MAYO CLINIC

Center for Tuberculosis

Decoding Class 5 TB: Navigating Diagnostic Challenges

Avish Nagpal, MD
Infectious Disease Consultant and Medical Director for Infection Prevention
Sanford Medical Center, Fargo, ND

Accreditation Statement

Accreditation Statement
In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

Credit Statement(s):

AMA
Mayo Clinic College of Medicine and Science designates this live activity for a maximum of 1.00 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACPE
Mayo Clinic College of Medicine and Science designates this educational activity for a maximum of 1.00 ACPE Knowledge-based contact hours. Participants should claim only the credit commensurate with the extent of their participation in the activity.
UAN Number: JA0000238-0000-25-030-L01-P

ANCC
Mayo Clinic College of Medicine and Science designates this activity for a maximum of 1.00 ANCC contact hours. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education (IPCE) credit for learning and change.

Other Healthcare Professionals:
A record of attendance will be provided to all registrants for requesting credits in accordance with state nursing boards, specialty societies or other professional associations.

For disclosure information regarding Mayo Clinic School of Continuous Professional Development accreditation review committee member(s) and staff, please go here to the course accreditation page.

Available Credit
- 1.00 ACPE,
- 1.00 *AMA PRA Category 1 Credit*™
- 1.00 ANCC
- 1.00 Attendance
- 1.00 IPCE

Disclosure:

No relevant financial disclosures to report and no mention of off-label use of any medications or products

Learning Objectives

- Differentiate between the five classes of TB
- Explain the clinical significance of Class 5 TB
- Identify the appropriate management steps for patients classified under Class 5 TB

TUBERCULOSIS CLASSIFICATION

Class	Type	Description
TB-0	- No TB exposure - Not infected	No history of exposure. Negative reaction to tuberculin skin test.
TB-1	- TB exposure - No evidence of infection	History of exposure. Negative reaction to tuberculin test skin test.
TB-2	- TB infection - No disease	Positive reaction to tuberculin skin test. Negative bacteriologic studies (if done). No clinical or radiographic evidence of TB.
TB-3	- Current TB disease	*M. tuberculosis* cultured (if done) or *both a* positive reaction to tuberculin skin test *and* clinical and/or radiographic evidence of current disease.
TB-4	- Previous TB disease	History of episode(s) of TB, abnormal stable radiographic findings in a person with a positive reaction to the tuberculin skin test, negative bacteriologic studies (if done) and no clinical or radiographic evidence of current disease.
TB-5	- TB suspect	Diagnosis pending (a patient should not be in this class for more than 3 months).

“Possible TB”

- Many cases referred to MCCT are for “evaluation of possible TB” or “TB rule out”
- 2-Tiered Decision Making
  - **Diagnostic:** Likelihood that TB disease present?
  - **Therapeutic:** Whether to preemptively start combination TB drug therapy (e.g. RIPE) vs delay/observation?
- More ‘time-sensitive’ for pulmonary cases

- **Challenging** set of patients to manage:
  - Patient care – want to get them better quickly
    - *How likely is TB?*
    - *What other testing needs to be performed?*
    - *When to treat?*
    - *What to treat with?*
  - Public Health / Infection control
    - *Avoid spread in cases of pulmonary TB / Laryngeal TB*
    - *Make sure appropriate infection prevention interventions are implemented in facilities*

Class 5 – TB suspect:

Suspicion of TB based on multiple considerations:

1. **Clinical** presentation
2. **TB Risk factors** / patient demographics
3. **Radiological** features
4. **Laboratory** (supporting) data

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

1. ***Clinical*** presentation / factors

- Whether typical (or atypical) symptoms or exam findings present – e.g.

a. Chronic coughing (e.g., lasting > 3 weeks), hemoptysis

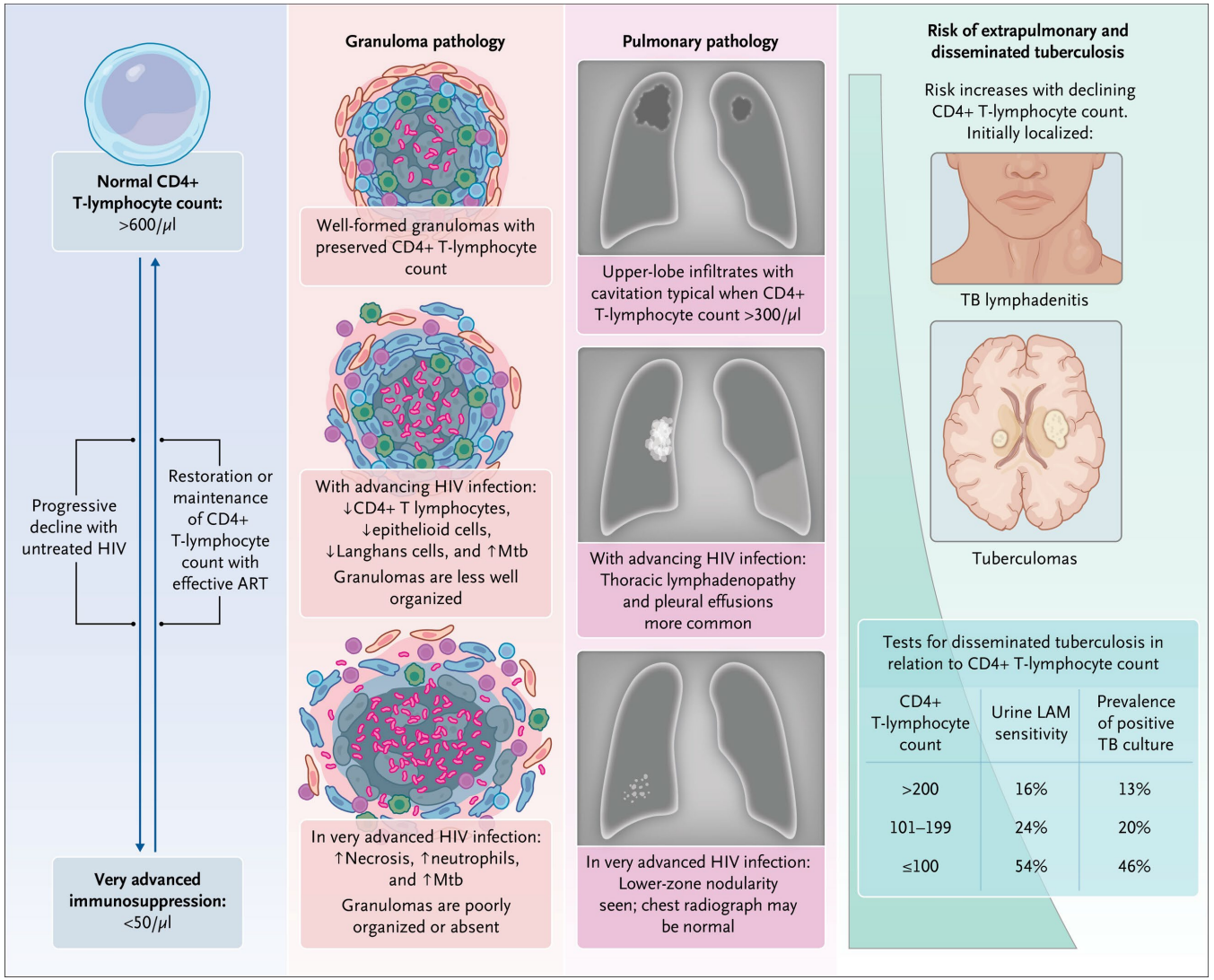
b. Systemic symptoms – e.g. Fever, chills, weight loss, night sweats

c. Exam findings of extrapulmonary TB – including
   - Adenopathy (head/neck, axillary, etc)
   - Hepatosplenomegaly
   - Abdominal ascites

Table 1. FACTORS THAT INFLUENCE THE CLINICAL FEATURES OF TUBERCULOSIS

Host Factors	Microbial Factors	Host–Microbe Interaction
Age	Virulence of the organism	Sites of involvement
Immune status	Predilection (tropism) for specific tissues	Severity of disease
Specificic immunodeficiency states		
Malnutrition		
Genetic factors (not yet defined)		
Coexisting diseases		
Immunization with bacillus Calmette-Guérin (BCG)		

Dunlap et al. Am J Respir Crit Care Med 2000;161(4):1376–95



Meintjes, G. and Maartens, G. N Engl J Med 2024;391:343-355
DOI: 10.1056/NEJMra2308181

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

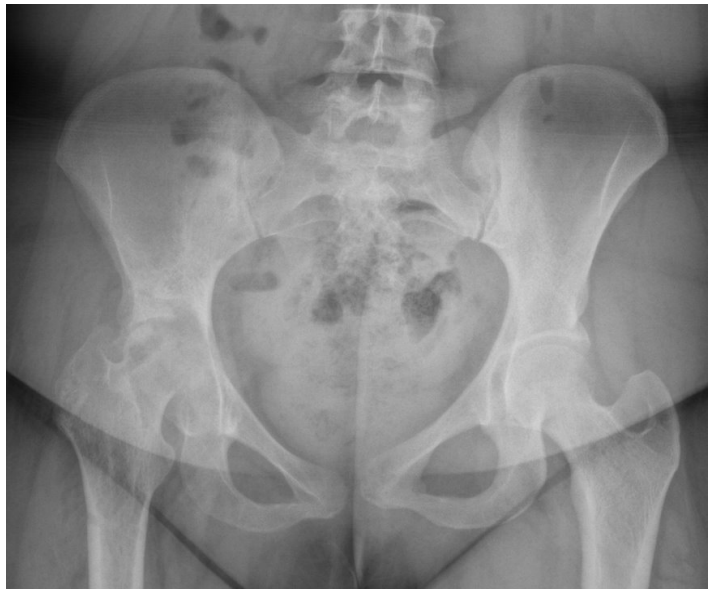
2. ***TB Risk factors*** present? – e.g.

