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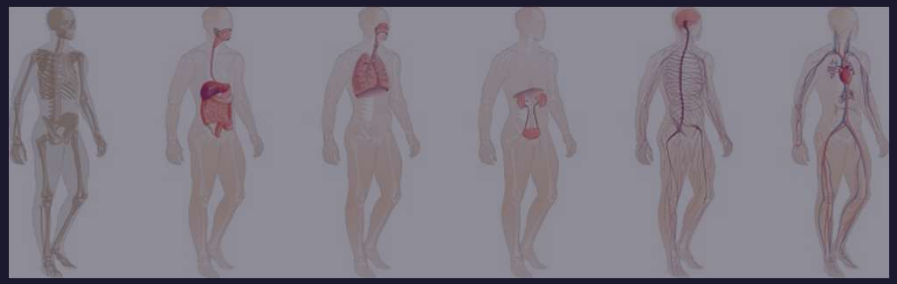

Clinical presentation and diagnosis of extrapulmonary tuberculosis

Tuberculosis Clinical Intensive
07/14/2023

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Conflict of interests

I serve on a clinical advisory board for Medicines Development for Global Health (not-for-profit).

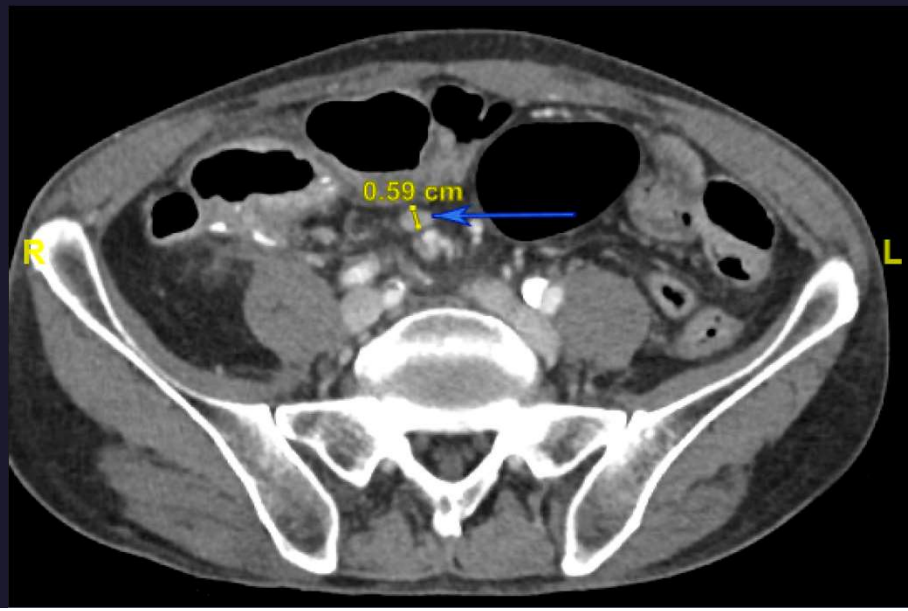
Objectives

- Main objective:
  - List at least 4 extrapulmonary manifestations of TB and potential approaches to confirm the diagnosis.
- Additional objectives:
  - Understand the [poor] performance characteristics of AFB stain/Cx, molecular and other diagnostics
  - Identify which cases of EPTB require different treatment durations (vs. pulmonary TB).

Case Presentation – First think TB!

67yoM from Vietnam admitted with rectal pain

- 2nd ED presentation, planned outpatient workup for anal fistula + ileocecal colitis with adenopathy (Crohn's vs. CRC),
- Initial ROS negative, but lower lobe nodules caught on CT A/P-> prompted dedicated CXR and Chest CT (Bil cavitation, >7 cm).
- Sputum AFB C/S: 4+ AFB, Mtb PCR+. Culture TTP 3 days.
- PMH: 2 yrs PTA (OSH) – intussusception – ileocecal resection, pathology with granulomas (AFB negative)

