

Pulmonary Fascinomas with a TB Attitude...

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Accreditation Statement



Accreditation Statement

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Available Credit

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

**ID doc told me about a patient on
consult list with a donkey bite?...**

**He recommended either *Donkeycycline*
or *Augmuletin*...**

**Ultimately the hospitalist
went with *Asstreonam***

Objectives

- Review challenging and atypical presentation of pulmonary TB
- Discuss diagnostic approach and treatment that seem most appropriate
- Help me & (some) learners identify and avoid missed opportunities



Cases

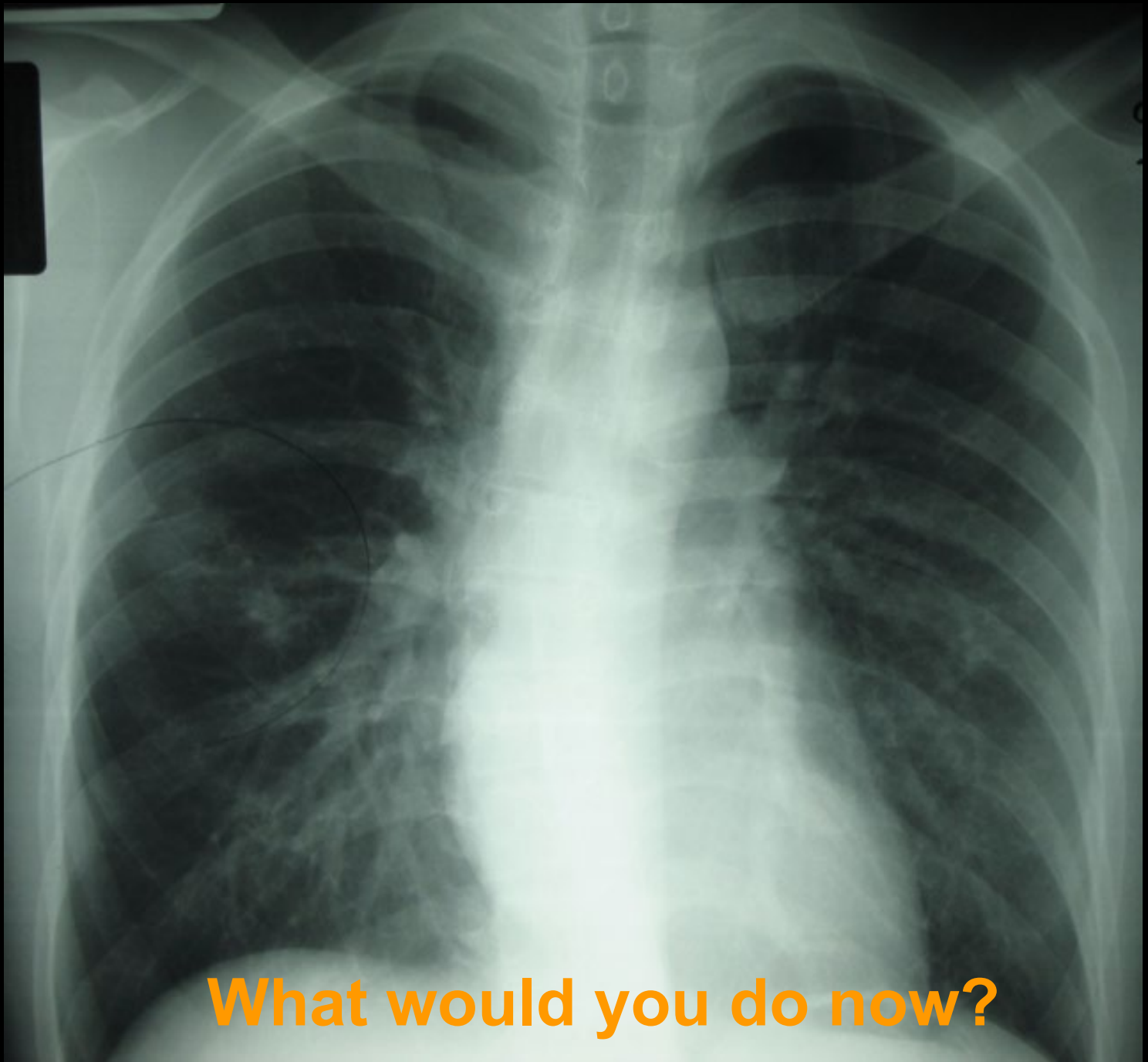
- TB or not TB
- Through the Retrospectoscope.....
- Bronchiectasis Surprise...
- TB & old guys...

Cases

- TB or not TB
- Through the Retrospectoscope.....
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TB or not TB, Case #1...

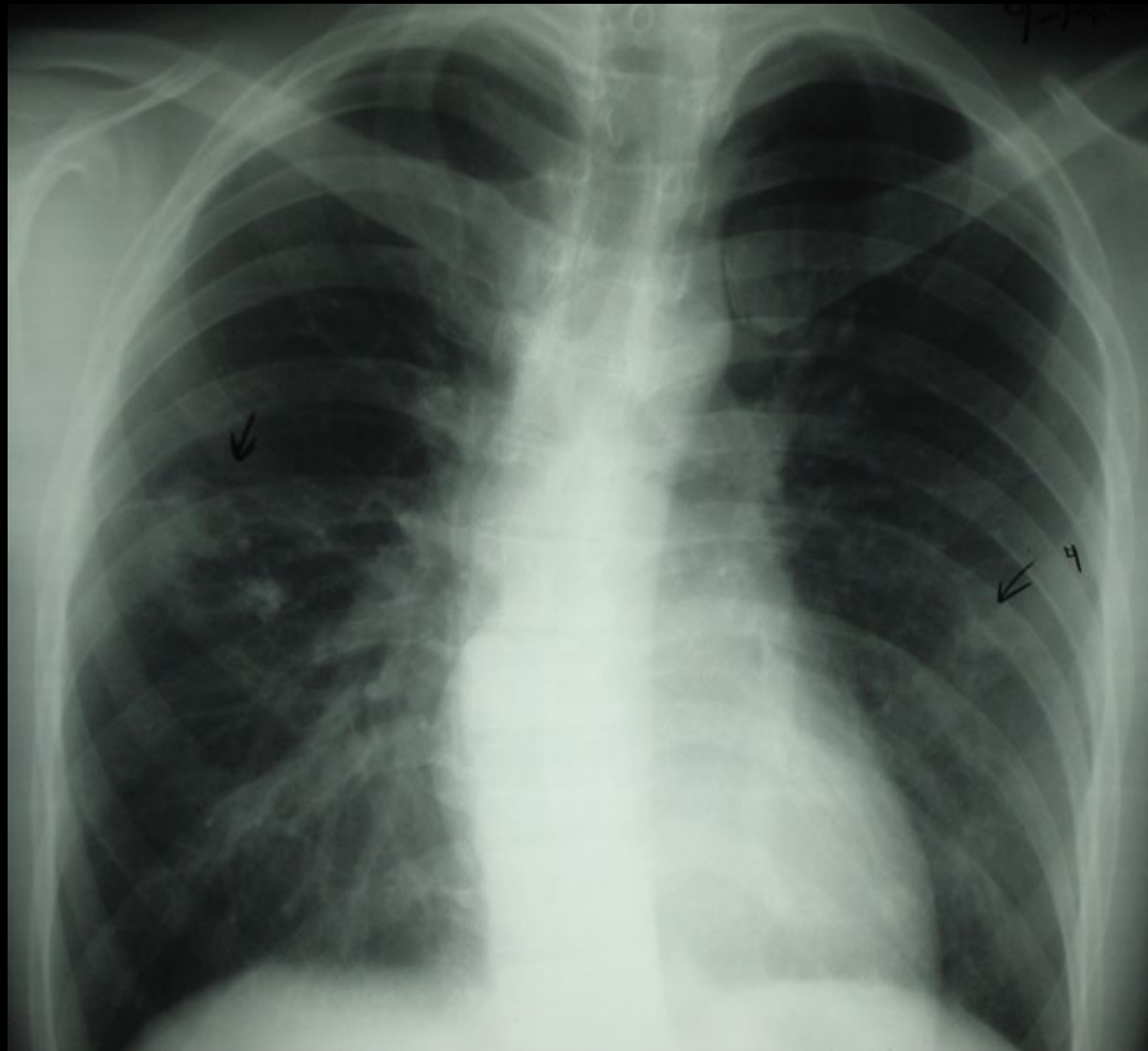
- 21 yo University student just arrived from India
- Asymptomatic, no exposure to active TB
- Screening program for new foreign students:
+ IGRA
- “I had BCG vaccine, that’s why my TB test positive”
- No HIV risk factors
- Chest x-ray...