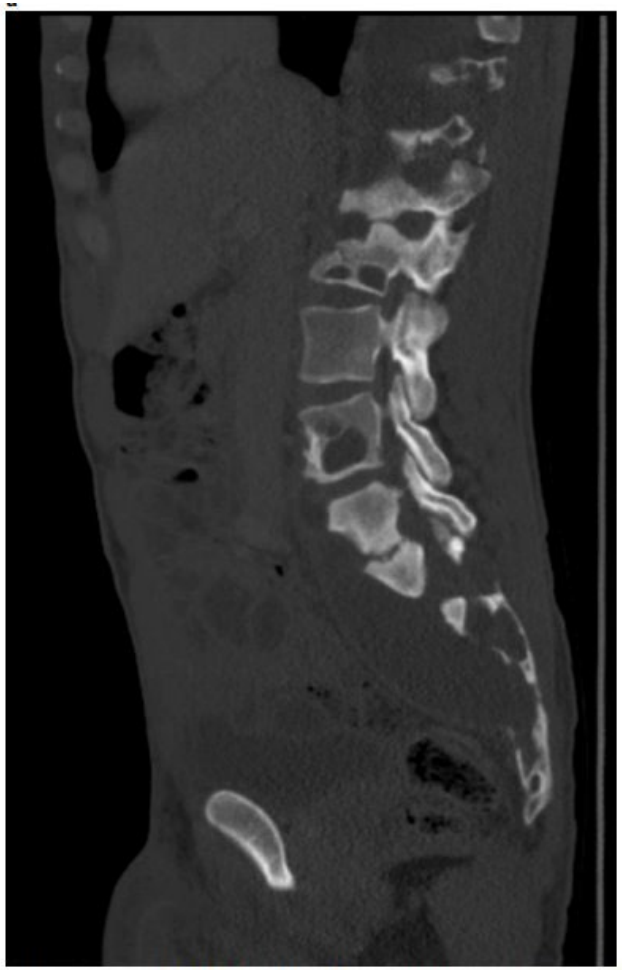
- Patient demographics - Born/lived in TB-endemic country
- History of LTBI or active TB disease – treated or untreated
- Recent contact with person known to have pulmonary TB disease (untreated)
- Other exposures (variable risk): Prison/jails; health care provider, congregate living settings, etc
- Co-morbidities

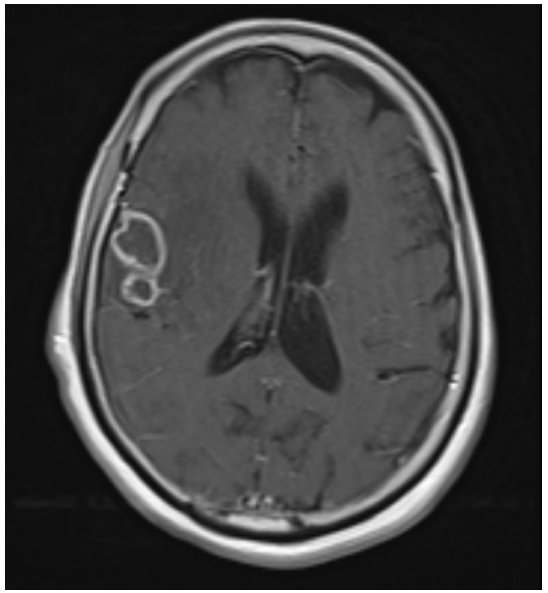
Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

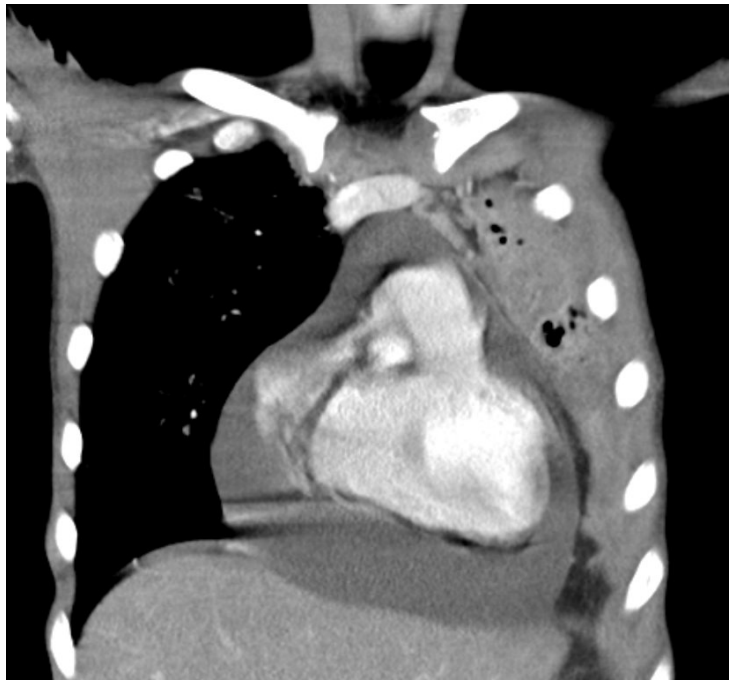
3. ***Radiologic*** findings c/w TB?

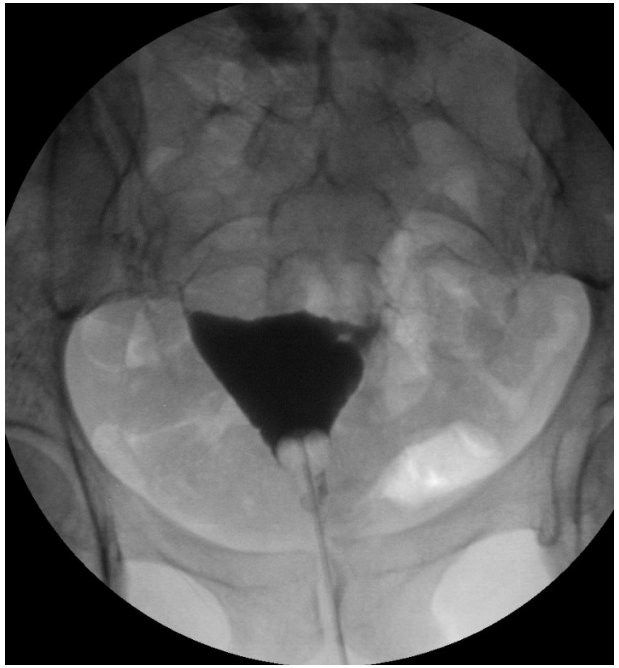
a. Upper lobe CXR, cavitary lesions (but acknowledging pulm TB can appear *like anything*)
b. Localized or systemic adenopathy
c. Hepatosplenic lesions
d. Bone lesions (e.g. vertebral lesions)
e. CNS lesions – (e.g. basilar meningeal enhancement on head MRI; tuberculomas, etc)











Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

4. ***Laboratory*** (supporting) data – for TB
   - *Cultures and PCR pending, negative or NA*

   a. Reactive TST
   b. (+) IGRA (QuantiFERON-TB or T-SPOT.TB)
   c. (+) AFB stain (sputum or tissue)
      - MTB
      - NTM – e.g. MAC, *M. kansasii*, *M. abscessus* complex, etc
      - Environmental or cross contamination
   d. Tissue histology – necrotizing (or non-necrotizing) granulomatous inflammation
   e. Molecular studies – NAAT, Next gen Sequencing, Broad Range PCRs

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

4. ***Laboratory*** (supporting) data – for TB

- *Cultures and PCR pending, negative or NA*

e. GU TB – abnormal UA (but negative cultures. Repeatedly.)

f. CNS TB (esp. meningeal) – elevated CSF protein, leukocytes (often lymphocytes), elevated ADA

g. Pleural fluid – pleocytosis (elevated WBC, often lymphocytes), elevated protein, ADA