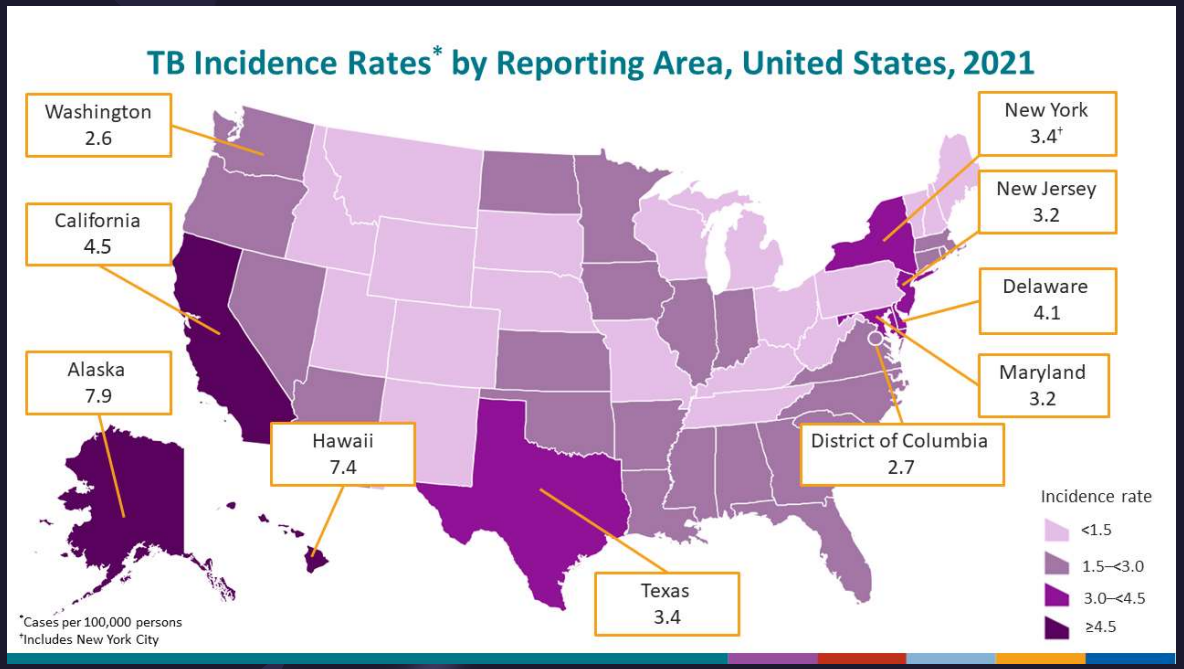


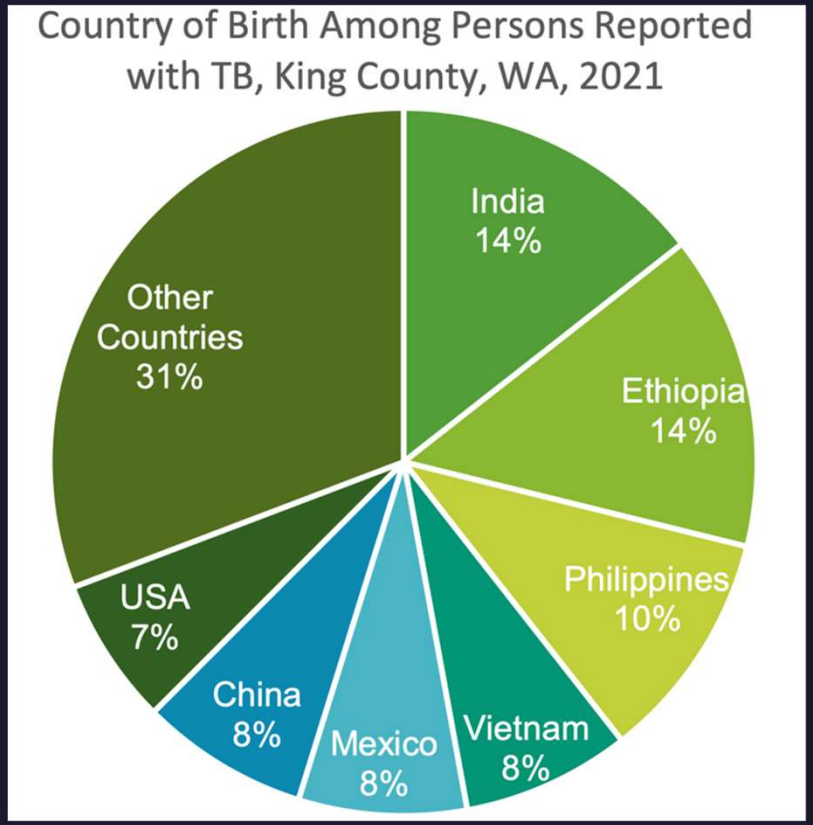
Case Presentation – First think TB!

EPTB lessons

1. First think TB – harness local epidemiology, be aware of TB mimics
2. Diagnostics rarely 'rule out' TB, many forms paucibacillary
3. Tissue/fluid sampling usually required. Pathology (granulomas) may be adequate.
4. Immune modulators – Predisposition to TB vs. a key adjunctive therapy