What would you do now?

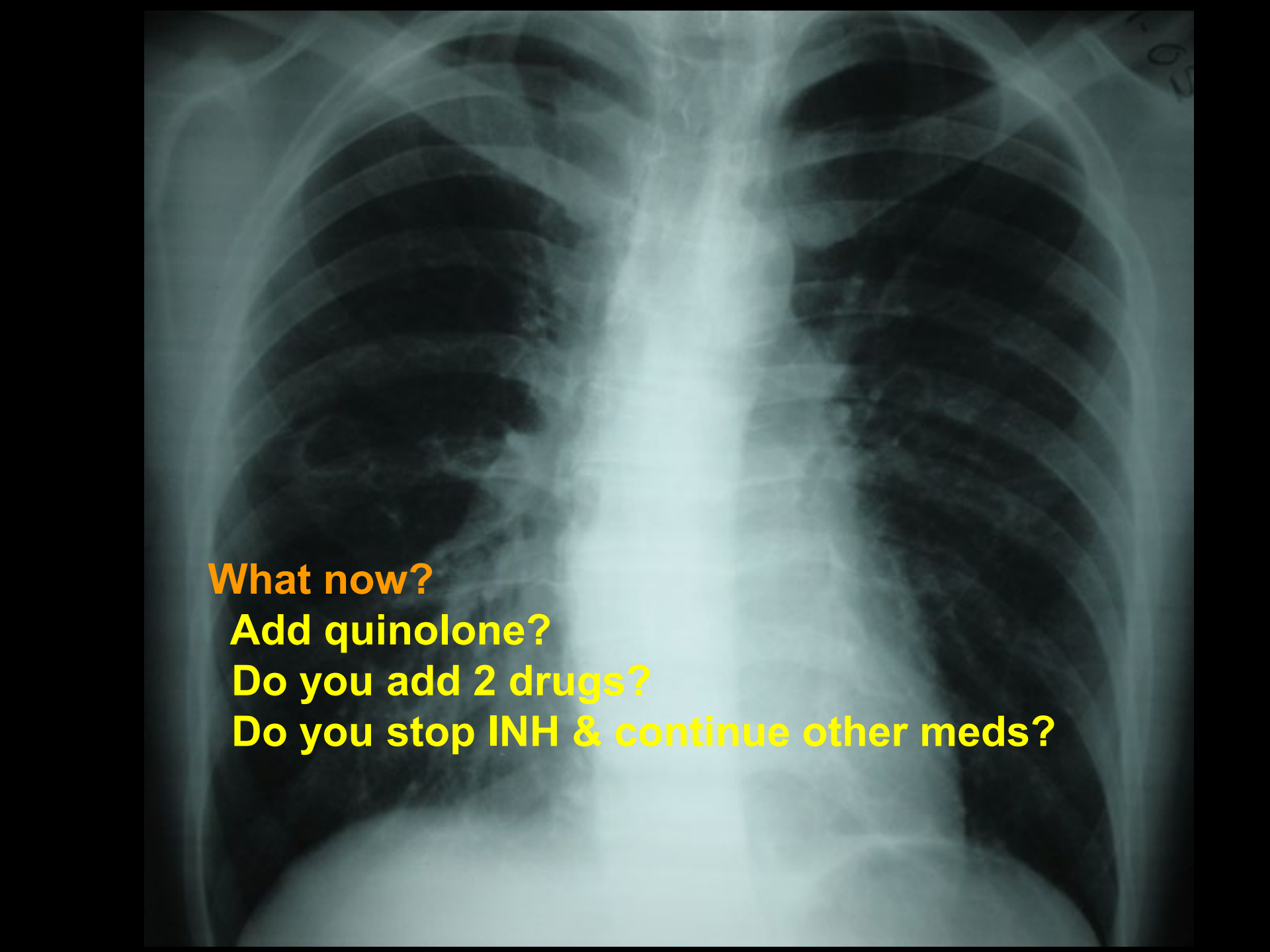
More Data...

- Unable to produce sputum in clinic; No AM sputum
- Bronchoscopy: Trans-bronchial biopsy negative, BAL AFB smears & TB NAAT negative
- Two weeks pass: Remains asymptomatic, balky
- What would you do now?
- ...Another Chest x-ray



More Data...

- Rx: INH, rifampin, pyrazinamide, & ethambutol, daily DOT (from date of abnormal chest x-ray)
- At 4 weeks BAL culture: *Mycobacterium tuberculosis*
- Then...susceptibilities show INH resistance
- Chest x-ray...

A frontal chest X-ray showing the lungs, heart, and bony thorax. The lungs appear clear with no significant consolidation or effusion. The heart size is within normal limits. The bony structures, including the ribs and spine, are visible. In the bottom left corner, there is overlaid text in orange and yellow.

What now?

Add quinolone?

Do you add 2 drugs?

Do you stop INH & continue other meds?

Recall Basic Principles Active TB Rx

- Active TB: Start Rx immediately upon suspicion
- Principles that underlie initiation of 4 drugs
 - Use drugs to which the bugs are sensitive
 - More bugs early, requires more drugs
- Ensure adherence to treatment (DOT)
- Never add a single drug to a failing regimen
- Don't be afraid to ask for help...