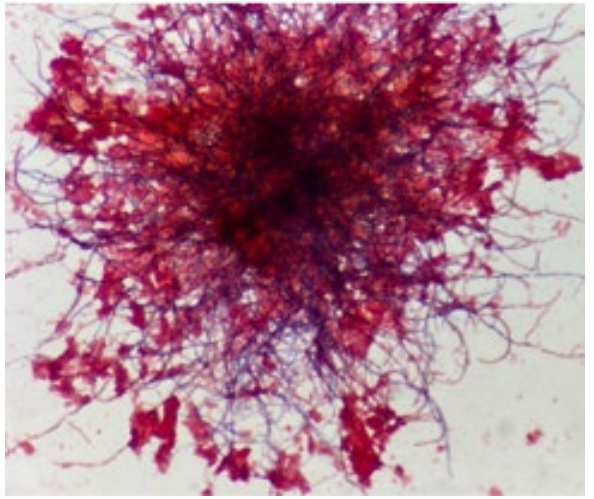
h. Peritoneal TB – ascites with pleocytosis (often lymphocytes), elevated protein

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

Confounders-I: Other AFB staining (+) organisms:

a. Non-TB Mycobacteria (NTM)

b. *Other mycolic-acid containing (AFB stain pos) bacteria – usual appear morphologically different/distinct:*
   - *Nocardia* sp
   - *Gordonia* sp
   - *Rhodococcus* sp
   - *Tsukamurella* sp
   - *Dietzia* sp



Microbial growth demonstrating positive staining with modified AFB stain in a patient with dissmeinated Nocardiosis

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

Confounders – II: Other Granuloma-forming pathogens in tissue (lungs or other tissue/liver, etc):

a. Non-TB Mycobacteria (NTM)

b. Fungal (histoplasmosis, blastomycosis, coccidiomycosis, etc)

c. Other:
   - Brucellosis
   - Q fever (*C. brunetti*)
   - *Bartonella*
   - Toxoplasmosis
   - *Rhodococcus*
   - Syphilis
   - Schistosomiasis (liver, bladder)
   - *Non-infectious (non-necrotizing): Sarcoidosis, Crohn's disease, temporal arteritis, etc

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

Confounders – III: other causes of adenopathy

Non-TB Mycobacteria (NTM)

a. Fungal (*histoplasmosis, blastomycosis, coccidiomycosis, etc)

b. Other:
   - Regional: *Bartonella* (Cat-scratch dis), GUD pathogens (syphilis chancroid, LGV, etc)
     Tularemia, *Yersinia*, Fungal (e.g. *Histoplasma, Blastomyces*)
   - Systemic: Syphilis, Brucellosis, Toxoplasmosis
     Lyme disease, Fungal (*Histoplasma*, *Cryptococcus*, HIV, EBV
   - *Non-infectious (non-necrotizing): Sarcoidosis, Lymphoma, Castleman's disease, etc

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

Confounders – IV: Other causes of cavitary lung disease

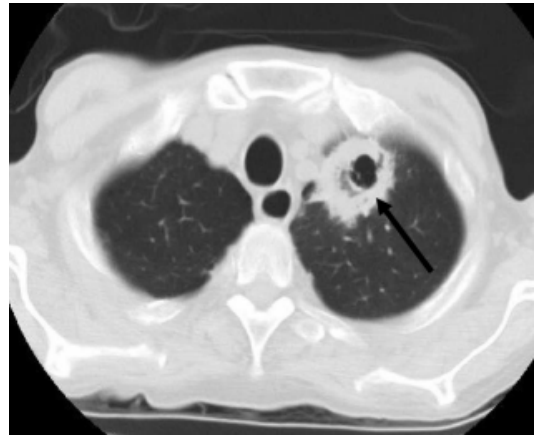
a. Non-TB Mycobacteria (NTM)

b. Fungal (Histoplasmosis, Blastomycosis, Coccidiomycosis, Aspergillosis, Mucormycosis., etc.)

c. Other:
   - *Nocardia* sp.
   - *S. aureus*
   - *P. aeruginosa*
   - Malignancy

Thin-walled cyst

Chronic aspiration



Clin Microbiol Rev. 2008 Apr;21(2):305-33

Class 5 TB – Suspect:
Likelihood of TB disease – considerations:

Non-TB Mycobacteria (NTM) – can be confounders:

a. May produce reactive (+) TST

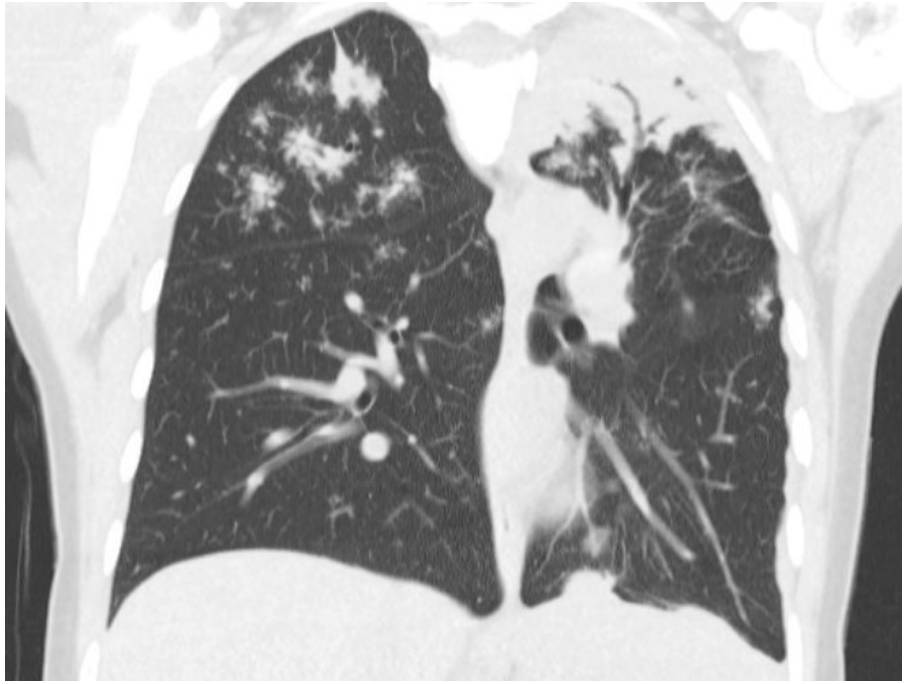
b. Will stain pos (+) AFB (Ziehl-Neelsen, Kinyoun), Auramine-rhodamine, FITE, etc

c. Select NTM that produce (+) IGRA:
   - *M. marinum* – extrapulmonary disease
   - *M. kansasii* – pulmonary disease
   - *M. szulgai*

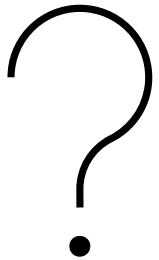
Case 1

- 38-year-old female RN, recent immigrant from the Philippines, was evaluated for lumps in both breasts and found to have adjacent left-sided axillary lymphadenopathy.
- Underwent biopsy. Pathological exam revealed presence of necrotizing granulomas.
- QuantiFERON® test negative.
- She elected against further work up.

- Two years later, a repeat QuantiFERON® was positive.
- Subsequent chest imaging is shown:



Polling question 1



What would be the next step in management?

A. Patient has TB. Start RIPE

B. Patient has walking pneumonia. Treat with Azithromycin

C. QuantiFERON-TB should be repeated due to discordant results

D. Induce sputum for AFB Testing

E. Perform a bronchoscopy with bronchoalveolar lavage

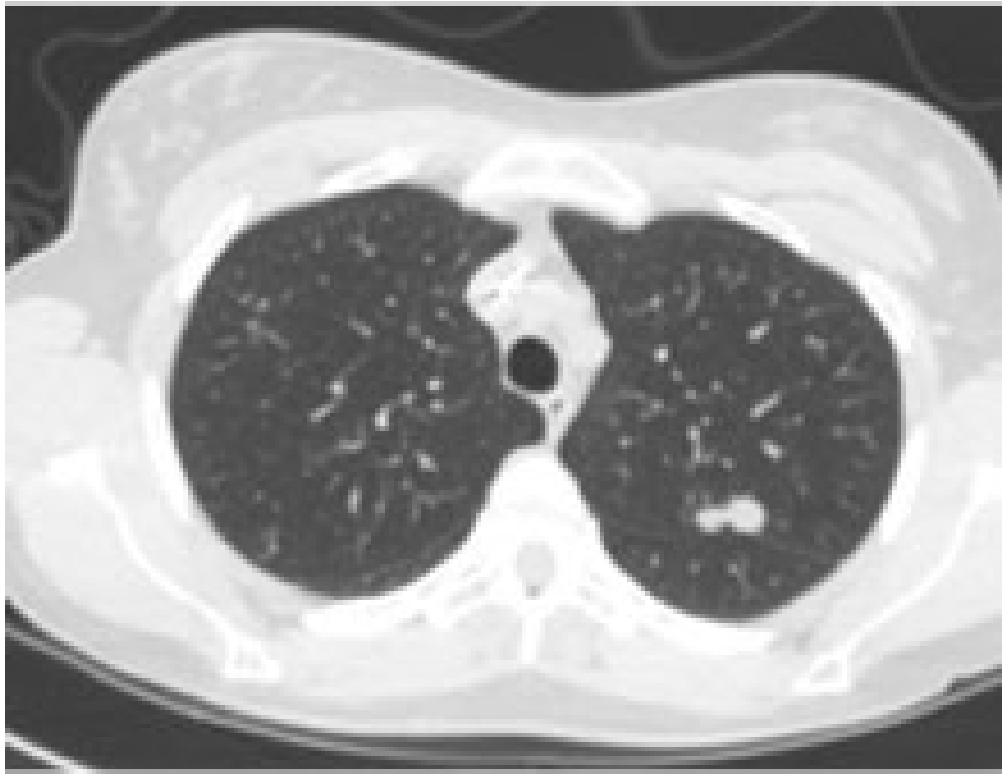
- A bronchoscopy is performed
- Lavage fluid tested positive for *Mycobacterium tuberculosis* complex on NAAT and culture
- Completed Treatment and remained asymptomatic throughout