Tuberculosis: epidemiology

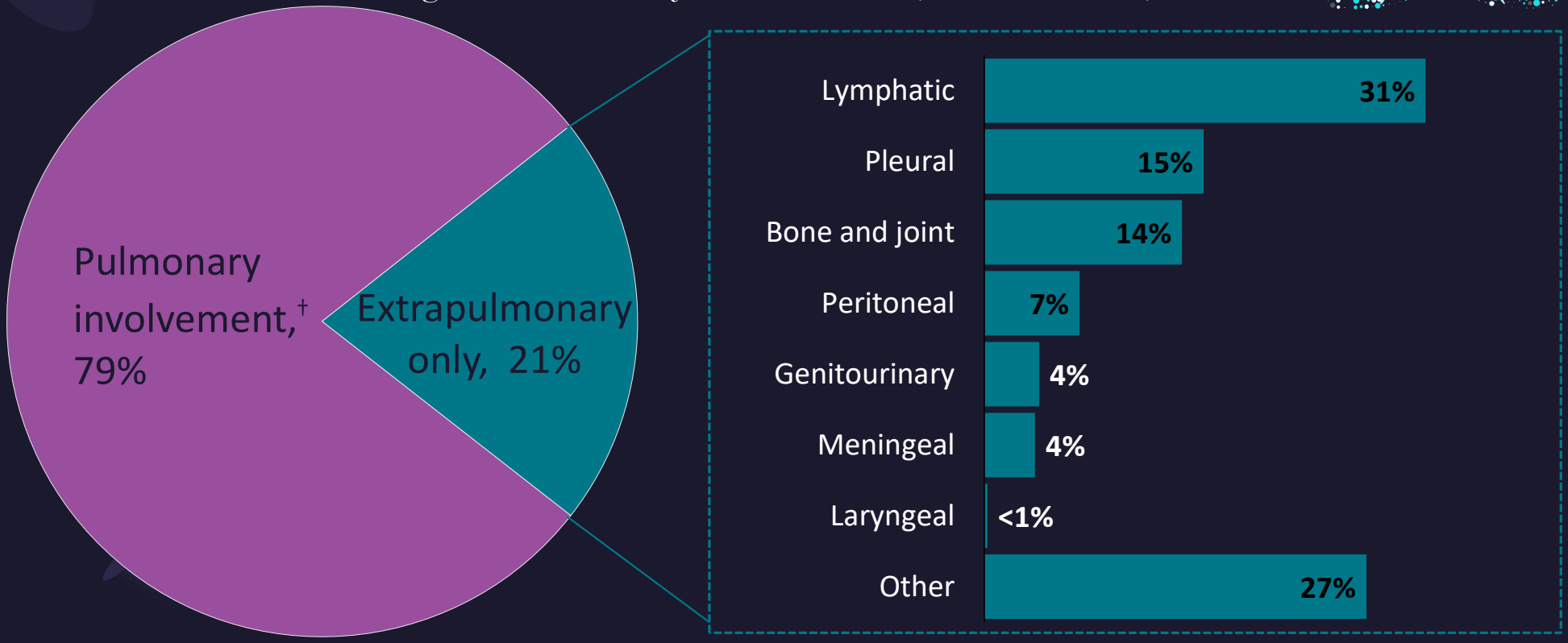




91% of 2021 cases born outside U.S,
2/3 of these are from 6 countries

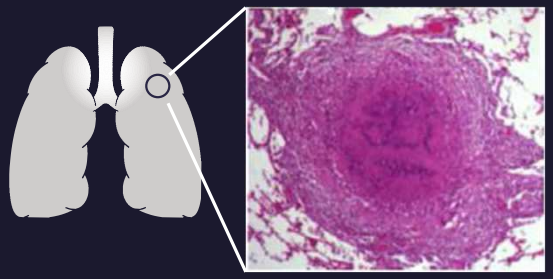
Extrapulmonary Tuberculosis (EPTB)

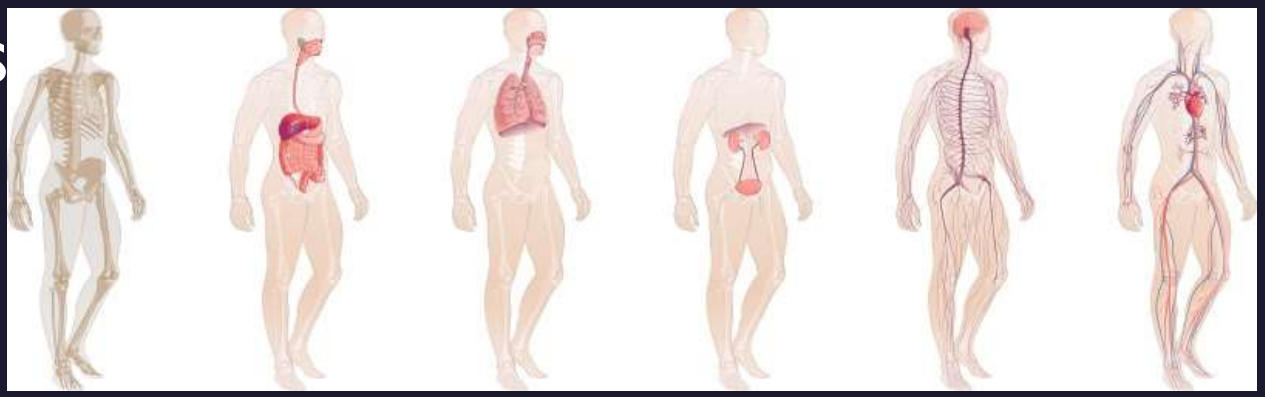
Percentage of TB Cases by Site of Disease,* United States, 2021



*Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.
†Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

EPTB pathogenesis

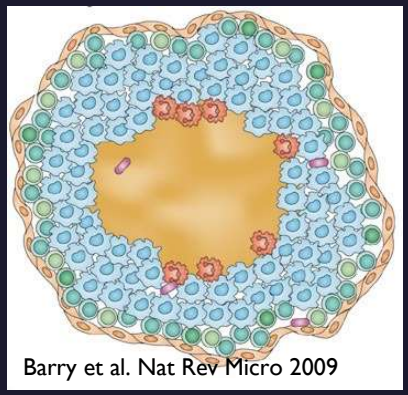




Early dissemination
- Primary disease seen in
  - Children
  - HIV/AIDS
  - BCG protective

HIGH INDEX OF SUSPICION
- Paucibacillary
  - miliary dz often sputum neg
- Insidious onset
- Nonspecific/protean dz manifestations

Early containment
- T cell, Mϕ
- TNFα



Barry et al. Nat Rev Micro 2009

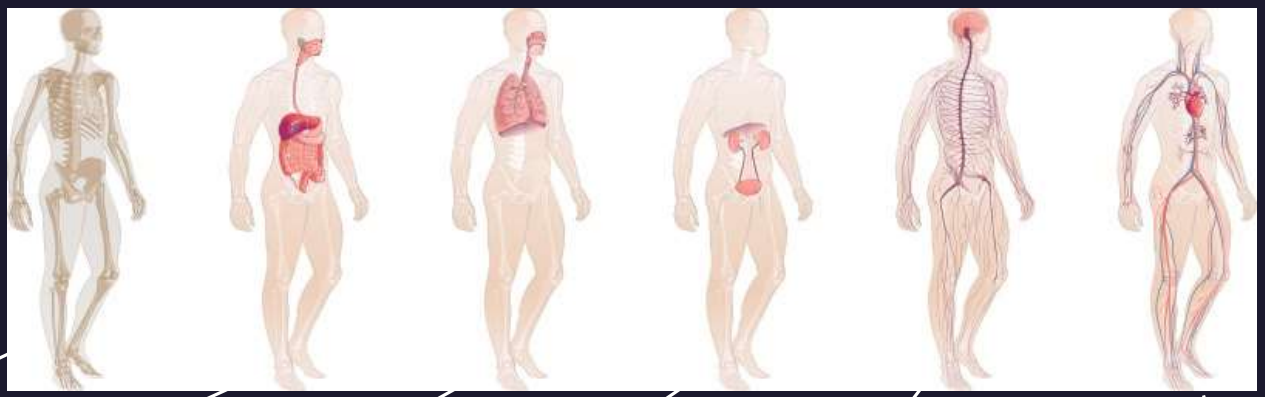
Reactivation
- anti-TNFα
- AIDS
- immune suppression