INH Mono-Resistant TB Rx

- No reference clinical trials...
- Daily supervised Rx (not 3x/week)
- Consider extending Rx to 9 or 12 months
- Recent suggested option, stop INH and...
 - Rifampin, pyrazinamide, ethambutol plus levoflox x 6 months
 - If responding, adding quinolone doesn't violate "do not add single drug" rule
 - To reduce toxicity, may stop PZA after 8 weeks
 - Alternative: switch to BPaL (bedaquiline, pretomanid, & linezolid)

...Rest of the story

- INH, rifampin, ethambutol, pyrazinamide
 - INH dropped after 6 weeks and levofloxacin added
 - PZA stopped after 1st 8 weeks
 - Daily DOT x 6 months (low organism burden)
- Chest x-ray...



X-ray at 9 months...

What Type of TB is this?

- Does this case match your experience with patients who have Active TB?
- Is TB a Binary Disease?
 - Inactive TB (LTBI) [~90%]
 - Active (pulmonary) TB [~10%]
- This case, Subclinical Active TB, highlights:
 - Spectrum of clinical TB
 - LTBI → Subclinical Active TB → Active TB
 - AND with TB screening → Proactive TB Detection...
 - ...In contrast to typical, Reactive TB Detection

Have you heard...

Some people want to ban pre-shredded
cheese. Their slogan?

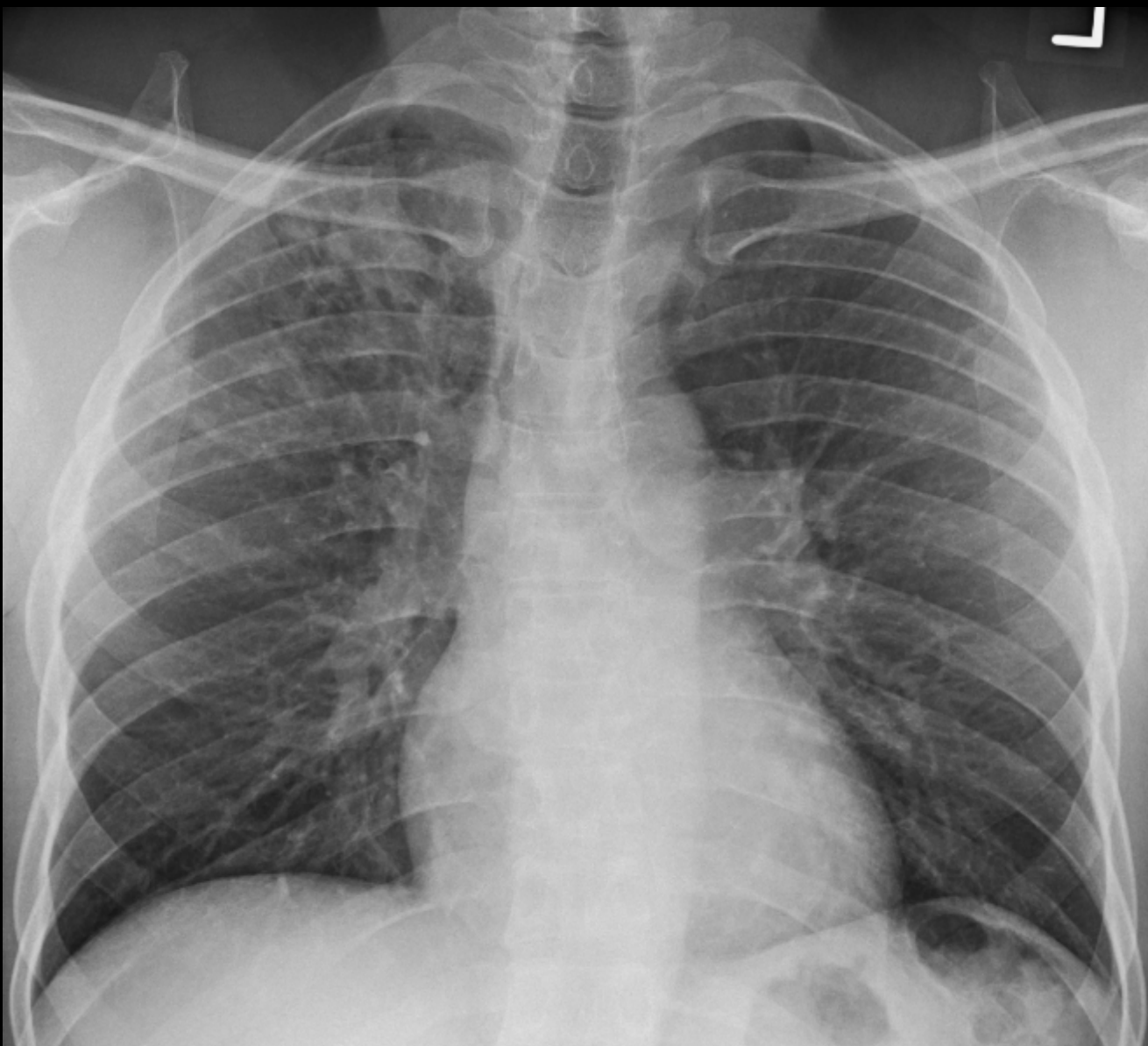
Make America Grate Again!

TB or not TB #2...

45 yo M, R shoulder pain referred to pulmonary clinic
...Primary care LIP heard wheeze R chest
...Chest CT showed RUL change “c/w Histo”

Pulm MD history: No respiratory symptoms ever

- PMH: HTN, GERD, Chronic R shoulder pain
- SH: Non-smoker; Works meat packing plant
From Congo, past 4 years in Iowa
- Exam: Unremarkable
- Lab: WBC 8.1, Histo serology neg, QFT-G 3.2/2.9
- Chest x-ray...