Case 2

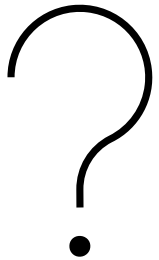
- 37-year-old female with rheumatoid arthritis requiring immunosuppression with Upadacitinib received a positive QuantiFERON test a year after exposure to TB.
- Symptom screen negative
- Chest X ray negative
- Prescribed treatment for latent TB.

Follow Up

- A few months later, gets a pre-employment Chest X ray
- New nodule in the right upper lobe.
- Follow Up CT:



Polling Question 2



What is the next step in management?

A. Refer to lung nodule clinic for surveillance

B. Patient has developed TB. Isolate and Start RIPE

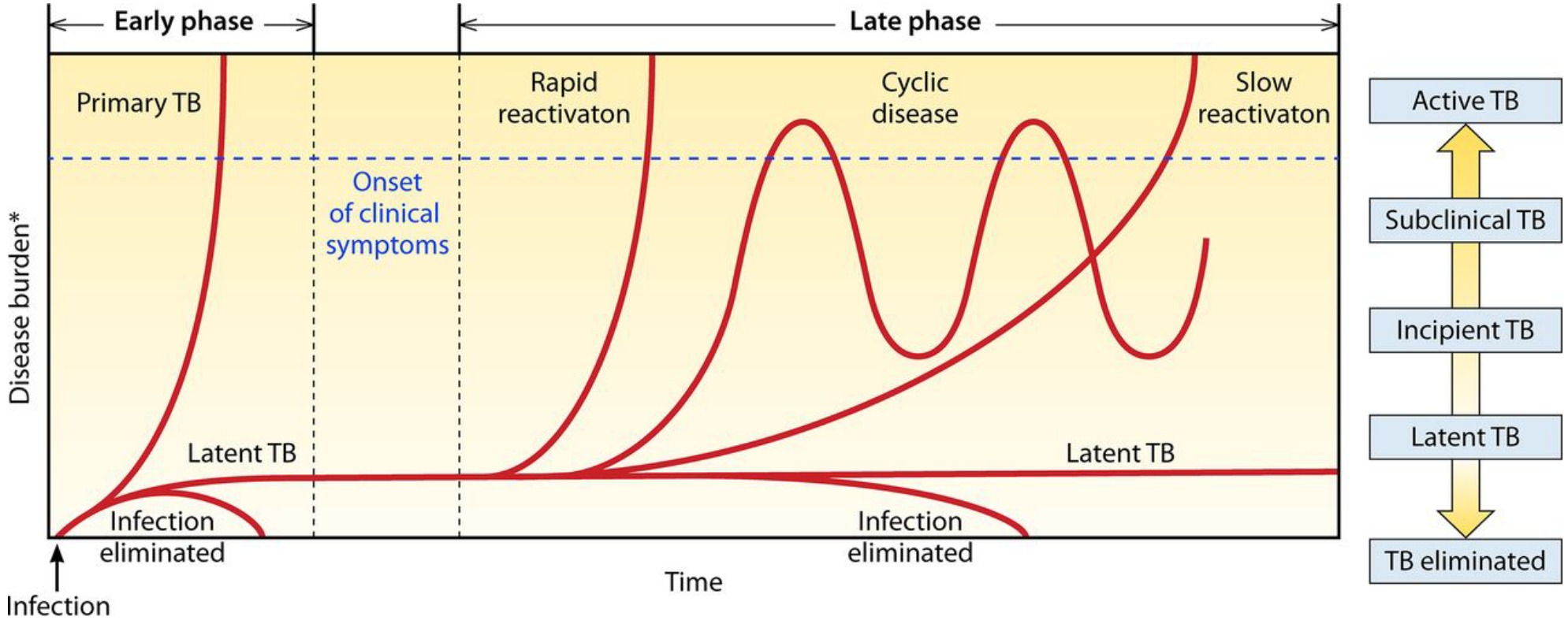
C. Biopsy the lung nodule to evaluate for malignancy

D. Perform Bronchoscopy with bronchoalveolar lavage

E. Reassure patient that lung nodules are common due to her residence in northern MN

- Patient admitted never completing LTBI Rx
- A bronchoscopy was performed
- Lavage fluid + for *Mycobacterium tuberculosis* by NAAT.
- Completed treatment for active TB
- Remained Asymptomatic throughout

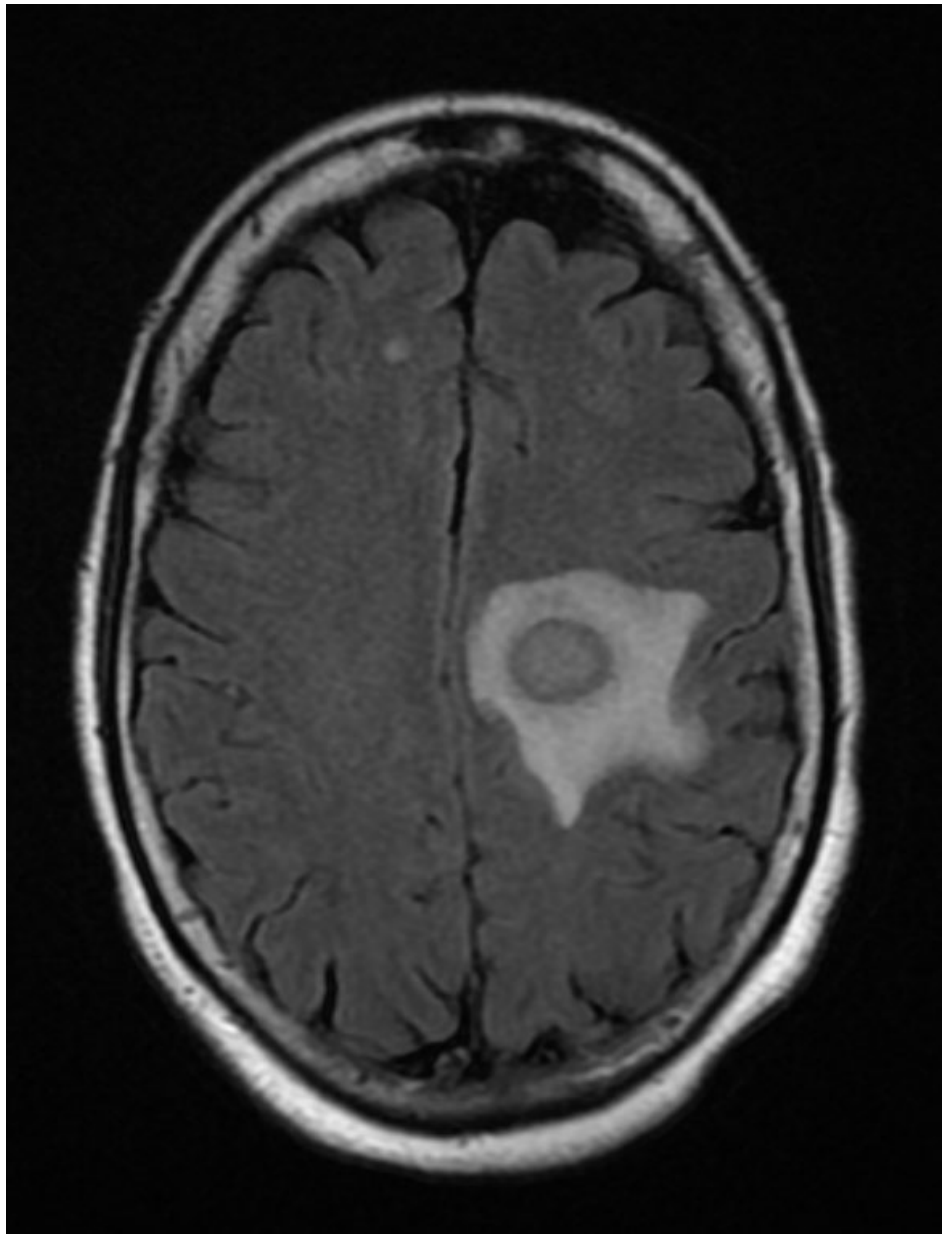
Pathways of TB Disease Progression



Drain P.K. et al. Clin Microbiol Rev 2018;31(4):e00021-18 https://doi.org/10.1128/cmr.00021-18

Case 3

- A 70-year-old AA female presented to the hospital with subacute onset of right sided weakness. Exam revealed complete right sided hemiplegia and partial aphasia. Vitals were stable. Labs indicated a normal WBC count and differential, mildly elevated CRP of 29 (Reference range: < 5 mg/dL)
- CT and MRI of the head was performed.