Risk factors

↑EPTB:PTB
- ?Sex

Kean et al. 2001, Dixon et al. 2009, Maartens et al. 1990, Kim et al. 1990, Humayun et al. 2022

EPTB forms



Skeletal TB

- Pott disease
- Osteomyelitis of growth plates

Abdominal TB

- Peritoneum, ascites
- Intestine, omentum
- Mesenteric LN

Pleural TB

- 1° progressive
- Severe DTH inflammatory response (paucibacillary)

GU TB

- 'Sterile' pyuria
- Infertility

CNS TB

- 1° /reactivation
- 'Rich foci' rupture → subarachnoid
- Hyperinflamm dz.

Pericardial TB

- Constrictive
- Contiguous spread LN vs. progression

Lymphatic TB

- 'King's evil', 'Scrofula'
- Common in childhood (NTM>TB)
- Surgical cure (but recommend drugs)

Disease patterns

Bacillary index

Hypersensitivity

- Body fluids
  - ocular, TBM
  - pleural, pericardial, peritoneal
  - Arthritis (Poncet's)
- Skin
  - Erythema induratum
  - *Lichen scrofulosorum*

Chronic scarring

- Pericardial
  - constrictive pericarditis
- Fistulas, strictures
  - GI
  - GU
- Infertility
  - Fallopian tubes
  - Prostate, vas deferens, seminal vesicles

Pauci

- Ocular
- Pericardial
- TBM
- Pleural/peritoneal*
- Cutaneous
  - Lupus vulgaris
  - TB verrucosa cutis
  - *Lichen scrofulosorum*
- Lymphadenitis*

Multi

- Miliary
- Laryngeal
- Renal
- MSK*, arthritis
- Cutaneous
  - Cold abscess
  - Scrofuloderma
- GI
  - ulcerations
  - enteritis/colitis

Lymphadenitis (Scrofula)

- Most common EPTB form
  - Cervical (60-90%)
- Usually painless
  - ulceration/abscess, extrinsic compression
- Rarely present with PTB
- HIV infection – commonly have
  - Constitutional symptoms, >1 chain
  - more PTB
- Paucibacillary, but culture yield good
  - Excisional (or core) Bx for Dx and DST ideal
  - Okay to start with FNA (esp immunocompromised)
- Surgery often curative…
  - …but offer ATT, paradoxical reactions can occur
  - Caseating granulomas sufficient to start therapy, though NTM common in children

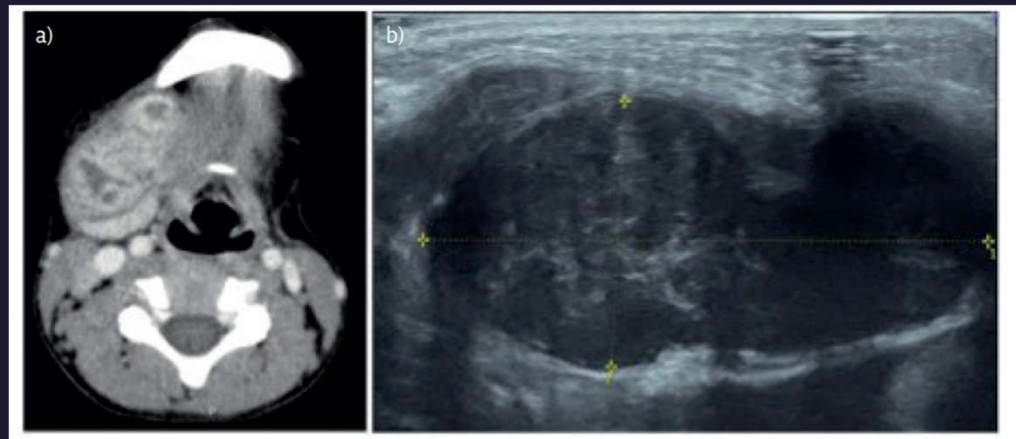


Figure 5 *Tuberculous peripheral lymphadenitis imaging. Computed tomography scan and ultrasound of an 8-year-old*

Figure 4 *Tuberculous peripheral lymphadenitis clinical presentation. Cervical tuberculous*