**Sputum induction: “Spit” but submitted anyway(!)
AFB smear 1+, Xpert MTB positive & RIF resistance negative**

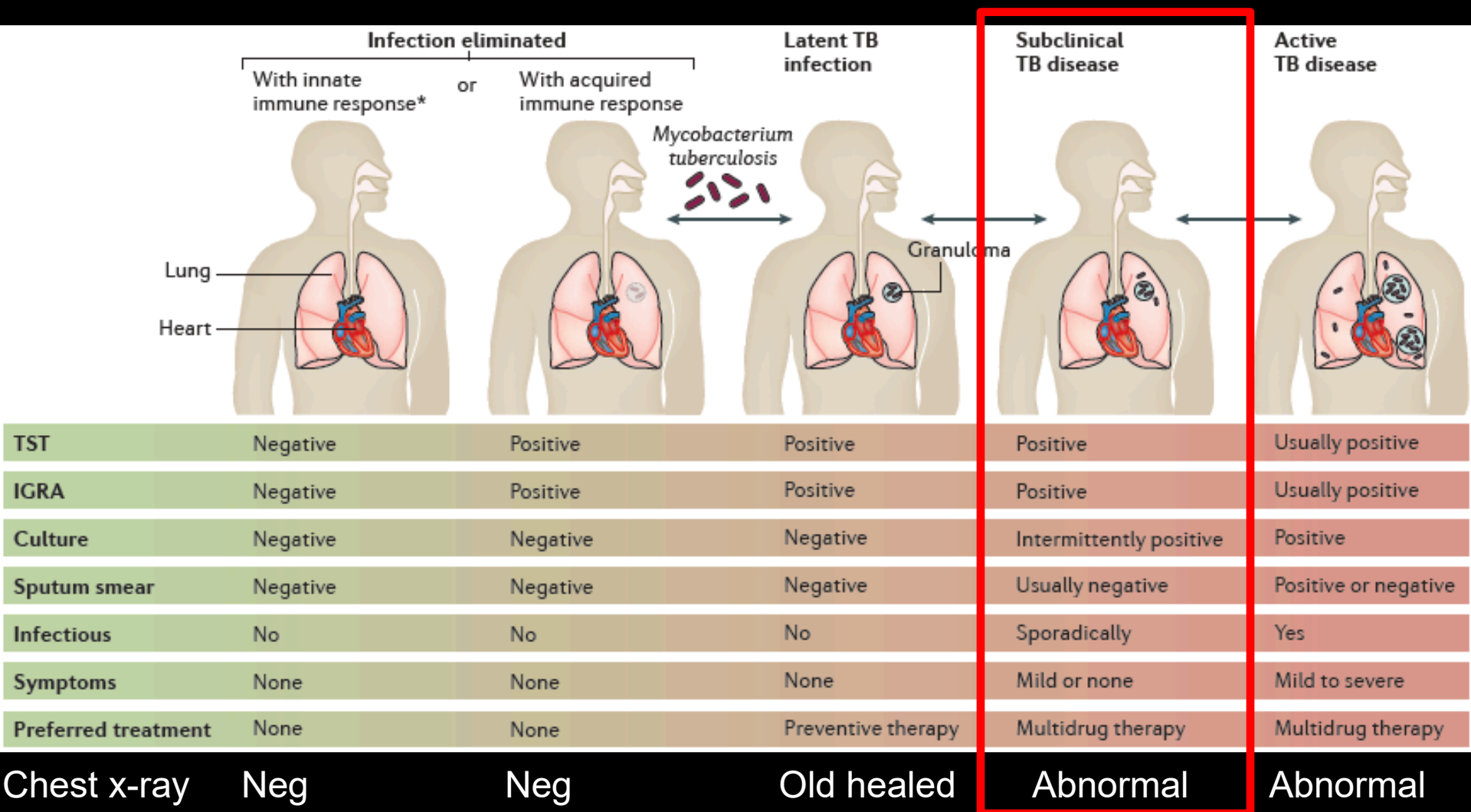
R Shoulder film from 2.5 years previous...



Have You Detected Subclinical TB?

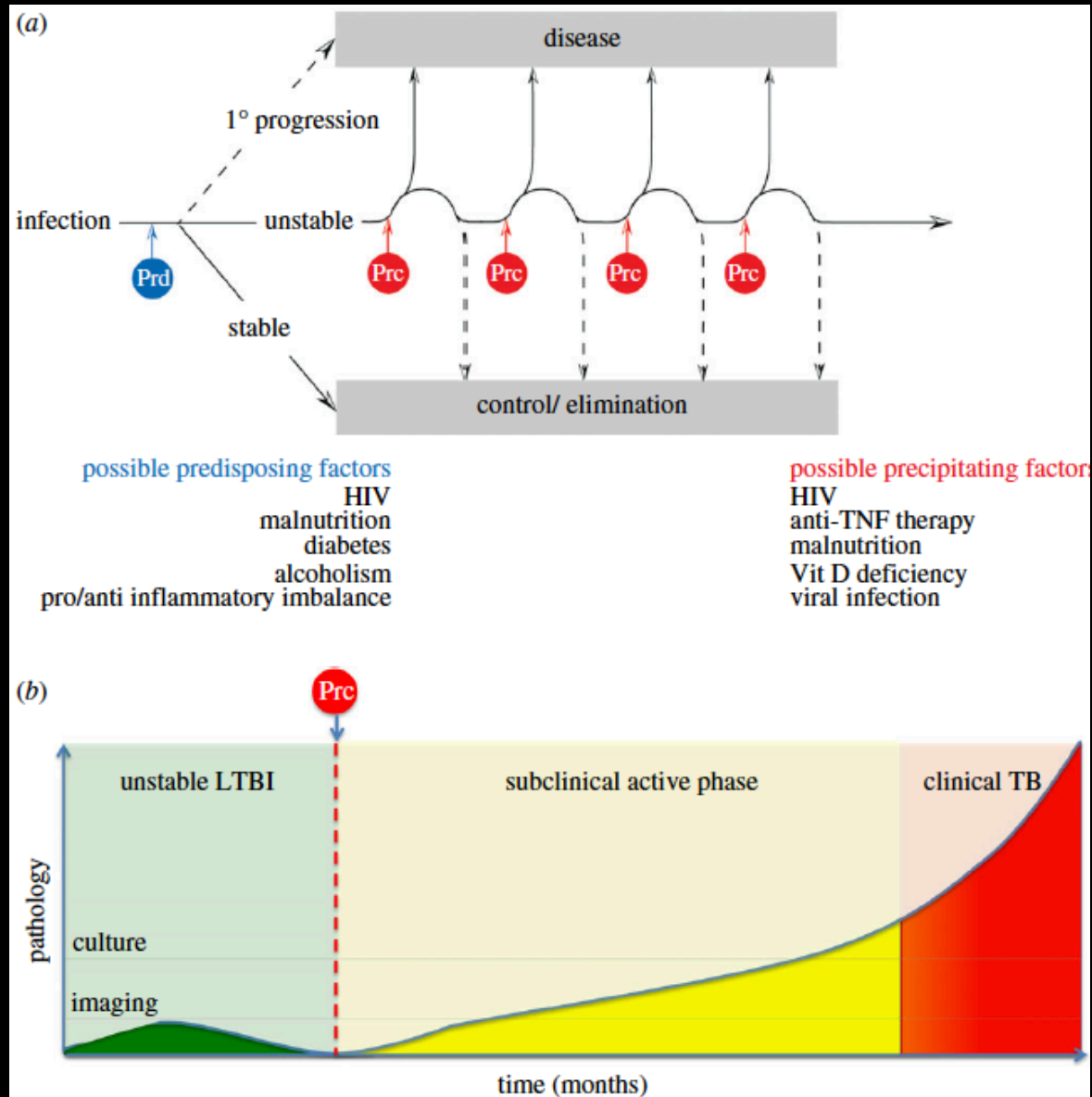
- Screened thousands students from TB Hotspots x20+ years yielding >25 active asymptomatic TB cases
 - Detection: Proactive (screening) r/t usual Reactive (symptomatic)
 - Asymptomatic with subtle, minimal radiographic findings, +/- AFB
 - Real value → Detecting & Treating asymptomatic active TB
- How long can this “in-between” phase persist?
- Generally, TB described as binary presentation:
 - Inactive TB or
 - Active (pulmonary) TB
- Perhaps view TB as dynamic continuum:
LTBI ↔ **Intermediate** ↔ Active (pulmonary) TB
Subclinical (or asymptomatic) Active TB

Dynamic Continuum View of TB...



