherally
- MSK and Skin- no leg edema, pink papules on chest, upper arms, neck and trunk, 3-4mm (palms, soles and legs spared) shallow nasal cutaneous ulcer, no eschar





## Imaging

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### Case continued~

- Patient was started on TMP/SMX 5mg/kg IV q8h for possible PJP
- Bronchoscopy and Skin biopsy was recommended
- Empiric fluconazole 800mg po x1

### Case continued~

Skin biopsy~

- Mild superficial perivascular dermatitis, negative for fungal organisms by silver stain. No viral cytopathic changes
- Rash began to dissipate

Bronchoscopy~

- No unusual anatomic findings
- BAL stain and culture sent

Lab results~

- CD4 3 VL 104,000 copies/mL
- RPR negative and Urine legionella negative

### GMS stain of bronchoalveolar lavage







### Case continued~

Our patient:

- Urine Histoplasma galactomannan antigen >25mg/mL
- Cryptococcal serum antigen negative
- Blood AFB NGTD
- PJP PCR not detected
- Was given LAmpB for 2 weeks and transitioned to Fluconazole
- Commenced on Biktarvy outpatient ( can be started within the 1<sup>st</sup> week of Rx

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



In the environment, *Histoplasm capsulatum* exists as a mold (1) with aerial hyphae. The hyphae produce macroconidia and microconidia (2) spores that are aerosolized and dispersed. Microconidia are inhaled into the lungs by a susceptible host (3). The warmer temperature inside the host signals a transformation to an oval, budding yeast (4). The yeast are phagocytized by immune cells and transported to regional lymph nodes (5). From there they travel in the blood to other parts of the body (6).

### Mississippi and Ohio River Valley

**Areas Endemic for Histoplasmosis** 

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### Histoplasmosis outside the US

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### Disease patterns seen in Histoplasmosis

- Acute pulmonary histoplasmosis
- Subacute pulmonary histoplasmosis
- Chronic pulmonary histoplasmosis
- *Mediastinal adenitis* chest pain, compressive symptoms
- *Mediastinal granuloma* amalgamated mass of necrotic mediastinal lymph nodes encased in a thin fibrotic capsule, often paratracheal or subcarinal can be up to 10 cm
- Mediastinal fibrosis- late complication, structures trapped in fibrotic tissue
- Histoplasmoma- slowly enlarging pulmonary nodule, necrotic center fibrous capsule
- Broncholithiasis- erosion of calcified lymph nodes into bronchi
- Presumed ocular histoplasmosis- weak evidence that this exists

### • Disseminated Histoplasmosis

### **Disseminated histoplasmosis**

- Most common mycosis in HIV/AIDS
- Primary infection or reactivation
- Hematogenously spread
- Nonspecific lab findings: elevated hepatic enzymes, LDH, bilirubin and ferritin
- Can lead to *Hemophagocytic lymphohistiocytosis* (*HLH*)-in which a massive immune stimulation results in macrophage activation and hemophagocytosis (life threatening)

# Respiratory specimens and bone marrow biopsy have highest yield in PDH

 Direct observation in tissue or body fluid specimens -budding yeast localized in mononuclear phagocytes



- Rapid diagnosis: Urine or Serum histo-galactomannan antigen (CSF, BAL possible)
- Up to 4 weeks required for culture- bone marrow/blood/BAL- positive in 75% of cases

## Quick review



Blastomyces dermatidisbroad based budding yeast



### Coccidiodes immitis



### **Morphology of yeasts**



Penicillium marneffei



Paracoccidioides brasiliensis



### **Description, diagnosis and comment**

**Description:** Thin-walled spheres (2 to 5 microns in size) with intracystic foci. In lung they appear as foamy intraalveolar eosinophilic exudates. The diagnosis is problematic when they are extrapulmonary and can be confused with *Histoplasma*. **Diagnosis:** *Pneumocystis* pneumonia

**Description:** Small oval-shaped yeasts (2 to 5 microns in diameter) with transverse septum (due to division by fission). **Diagnosis:** *Penicillium marneffei* 

**Description:** Variable size yeasts (4 to 60 microns in size) with multiple buds surrounding the parent cell. Described as "pilot wheel". Some cells may only have 1 or 2 buds and should not be confused with other yeasts such as *Sporothrix* or *Cryptococcus*. **Diagnosis:** *Paracoccidioides brasiliensis* 

**Description:** Asteroid bodies (star-like eosinophilic material surrounding yeasts or yeast-like structures) are found in up to 92% of sporotrichosis cases. Less frequently found are round, oval or cigar shaped yeasts (2 to 6 microns in diameter or larger) (inset) with narrow based or tube-like budding (budding not present in the inset). **Diagnosis:** Asteroid body and small oval yeast (with narrow based budding –if present). **Comment:** The morphology is consistent with *Sporothrix schenckii;* however, *Candida glabrara, Histoplasma,* 

*Leishmania*, and sarcoidosis can have this morphology.



### Demonstration of yeast in mediastinal lymph nodes or lung tissue does not distinguish active from healed histoplasmosis

### Not all disease patterns require treatment

Disseminated Histoplasmosis is <u>fatal if untreated</u>

LAmpB for 1-2 weeks followed by Itraconazole for at least 12 months until antigenemia/antigenuria is resolved

Echinocandins are not active against Histoplasma



# A reminder about Histoplasmosis prophylaxis

• The Adult and Adolescent Opportunistic Infection Guidelines recommend primary ppx with <u>Itraconazole 200mg po daily</u> if:

CD4 <150 cells/mm<sup>3</sup> and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (greater than 10 cases/100 patient-years)

Discontinue once CD4 > 150 cells/mm<sup>3</sup> or greater for at least 6 months. Restart if the CD4 count drops below 150 cells/mm<sup>3</sup>

# Histoplasmosis in the most common mycosis in HIV/AIDS and can lead to HLH

- Cdc.gov
- Wheat, Lawrence J et. Al, Histoplasmosis, Infect Dis Clin N Am 30 (2016) 207–227
- Zanotti P., Chirico C., Gulletta M., Ardighieri L., Casari S., Quiros Roldan E., Izzo I., Pinsi G., Lorenzin G., Facchetti F., Castelli F., Focà E. Disseminated histoplasmosis as AIDS-presentation. Case report and comprehensive review of current literature. Mediterr J Hematol Infect Dis 2018, 10(1): e2018040, DOI: http://dx.doi.org/10.4084/MJHID.2018.040

## THANK YOU