Natali et al. Breathe 2020

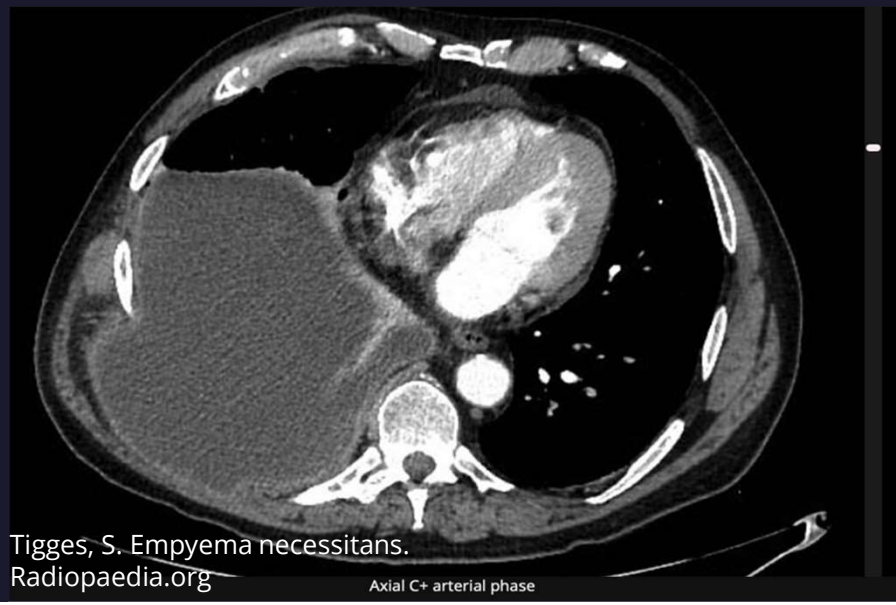
Pleural TB

- Most common etiology of pleural effusion (endemic regions)
- Young males
- Primary or reactivation
  - Subpleural granuloma rupture
  - Lymphatic dissemination
  - TB-HIV – common reactivation TB manifestation
- Fever, cough, pleurisy
- Imaging
  - Unilateral effusion (R>L)
  - Often apical parenchymal disease (reactivation)
- Self-limited or chronic
  - Empyema necessitans
  - Fibrothorax

Vorster 2015 J.Thor Lung Dis

Diagnosis

- Pleural fluid analysis
  - Exudative (Protein and LDH high)
  - Lymphocyte predominate (>75%)
  - AFB C/S, PCR
  - ADA Se
  - IFN-γ level
- Pleural biopsy



Tigges, S. Empyema necessitans. Radiopaedia.org

Skeletal TB

- Osteoarticular seeding (hematogenous)
  - Spine, hip and knee = 70-80% of infections
  - Tuberculous spondylitis (Pott's) = ~2% of all TB infections
- Subacute, +/- localized +/- constitutional symptoms
  - Paraspinal abscess, vertebral collapse + paraplegia, deformity
- Imaging
  - Endplate destruction (thoracolumbar), Gibbus deformity
  - Multilevel with 'skip lesions' due to anterior ligament extension
  - (Large joint) Effusions, synovial hypertrophy, usually monoarticular
  - Dactylitis (small bones) more common in children
- Diagnosis
  - Often FNA first (C/S + molecular), core biopsy may be required
  - Synovial fluid analysis (C/S + molecular + ADA, ?IGRA)

D. Horne
M. Narita

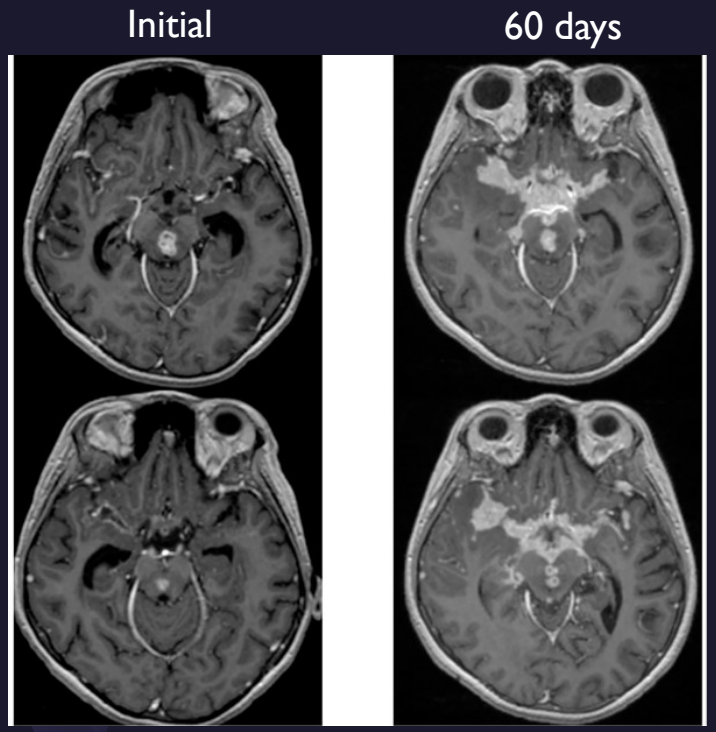
CNS TB (TB meningitis/TBM)

- Rich foci rupture->subarachnoid-> DTH
- Presentation
  - AMS, CNS III/IV/VI/VII palsy, seizure (tuberculoma)
  - Mortality 25-50%, HIV 65%, HIV+ARV <40%, MDR >80%
- Diagnosis
  - Paucibacillary – Need adequate CSF (>10cc)
  - Pleocytosis 100-500 (PMN early, Lymph late)
    - Glucose <45 g/dL, protein 100-500 mg/dL
    - ADA 93% Se (<4 U/L) 96% Sp (>8 U/L)
    - PCR 62% Se, 98% Sp (Xpert ultra ~70% Se)
  - CT+contrast/MRI+Gd
    - tuberculomas
    - basilar arachnoiditis, leptomeningeal enhancement
    - hydrocephalus
    - vasculitis/infarct
- Expedite treatment [empiric]
  - HIV and adjunctive steroids (later slides)
  - Paradoxical worsening

Lewinsohn et al. 2017
Huynh et al. 2022
Dian et al. 2020

CNS TB (new slide)

Fig 2. Paradoxical response with basal meningeal enhancement after 60 days treatment.



- 89% (33/37) participants w/ new/worsening MRI findings
  - Minority had worsening symptoms--13/33 (39%)
  - Most had new/enlarging tuberculomas –27/33 (82%)
  - Most had worse/expanding meningeal enhancement (76%)

Table 4. Outcome of paradoxical response.