Progression ↔ Regression

Prolonged Subclinical Active Phase



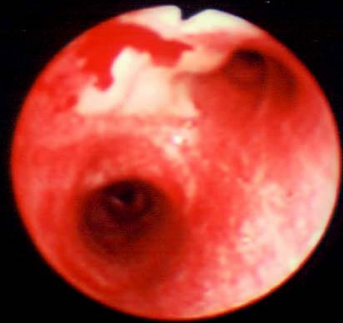
Subclinical Active TB or Asymptomatic Active TB

These patients...

- Report no (minimal) symptoms generally
- Demonstrate immune response to TB...
Positive TST or IGRA
- Sputum results...Smear negative,
Culture positive inconsistent
- Chest x-ray: more subtle abnormalities
Chest CT: may/may not clarify
- Sporadically infectious
- Treat as one would treat active TB:
Multidrug/DOT TB treatment

Screening → Asymptomatic Active TB Detection

- US Student Visa: TB screening not required
- UI performs comprehensive TB screening of newly enrolled foreign-born students (high risk countries)
- Active cases occasionally surface:
 - +TST or IGRA, asymptomatic, BCG, Balky...
 - Subtle, non-cavitary Chest x-ray infiltrate
 - Smear negative, culture positive (AM sputum x3)
 - Bronchoscopy in many but not all
 - Note: Smear negative, culture negative uncommon
 - Often faster response to treatment (small organism burden)
- Successful management: Teamwork
 - Vigilant/Supportive Student Health Service
 - University Administration (\$ for testing, QFT-G)
 - Department of Public Health



R Up
Lok

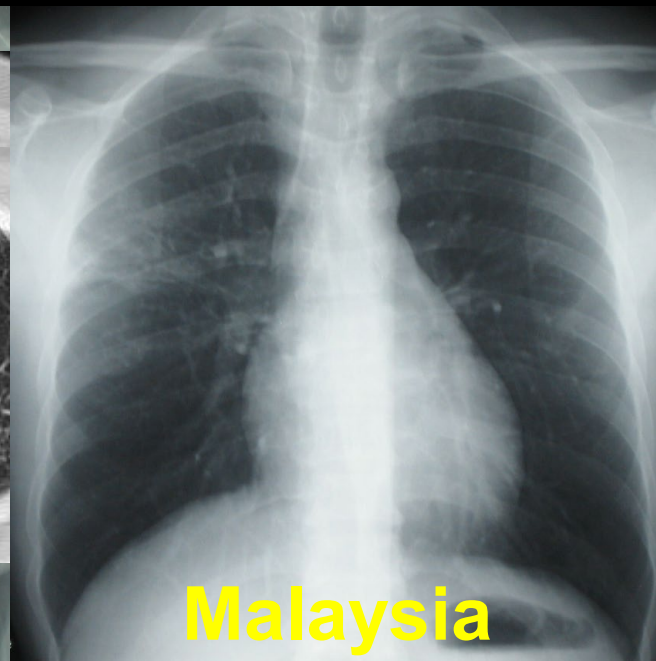
Bronchus Intermedius



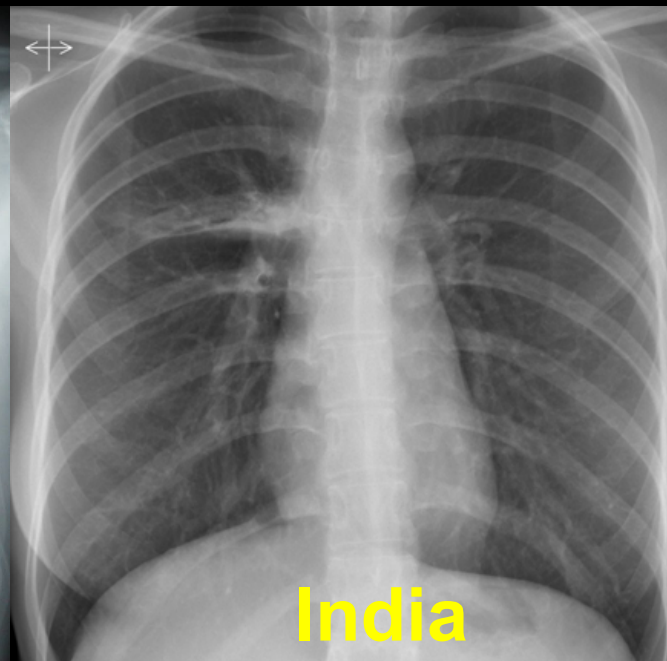
Screening → Asymptomatic Active TB



Argentina



Malaysia



India

Screening → Asymptomatic Active TB Detection (BCG hx), IGRA+, Subtle CXR infiltr., Smear-, Culture±

- US Student Visa: TB screening not required
- Comprehensive TB screening of enrolled foreign-born students
- Active cases occasionally surface:
 - +TST or IGRA, asymptomatic, BCG, Balky...
 - Subtle, non-cavitary chest x-ray infiltrate
 - Smear negative, culture positive (AM sputum x3)
 - Bronchoscopy in many but not all
 - Note: Smear negative, culture negative uncommon
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- **Successful management: Teamwork/Cooperation**
 - Vigilant/Supportive Student Health Service
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**Asymptomatic Active (Subclinical) TB
Detected Proactively through Screening**

Asymptomatic (Subclinical) Active TB

Take Home Points

- Often unrecognized; not detected by symptom-based screening
- Likely common; Estimates 15-50% TB cases
- Potentially persists for months/years...
 - Intermittently contagious (Progression $\leftrightarrow$ Regression)
 - Contributes to challenges for achieving total TB eradication
- Multidrug TB treatment required; LTBI treatment insufficient
- Cases presented also demonstrate:
 - When in doubt...start treatment for active TB
 - Submit “spit” (insist lab process for AFB) whenever suspect active TB
- Questions persist...Ripe for further investigation!

Cases

- TB or not TB
- Through the Retrospectoscope.....
- Bronchiectasis Surprise...
- TB & old guys...

Through the Retrospectoscope

- At a small county hospital ER Doc entered this on chest x-ray request for a 36 yo Mexican man:
“Cough, dyspnea, fever x 15 days”
- Subsequent Radiology report:
“RUL pneumonia with central pneumatocele. This is usually associated with Staph aureus or Haemophilus. Recommend correlation with clinical picture.”



What would should also be considered besides *S aureus* & *Haemophilus*?
Sputum showed 3+ AFB & was NAAT+ for *M tuberculosis* (Rif susceptible)

AS 2
e 5:07:59 PM

26 yo F w Vague Respiratory Symptoms

Sputum showed 3+ AFB...

Take home message:

Look at the CXR (upper lobe infiltrate?)
Consider TB!!!

UIHC Chest X-ray

Two months later...

Cases

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Bronchiectasis Surprise!