Considerations?

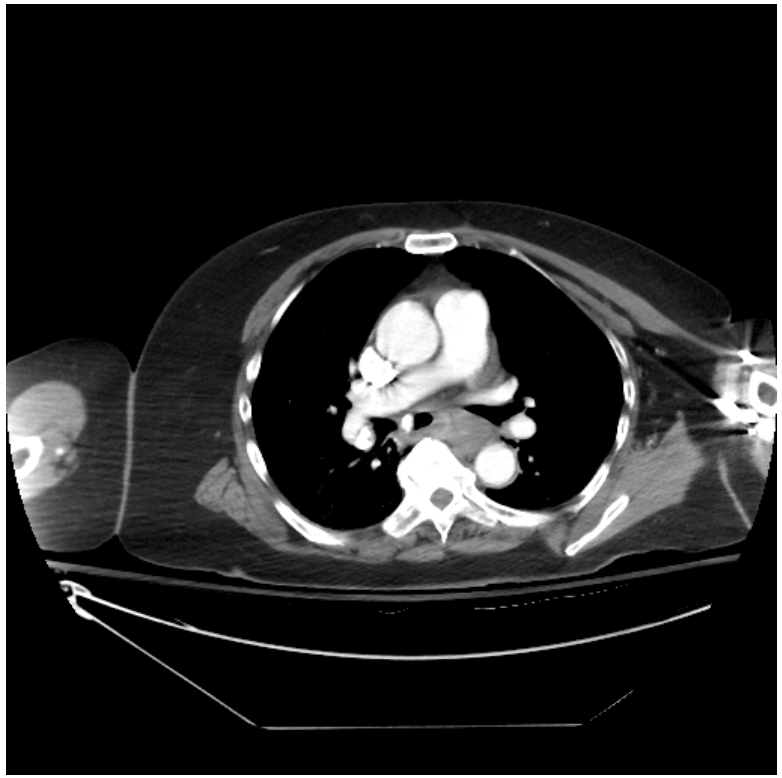
- Brain abscess
- CNS TB
- Metastatic disease
- Opportunistic infections like Toxoplasmosis
- Primary CNS Lymphoma
- GBM

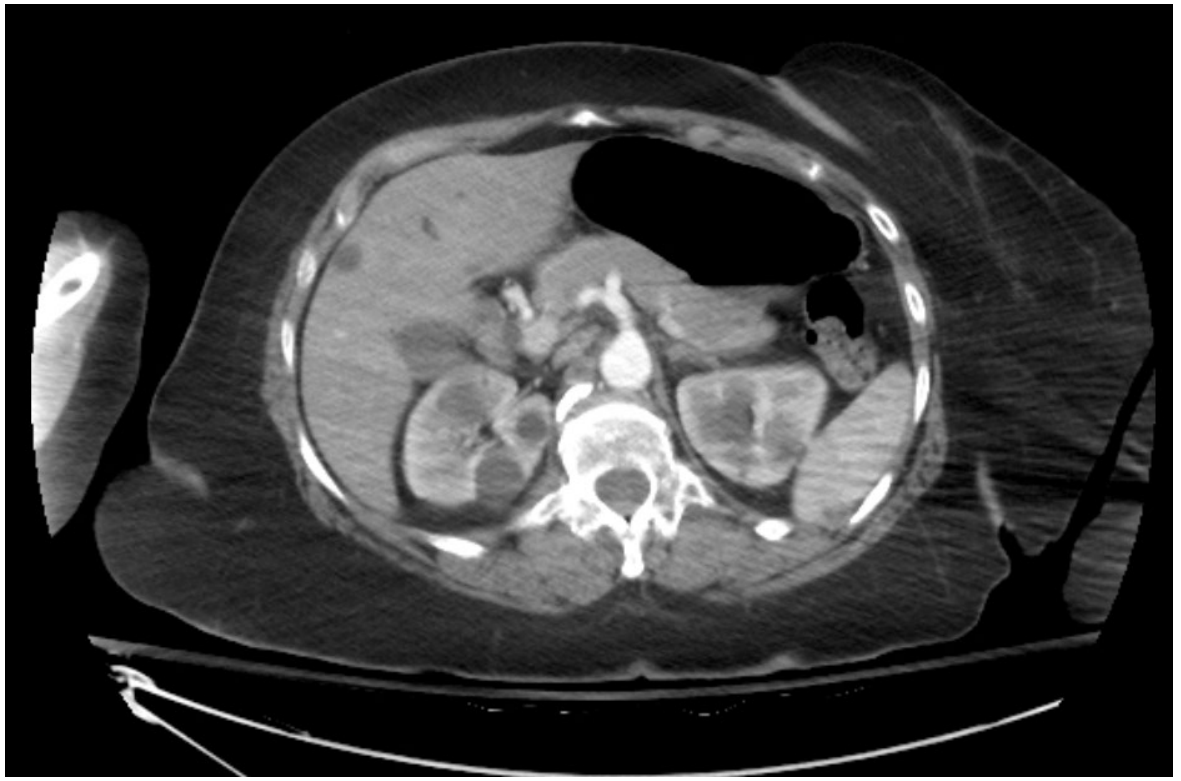
Further testing

- Blood cultures negative
- Echo negative for vegetations
- HIV screen negative
- IGRA testing negative

- Next step?

Further Imaging



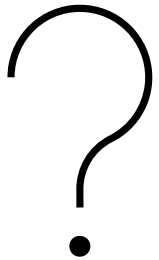


Follow up

- CT chest revealed a matted posterior mediastinal mass
  - ? Lymph nodes vs malignancy
- CT Abdomen revealed multiple hepatic and renal cysts
- Patient born in US and lived in multiple states
- No obvious TB exposure
- Traveled to Italy many years ago and had a minor MVA in Naples
- Traveled to Nigeria for 3 weeks in March 2025

- EGD with Mediastinal biopsy is performed
- Path: Acute inflammation with multiple granulomas and calcification
- No new microbiological data available

Polling Question 3



What is the next step in management?

A. Perform a brain biopsy

B. Repeat EGD to obtain cultures of mediastinal mass

C. Patient has TB. Start RIPE

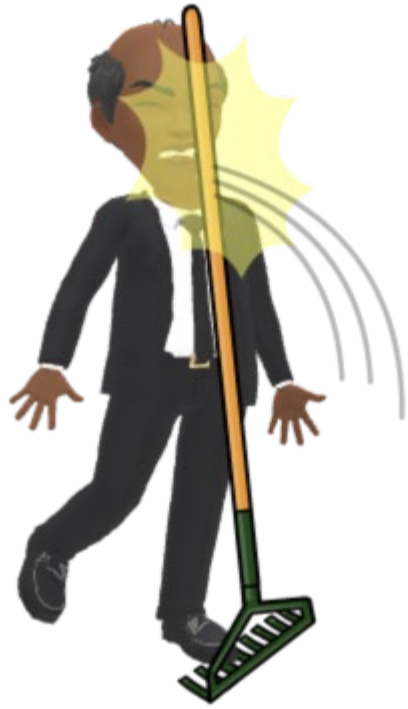
D. Start antifungal therapy

E. Start steroids for Sarcoidosis

- Blastomyces and Histoplasma Urine and Serum Ag negative
- Cryptococcal Ag negative
- Fungal serology negative
- Toxoplasma Serology negative

- Karius ® test negative
- AFB / Fungal blood cultures negative at 3 weeks
- Broad range PCR on Mediastinal Tissue requested
- Patient started on Vancomycin / Pip-Tazo
- LP recommended
  - CSF analysis: 16 WBCs; 97% Lymphocytes; Protein 61.9, Glucose 50