6m outcome	Clinical + radiologic N = 13	Clinical N = 2	Radiological N = 20	No paradoxical response N = 2
Mortality	2 (15%)	1 (50%)	0	0
GOS* 4 or 5	7 (54%)	1 (50%)	20 (100%)	2 (100%)

*Glasgow Outcome Score

Dian S, Hermawan R, van Laarhoven A, Immaculata S, Achmad TH, et al. (2020) Brain MRI findings in relation to clinical characteristics and outcome of tuberculous meningitis. PLOS ONE 15(11): e0241974. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0241974

Abdominal TB

	Findings	Complications
Peritoneal	Ascitic fluid analysis (next)	
Esophageal	Ulcerations Mediastinal LAN	Bleeding, fistula, perforation
Intestinal (TB enteritis)	Circumferential ulcerations (next)	
Gastroduodenal	Gastric Outlet Obstrx Non-healing ulcer	Perforation, bleeding
Colorectal	Fissure, non-healing ulcer, abscess, bleeding	Perforation, fistula, obstruction
Hepatobiliary	Pseudotumor, hepatomegaly, cholestasis	Cholangitis, hepatitis, abscess
Gall bladder and pancreas	Cholecystitis Pseudotumor, pancreatitis	Perforation (rare)

Malikowski et al. 2018

Abdominal TB: Peritonitis

- 31-58% of abdominal TB
  - "Wet" and "Dry type" with "doughy abdomen"
- Usually reactivation of LTBI (coexistant active PTB or TB enteritis is rare)
- Hematogenous seeding; direct extension from intestine/fallopian tubes less common.
- Risk factors:
  - cirrhosis
  - ESRD
  - HIV
  - EtOH

Sanai et al. 2005, Riquelme et al. 2006, Lewinsohn et al. 2017, Nakhale et al. 2016

Abdominal TB: Peritonitis

- Diagnosis:
  - Peritoneal fluid rarely AFB smear-positive (Sn <5%)
    - AFB culture Sn 45-69%
  - CT: Ascites, hypervascular peritoneum, tubercular nodules, mesenteric LAN, adhesions, omental thickening
  - Laparoscopy: Visual diagnosis or w/ peritoneal biopsy (sensitivity 79-100%)
  - ADA 79-100% sensitive and 83-97% specific (threshold >26-40 U/L)

	Cirrhosis (no SBP)	**Cirrhosis (w/ SBP)**	**Peritoneal TB**	**CHF**	**Nephrotic Sx**	**Malignancy**
Mean AFTP (g/dL)	1.87 (±0.7)	0.93 (±0.1)	3.15 (±0.33)	1.64 (±0.66)	2.6 (±0.14)	2.7 (±0.14)
SAAG (g/dL)	2.12 (±0.5)	1.37 (±0.1)	0.67 (±0.15)	2 (±0.4)	0.88 (±0.31)	0.98 (±0.14)

Sanai et al. 2005, Riquelme et al. 2006, Lewinsohn et al. 2017, Nakhale et al. 2016

Abdominal TB: Intestinal

Pathogenesis:

- Exposure:
  - Hematogenous
  - Milk (e.g. *M. bovis*)
  - Ingested sputum in active PTB
  - Contiguous spread, rare (e.g. lymph node direct invasion)
- Invasion into submucosa (esp. terminal ileum)
- Granulomatous inflammation, ischemia (arterial invasion)

Presentation:

- Insidious. Diarrhea, chronic abd pain, weight loss/B symptoms
- Ulcerative, hypertrophic and ulcerohypertrophic forms
- Initial presentation is often due to complication:
  - Stricture, obstruction, fistula formation
  - Bleeding
  - Perforation