85 yo W F non-smoker, productive cough x8 wks;

No chronic meds o/t albuterol as needed

SH: Worked in Foreign Service: Japan, Indonesia, Saudi Arabia (no medical work nor TB exposure)

PMH, FH, ROS unremarkable

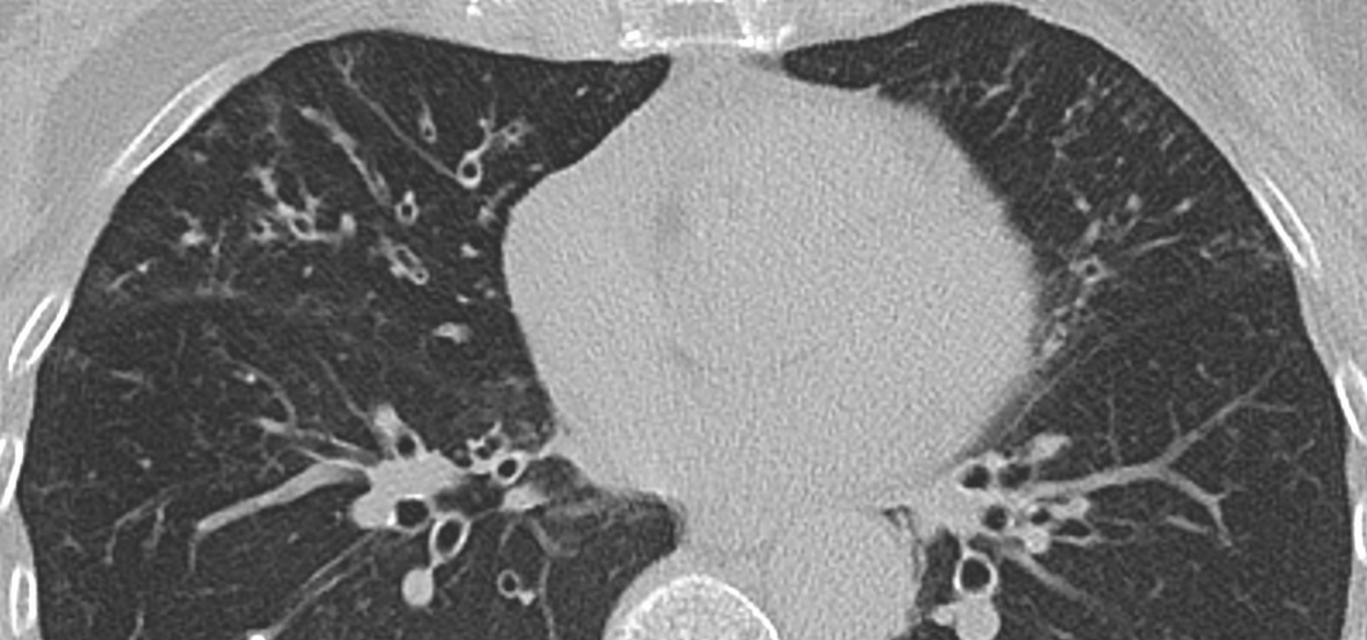
Exam: VSS, lungs w bilateral LL rales/rhonchi

Labs: A1AT normal; IgG, M, A, E normal; No CF gene

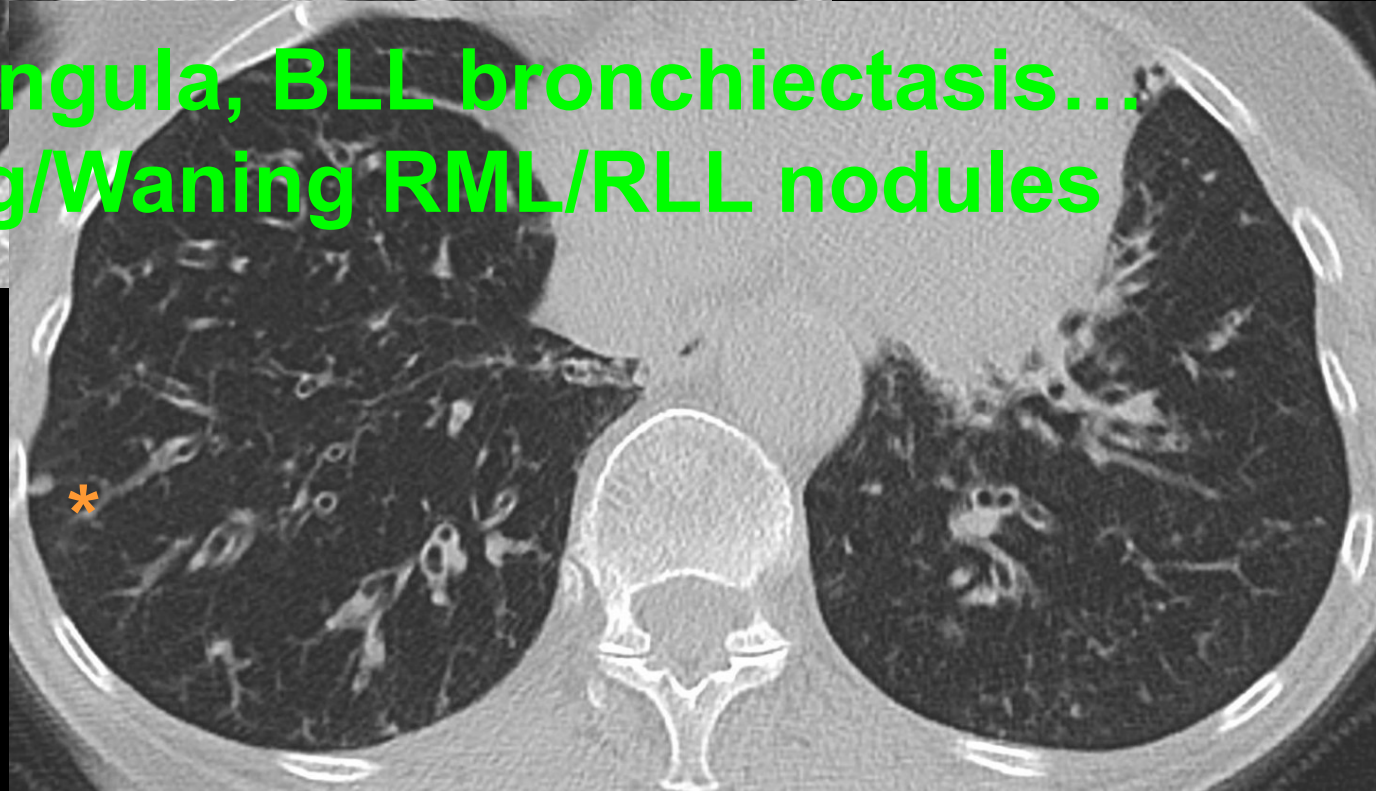
PFTs: Minimal obstruction

CXR: Bilateral LL changes...

Two prior chest CTs following benign nodules...



RML, Lingula, BLL bronchiectasis...
Waxing/Waning RML/RLL nodules



More Data...

Sputum grew mixed flora

(no *S aureus*, *P aeruginosa*)

AFB smear x3 negative, cultures pending

3 weeks amox/clav & ↑ airway clearance effort...

Reports cough less intrusive

Overall much improved at 4 week follow-up

6 weeks TB lab calls (1 of 3 AFB specimen):

M tuberculosis, susceptibilities pending

What would you do now?