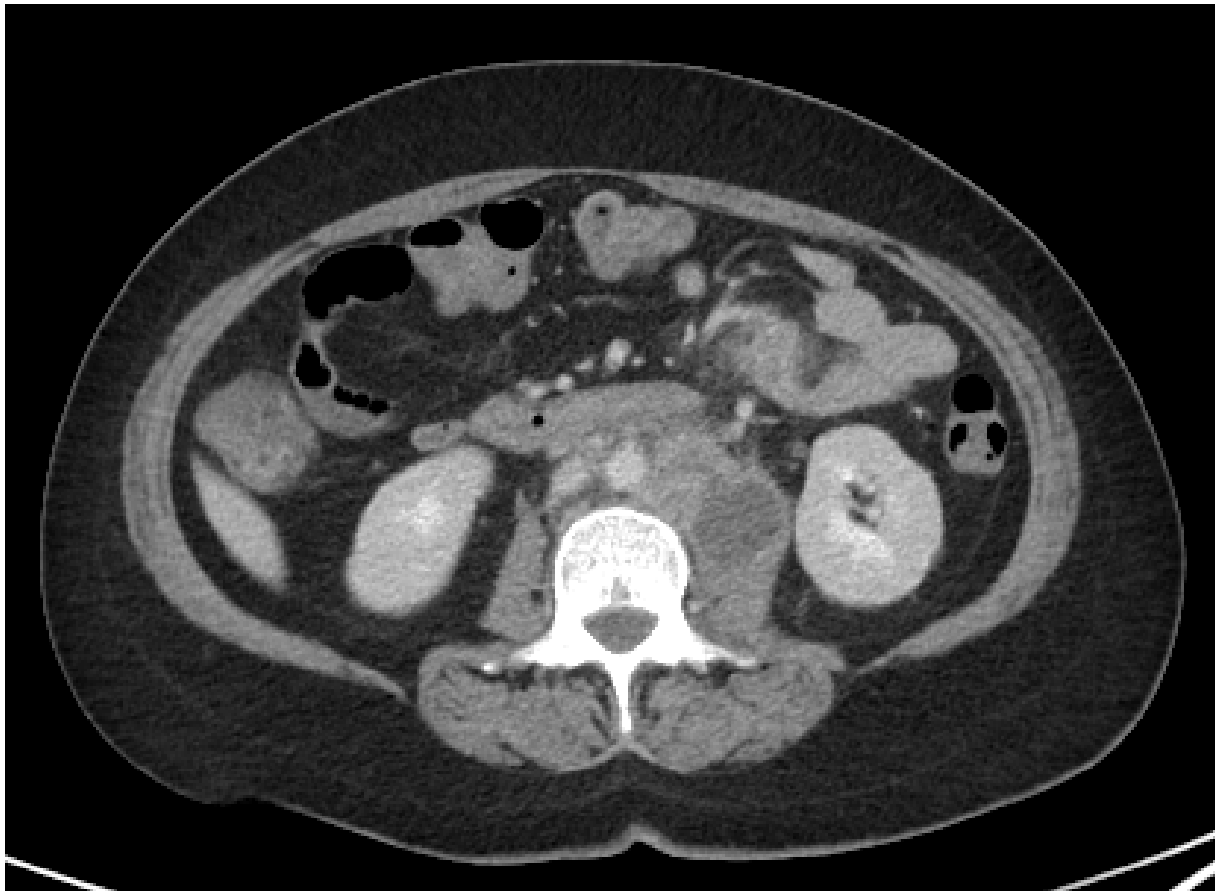
- Ultimately, a brain biopsy is recommended
- Frank pus aspirated
- Gram stain GPC; Culture negative
- AFB and Fungal stain negative; Culture pending
- Broad range PCR: *Streptococcus intermedius*
- Does the patient have two processes???



- Broad Range PCR on mediastinal tissue: *Streptococcus intermedius* + other oral flora

Case 4

- 40-year-old female with advanced HIV, CD4 14 and viral load 390,785 was seen in the clinic to re-establish care. She had symptoms of fever, night sweats, weight loss and anorexia for the last many months. Imaging revealed presence of significant generalized LNE with left psoas abscess.
- Has history of positive PPD 30 mm with incomplete treatment for LTBI



- A biopsy of the lymph nodes was performed in November 2024
- A drain is placed in left psoas abscess
- AFB stain is strongly positive
- Is this TB or MAC?

REVISED **Culture Refer for ID, Mycobacterium** MCR

Abn

SOURCE: LYMPH NODE, LYMPH NODE TISSUE

** Additional Report **

CULTURE REFER FOR ID, MYCOBACTERIUM **FINAL**

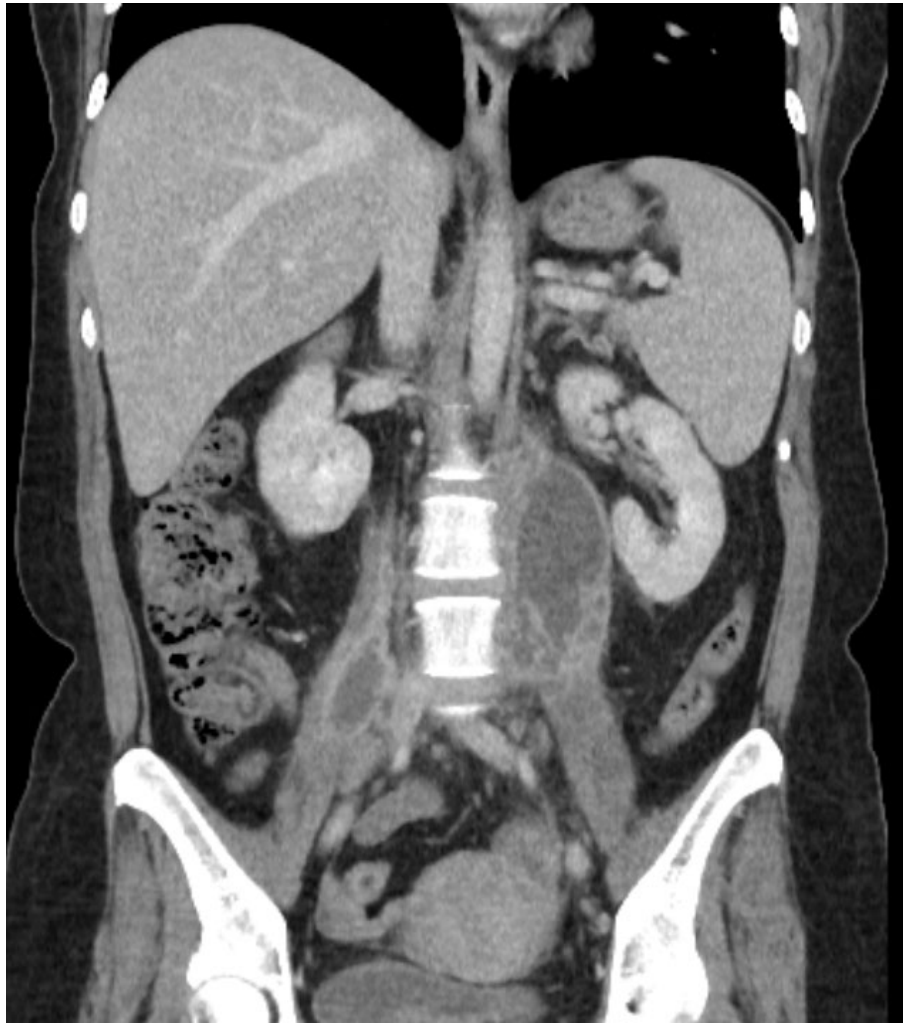
MYCOBACTERIUM AVIUM -
This species is a member of the M. avium complex.
[redacted]
Negative for M. tuberculosis complex to date
by PCR.

Follow up

- Patient is initiated on cART (ABC/3TC/DTG)
- Azithromycin, Ethambutol and Rifabutin daily ?12 months
- 11 months later:
  - Doing great
  - CD4 228
  - Viral load undetectable
- Would you repeat a CT for follow up of LNE?

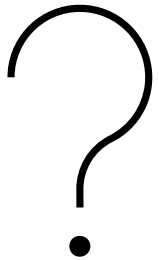
Follow up phone call @ 12 months

- Reports night sweats, low back pain, bloating
- Feeling generally unwell
- BTW, has also developed a cough



1. Necrotic mesenteric lymphadenopathy, increased in size
2. Large multiloculated left psoas abscess, stable, measuring 4.5 x 3.1 cm
3. Inferior right psoas abscess, slightly increased, measuring 2 x 2 cm

Polling Question 4



What is the next step in management?