Sanai et al. 2005
Riquelme et al. 2006
Malikowski et al. 2018

Abdominal TB: Intestinal

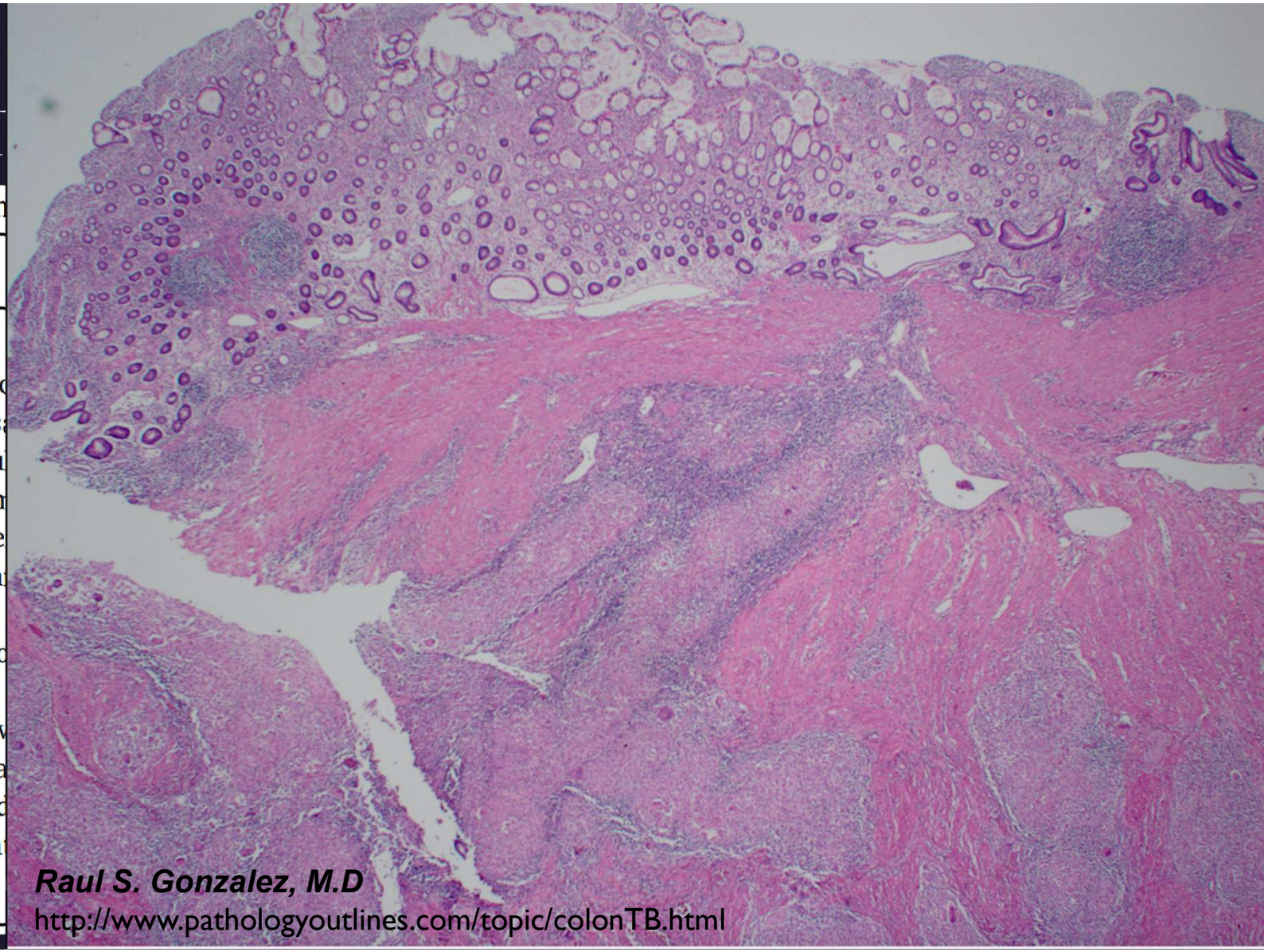
Diagnosis:

- chronic inflammatory findings:
  - ESR/CRP, anemia, hypoalbuminemia
- CT with concentric intramural thickening, necrotic LAN, "cold abscess".
- Stool AFB C/S and PCR (can be + in PTB).
- Endoscopy
- TISSUE (LN, luminal biopsy) -> AFB C/S and PCR

Sanai et al. 2005
Riquelme et al. 2006
Malikowski et al. 2018

Abdominal T

Tuberculous en	Crohns
No Ascites	
Linear ulcers,	
Normal mucos	
Mucosal granu	
Granulomas sm micromete	
Granulomas in biopsy)	
Granulomas no caseating	
Normal IC valv	
No acid-fast ba	
No or low-grad	
Small inflamm	



Raul S. Gonzalez, M.D

http://www.pathologyoutlines.com/topic/colonTB.html

EPTB as a masquerader

Syndrome	Differential	Investigations
Lymphadenitis	Lymphoma, Sarcoid, NTM, fungal	**CHEST X-RAY (always)!!!** Excisional bx (FNA may be sufficient for TB)
Pleural effusion	Malignant PE (lung, breast, NHL/HL, Ovarian)	CT C/A/P for primary tumor Thoracentesis (cytology, AFB**, ADA, PCR) Pleural biopsy +/- VATS
Meningitis	Fungal (CM, Histo), Vasculitis, SLE, Toxoplasma Leptomeningeal carcinomatosis	CSF (PCR, ADA, AFB C/S) MRI brain w,w/o
Enteritis/colitis	Colorectal cancer Inflammatory Bowel Disease • Ascites more common in TB	Colonoscopy, biopsy (granulomas) • LN biopsy • Stool AFB C/S
Peritonitis	Peritoneal carcinomatosis (malignant ascites) SBP *Nephrotic syndrome (also ↓↓ SAAG)*	Paracentesis (cytology, AFB, ADA, PCR) • TB: SAAG ↓↓↓, %lymph ↑↑↑ (>30%) CT A/P for primary tumor or necrotic LNs

**Note: AFB C/S has low sensitivity for many EPTB fluids, tissue better when available (path may just show granulomas)

Horne and Narita BMJ 2020

EPTB Workup – General considerations

- CXR and dedicated imaging of site
- Sputum C/S for AFB even without pulmonary signs or symptoms
  - Transmission risk, non-invasive sampling
- Smear microscopy and AFB culture (tissue) – but often paucibacillary…

Sensitivity by specimen*	Smear	Culture	ADA	IFNγ
Pleural fluid	0-10%	23-58%	89-99% (Sp>90%)	89% (Sp 97%)
Pleura tissue	14-39%	40-58%		
CSF	10-30 %	45-70%	59-79% (8 U/L)	
Peritoneal fluid	<5%	45-69%	100% (40 U/L)	93% (Sp 99%)

- HIV test in all patients
- Despite generally discouraging use of TST/IGRA during workup for active TB, IGRA is useful during EPTB evaluation.
  - Negative IGRA still not helpful

*Compiled by Lewinsohn et al. 2017 CID (ATS/IDSA guidelines)

EPTB Treatment

- Drug selection and duration generally follows that for pulmonary TB
  - 2 months intensive (4 drug, usually HRZE/RIPE) then 4+ months continuation (2-drugs)
  - MDR/XDR – consult with specialist
  - If fully-susceptible, EMB can be dropped early
- Duration (Table for drug-susceptible TB)