- Communicate with Public Health Dept (PHD)
- Immediately start INH, RIF, PZA, ETB by DOT
- Establish in-home Airborne Infection Isolation
- Collect additional sputa AFB smear/culture (3)
- **Results:**
 - Pt adheres well to recommendations
 - Public Health nurse starts patient on DOT
 - Additional sputum AFB smear negative x3

Bronchiectasis & TB...Instead of NTM?

It happens, very rarely

Additional data: QFT-G x 5 negative -- Including
at completion of Foreign Service

Seems that active TB not likely...

**How do you make sure that she
does/does not have active TB?**

Solution...Lab Cross-Contamination

- Whole Genome Sequencing (WGS)...
This TB isolate matched that of another active case being worked up at the same lab, at the same time
- False positive → Stopped TB treatment (~8 weeks)
- Meta-analysis lab cross-contamination:
 - > 30 case series included
 - 2% of all positive TB cultures
 - 15% when only 1 culture positive out of several submitted
 - Leads to unnecessary patient hardship, potentially harmful adverse effects from treatment
 - Strict in-lab technical standards must be maintained...

Back story: Lead lab tech (also worked this case) insisted cross-contamination could not occur in their lab. Initially refused WGS... PHD backed me up, helped with cost, lab relented [Must Persist!]

More Mycobacteria—Bronchiectasis Overlap

66 yo F non-English speaking with chronic productive cough for “long time”

Denies dyspnea, hemoptysis, F/C/S, weight loss

PMH: DM II, Hypertension

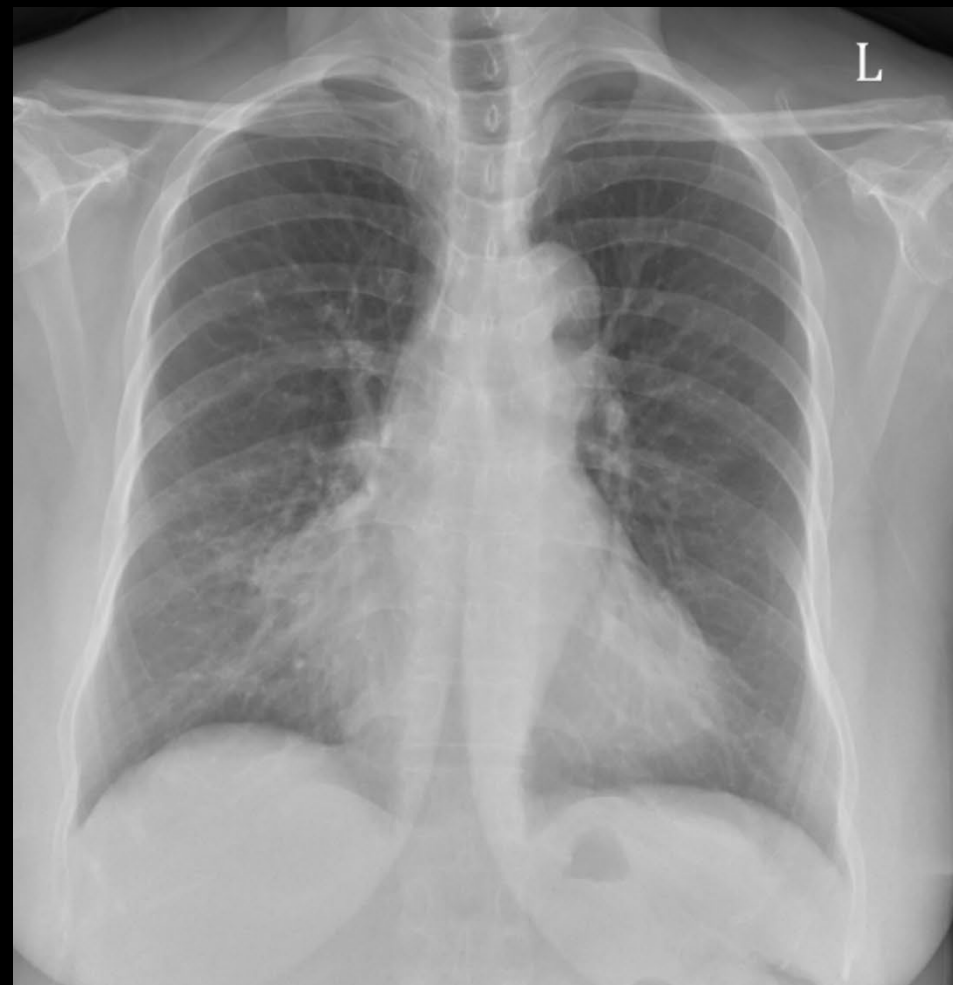
SH: Nonsmoker, No EtOH, - HIV risk factors;
From Marshall Islands 3 months ago

FH: No one with TB ever

Exam: clear lungs, extensive hypopigmented plaques bilateral feet/ankles (Leprosy?)

Lab: Positive QFT-G & abnormal Chest X-ray

What now...



Sputum for AFB x 3 smear negative; cultures negative so far x 2.5 weeks

Mayo TB consultant suggest bronchoscopy. Must r/o active TB

Chest CT ordered instead...

Outside Chest CT...

Tree-in-bud

Seems more consistent w/ RML
nodular bronchiectasis...

Sputum sent for AFB

What about QFT-G result?

TB1 0.51

TB2 0.43

NTM 0.14

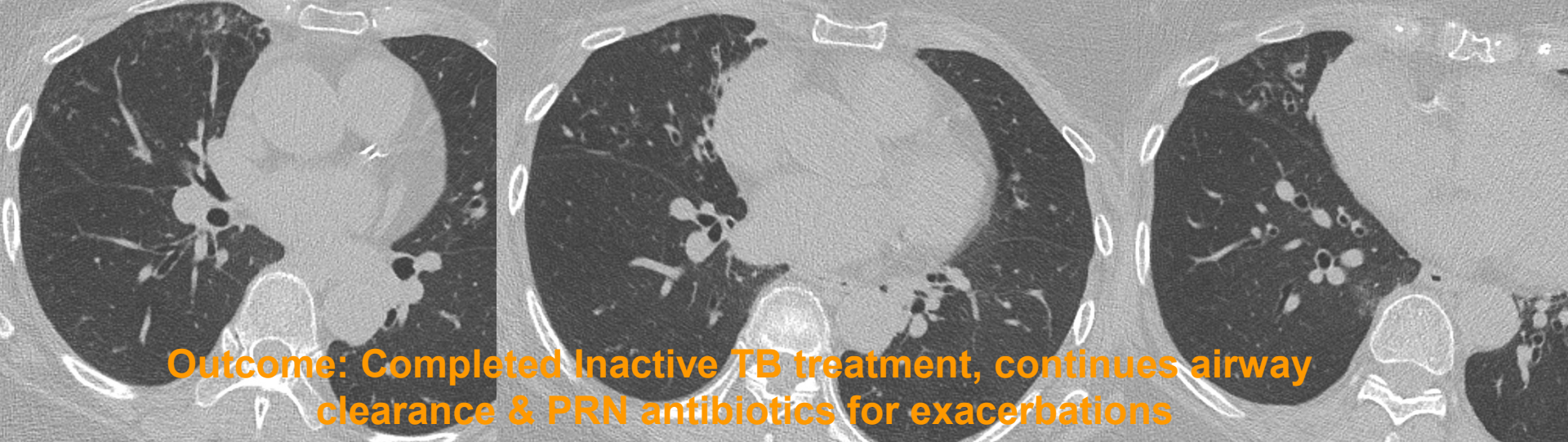
Not TB nor NTM!