A. Patient has unmasking of TB Infection. Start RIPE

B. Patient likely has Rifampin resistant TB. Start BPaLM

C. Patient has IRIS. Start steroids

D. Stop antiretroviral therapy due to its side effects

E. Obtain repeat biopsy

Culture Refer for ID, Mycobacterium MCR

Abn

SOURCE: BACK, BACK FLUID

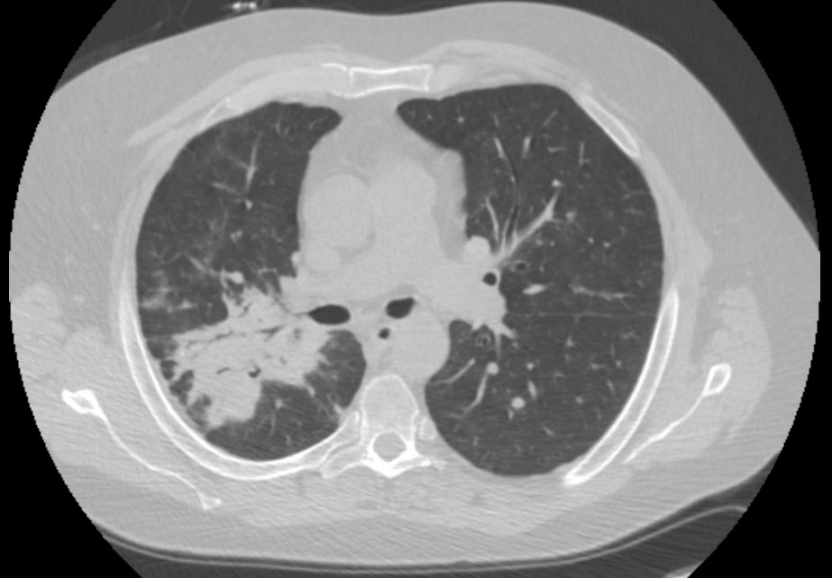
CULTURE REFER FOR ID, MYCOBACTERIUM **FINAL**

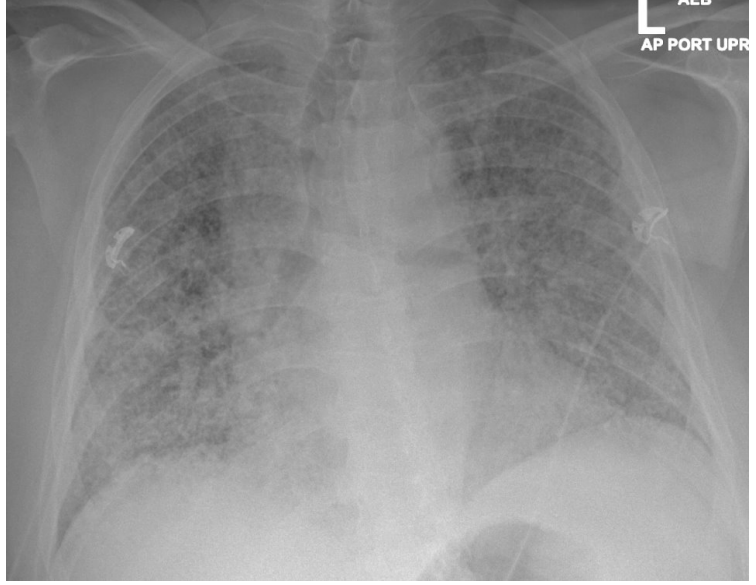
MYCOBACTERIUM AVIUM COMPLEX - [redacted]

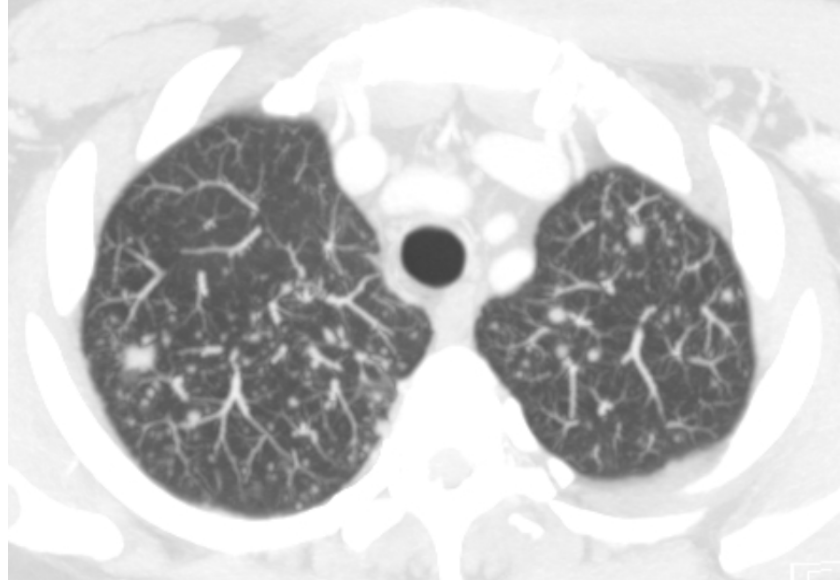
Negative for M. tuberculosis complex to date
by PCR.

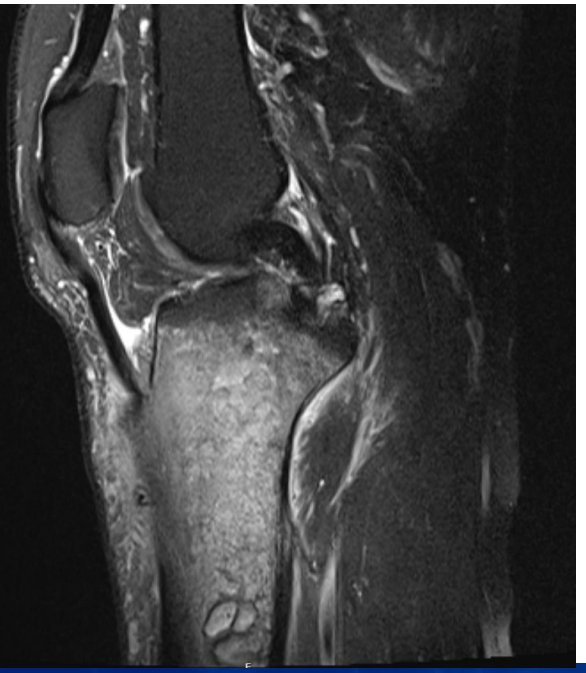
Remember the common TB mimics

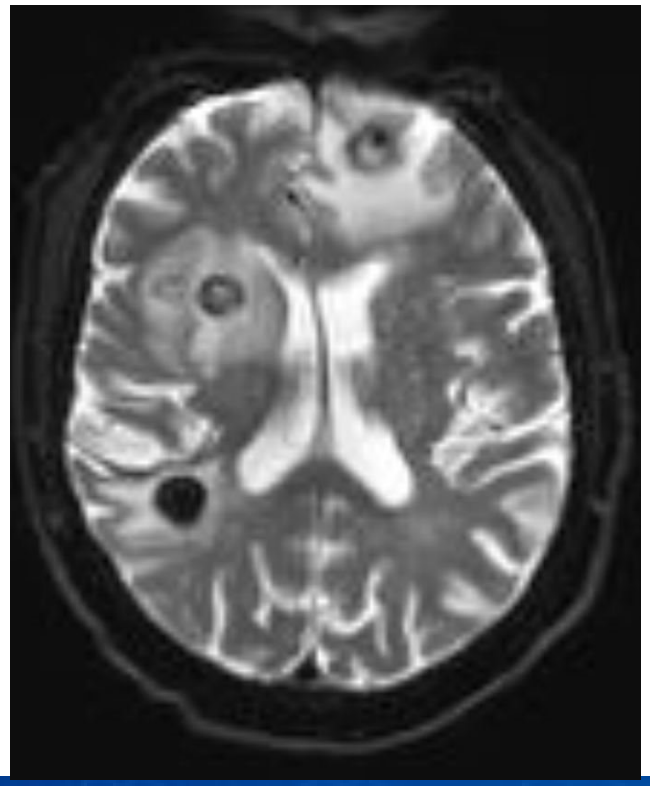
- Sarcoidosis
- Crohn's Diseases
- Lymphoma
- Necrotizing pneumonias eg: MRSA
- Kikuchi Disease
- Nocardiosis
- NTM Infections
- and...