Syndrome	4?	6 months	9 months	12 months	Notes
Lymphadenitis	?				
Pleuritis	?				
Meningitis					
Ocular					Includes 2 mo intensive
Skeletal			Extensive, large joint		
GI/peritonitis					
Renal					

- 4-month Rifapentine/Moxifloxacin/Z/H not studied (Dorman et al. NEJM 2021), discouraged in 2022 MMWR …
  - …consider for "likely to be paucibacillary…and not require prolonged treatment (i.e., pleural or lymph node TB)

Treatment – special considerations

Corticosteroids

- TB meningitis (Thwaites 2004)
  - Dexamethasone protective for death (RR 0.69, *P* 0.01),
    - NOT death-or-disability (RR 0.81, *P* 0.22)
  - Benefit for HIV+/- and across severity groups
    - Large RCT (Indonesia/Vietnam) in HIV+ is pending (PMID: 30320225)
  - Probably host genotype dependent (*LTA4H*, Tobin 2012). Ongoing trial (NCT03100786)
  - ATS/IDSA guidelines support treatment with 6-8 week taper

- Pericarditis (Mayosi 2014, Wiysonge 2017)
  - ATS/IDSA 2016: Recommend against as RCT (Mayosi et al.) showed no protection from composite endpoint (mortality/constriction)
  - HIV-negative: Protective from death due to pericarditis (RR 0.39 [0.19-0.80])

Treatment – special considerations

TB meningitis

Rifampin dosing (IV versus PO, intensified dosing)

- Ruslami 2013: IV (13 mg/kg, n=29) vs PO (10 mg/kg, n=31) -> AHR 0.42, *P* 0.03
- Dian 2013 (n=60): PO 10, 20, 30 mg/kg -> RIF exposure (plasma+CSF) 3-5X higher, mortality 35%, 45%, 15% (*P* =0.15) without increased adverse events.

Fluoroquinolone or linezolid

- Better CNS penetration (levofloxacin/moxifloxacin and linezolid)
- Heemkerk 2017 (n = 817 patients): RIPE/dex (10 mg/kg RIF) versus RIPEL (RIF 15 mg/kg PO) -> HR 0.94, *P* = 0.66, no adverse event difference
- Rifampin reduces linezolid exposure

Treatment – special considerations

TB-HIV

- Timing of ARV initiation in TBM (e.g. TBM-IRIS).
  - TBM-IRIS seen in up to 50% of cases.
  - No mortality benefit to immediate ART (<7d vs. 8wks), more severe adverse events (Torok 2011).
  - ATS/CDC/IDSA 2016: Delay ART until 8 weeks in all patients regardless of CD4.
  - DHHS OI 2022: Consider ARV start <2 weeks if CD4 <50 (high-resourced settings with monitoring).
- Drug-drug interactions
  - Use a rifamycin
  - Consult with pharmacy (and https://clinicalinfo.hiv.gov/en/guidelines)
- Dexamethasone
  - Same as HIV-uninfected pending ongoing clinical trial (NCT03092817)

EPTB: Take home points

First think TB!

- High clinical suspicion required
- Harness local epidemiology

EPTB the masquerader

- Malignancy
- Crohn's

ALWAYS get CXR

Consider TST/IGRA

Tissue is issue

- AFB stain poorly sensitive
- Cx higher yield, allows DST
- Histopathology can secure Dx

Case 2

- 70yo M (Singapore) admitted with stroke. Routine KUB (ileus) reveals renal and tubular calcifications. Asymptomatic, serum Cr 0.91
- Next step(s)?
  A. Renal biopsy
  B. Urine Cx (including AFB C/S) then ciprofloxacin
  C. IGRA
  D. Chest imaging (X-ray, CT)
  E. Nephrectomy

Case 3

- 61yoF h/o HTN with 6 years L eye blurring/floaters (Portugal).
- Prior treatments for retinal vein occlusion

Ocular fundus of the right eye with intraretinal haemorrhages and of the left eye showing vascular sheathing, neovascularisation and capillary non-perfusion.

- New intraretinal/vitreous hemorrhages, neovascularization c/f retinal vasculitis
- Workup: IGRA+. Negative ACE, Syphilis IgG, autoimmune panel, Sputum Cx, CXR
- Next step(s)?

A. Treatment pending aqueous/vitreous sampling
B. Topical (+/- systemic) steroids
C. INH x 9 (or 3HP or 4H)
D. RIPE
E. Shouldn't ophthalmology handle this?

Patricio et al. 2013
http://dx.doi.org/10.1136/bcr-2013-008924

Case 4

Syndrome? Etiology DDx?

- 42yoF h/o asthma, IBD p/w non-pruritic, painful, red nodules on feet->posterior legs.
- Prior Rx for sinusitis (TMP/SMX)
- PPD >20 mm, punch bx lobular granulomatous inflamm with thickened vessel walls , AFB stain/PCR negative.

DOI: 10.1056/NEJMcps040422

Case 4

Syndrome? Etiology DDx?

Erythema nodosum

- Sarcoid, GPA, IBD
- Drugs
- Enteric infx, Chlamydia, Mycoplasma
- TB (Erythema nodosum induratum of Bazin)
  - More commonly posterior legs
  - Usually AFB negative (hypersensitivity)
  - More common at time of PPD conv
  - RIPE vs. monitoring (then TPT).

DOI: 10.1056/NEJMcps040422

- 42yoF h/o asthma, IBS p/w non-pruritic, painful, red nodules on feet->posterior legs.
- Prior Rx for sinusitis (TMP/SMX)
- PPD >20 mm, punch bx lobular granulomatous inflamm with thickened vessel walls , AFB stain/PCR negative.

References

Evaluation (Please Scan Me!)

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