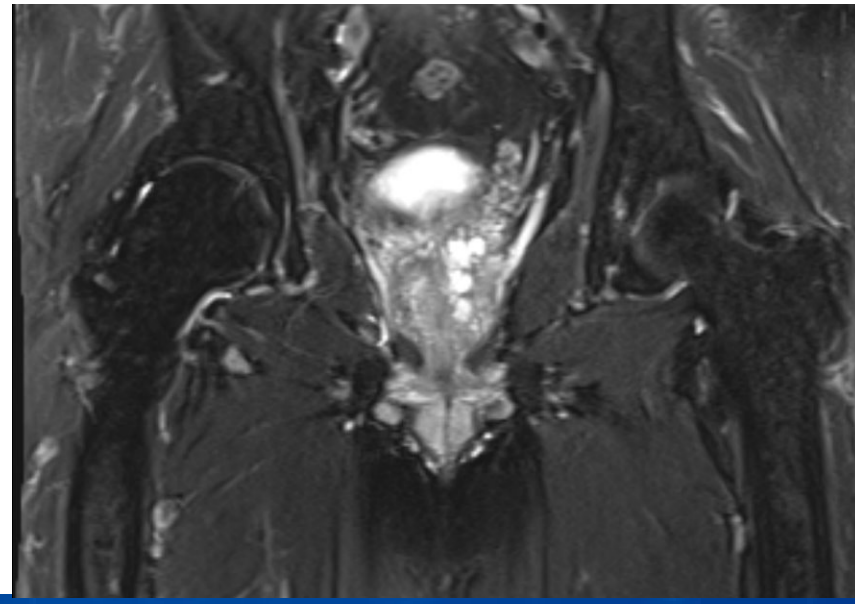



AP PORT UPR







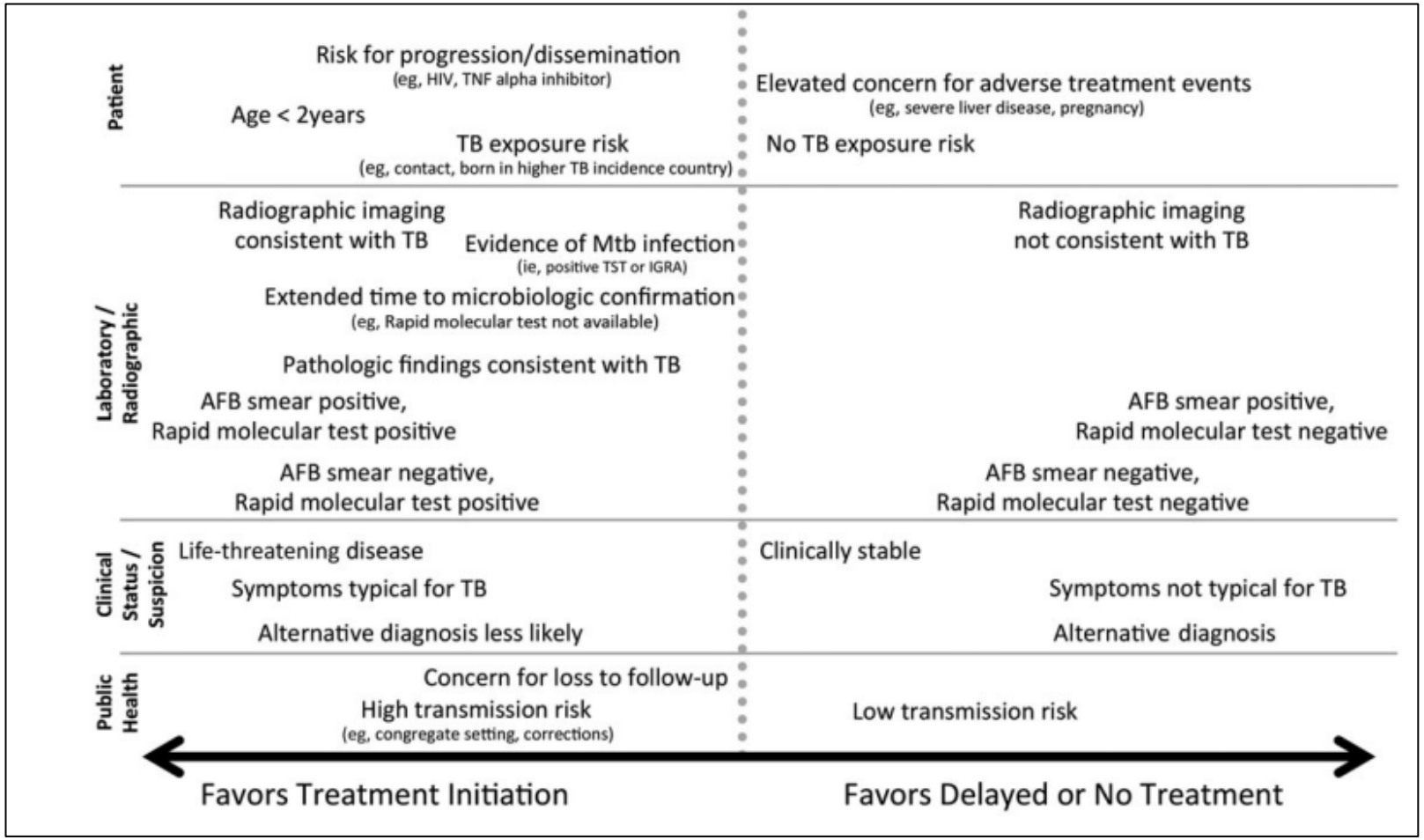


When to start treatment for TB disease?

- Confirmed M. tuberculosis disease: **Class-3**
  - Culture (+) MTB – typically delayed 2-4 weeks
  - Pos (+) rapid molecular test / NAAT

- Possible / Probable TB disease: **Class-5**
  - Can be challenging

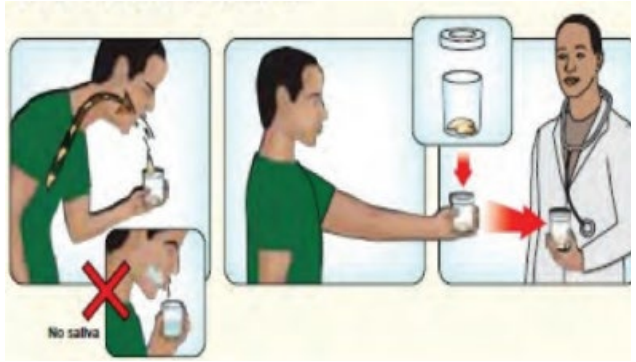
Factors to consider regarding preemptive treatment for active TB (Class-5)



Clin Inf Dis 2016;63(7):e147–95

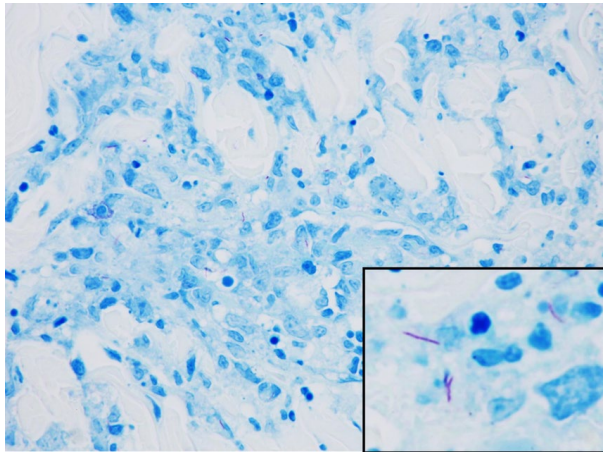
Culture Negative (-) TB

- 10-15% of pulmonary cases – many reasons:
  - Patient not able to produce quality sputum samples
  - Lower MTB bacillary burden
    - Non-cavitary,
    - Mild / localized disease
  - Poor patient effort in producing sputum samples (often non-induced)
  - Bronchoscopy / BAL in cases of pulmonary TB
    - Not 100% sensitive but influences treatment decisions



Culture Negative (-) TB

- Extrapulmonary TB disease – often *pauci-bacillary*
  - Tissue biopsies may not demonstrate (+) PCR, AFB stain or cultures
  - Often ‘heterogenous’ distribution of MTB bacillary in diseased tissue (lymph node, liver, etc)
  - Supporting clinical, radiological and laboratory findings can be helpful:
    - Support / Exclude alternative causes / pathogens
    - Invasive testing often necessary:
      - LP, Thoracentesis, Paracentesis, Tissue biopsies



Treating Class 5 TB (TB Suspect)

Impression: TB disease probable, less likely other diagnoses

- Start standard INH/RIF/PZA/EMB – while awaiting culture results
  - Important to ensure DOT for optimized patient compliance & monitoring
  - Usually more pressing need to preemptively start TB treatment in
    1. Patients with possible/suspected pulmonary TB disease
    2. Immunosuppressed patients

- MTB cultures monitored for 42 days:

A. Culture (+) Positive growth of MTB: confirmed active (class 3) TB disease
  - Complete full duration of TB therapy, guided by drug susceptibility testing (DST) results

B. No MTB growth after 6 weeks: possible “culture-negative” TB vs not TB disease
  - Next steps……

Treating Culture-TB (TB Suspect)

- MTB cultures finalized at negative (at 6 weeks)
- Re-evaluation of patient after 8-10 weeks of RIPE treatment
  - Repeat CXR (or CT chest if done) – any improvement?
  - Clinical status (during the 8 weeks of RIPE) – any improvement?

  - If cultures remain neg (-), AND
  - There is *any clinical OR radiographic improvement* while on treatment during the first 2 months, then

    → *Clinical TB (Class 3) diagnosis made* → continue & complete treatment for active disease:

Culture-negative TB – different mgmt. options can apply

- **CDC/ATS/IDSA:** 4 months total therapy
  - 2 mo (INH/RIF/PZA/EMB)
  - 2 mo (INH/RIF)
- **In Minnesota,** 8%-18% of TB cases are INH-resistant; large percentage of these patients are Somali
  - Concern for INH-resistant culture-neg. TB and risk of MDR TB development
  - Mayo/Olmsted Co: Continue all 4-drug TB drugs for 4-6 months therapy

Questions and Answers

Thank you