RML Bronchiectasis Exacerbation

TM.
ITM?

Received 3 weeks doxycycline & Airway Clearance → Cough less productive, persists.

Chest CT 3 months later at first UIHC visit:



Outcome: Completed Inactive TB treatment, continues airway clearance & PRN antibiotics for exacerbations

Tree-in-Bud Lesion

Appreciated on high resolution chest CT:

- A/w NTM or TB infection—not pathognomonic
- Lung inflammation usually a/w bronchiectasis
- Large and small (<5 mm) nodules (centrilobular)



Clever Scientists...

Have weighed rainbows and found that
they are...

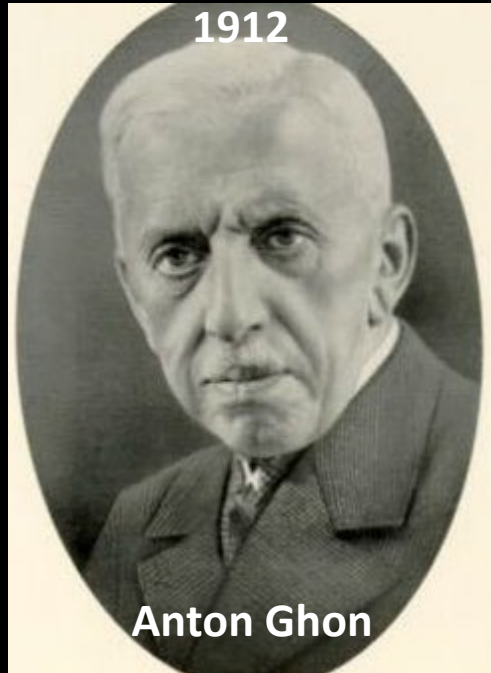
P**R****E****T****T****Y** **L****I****G****H****T**

Cases

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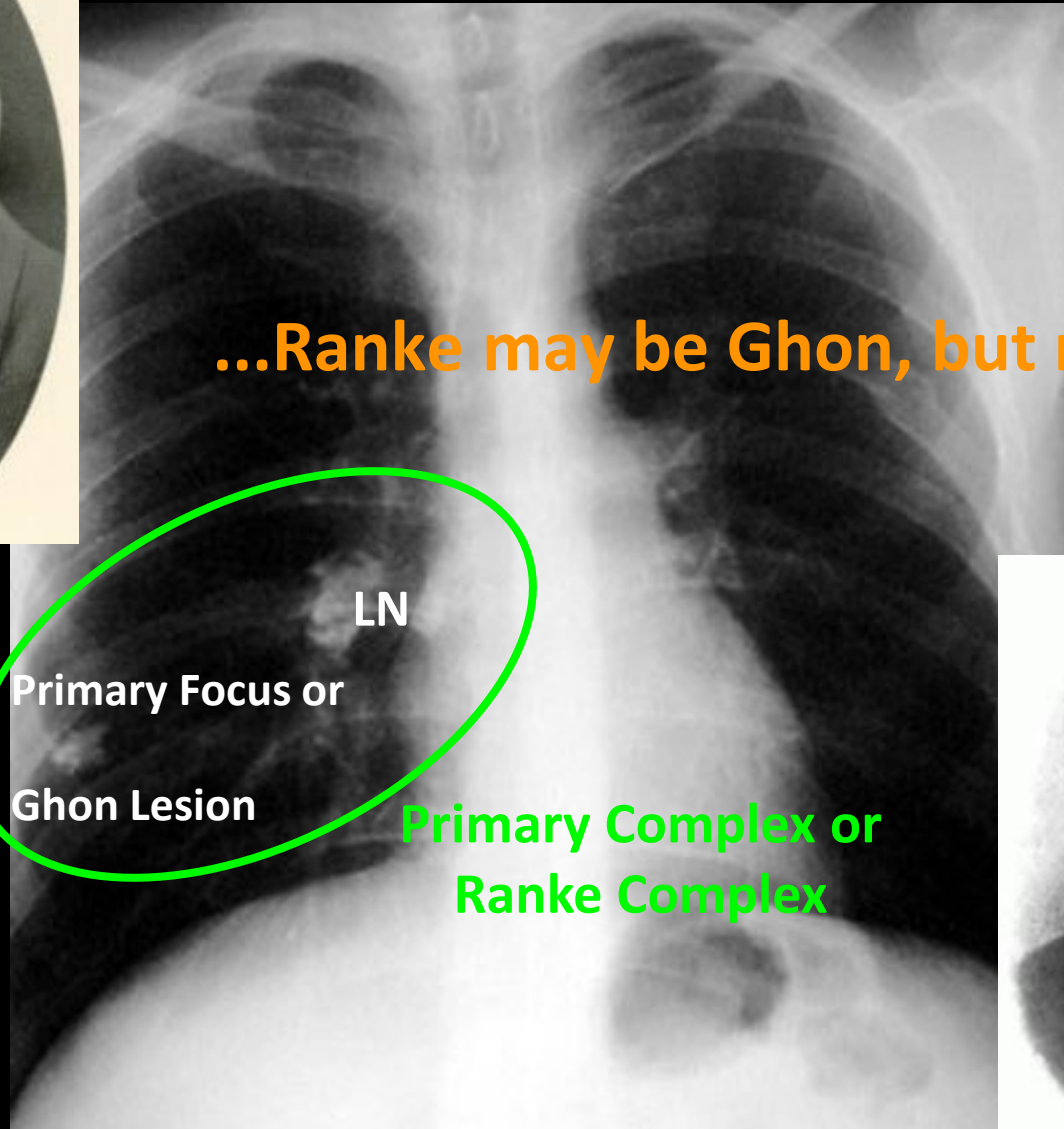
What's This?

1912

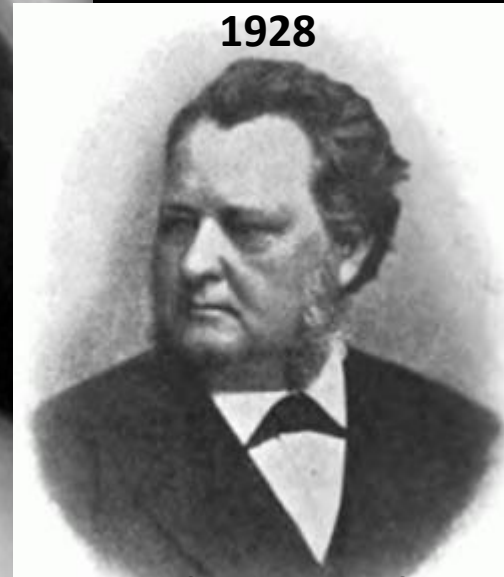


Anton Ghon

...Ranke may be Ghon, but not forgotten



1928



Karl Ernst Ranke

Cases

- TB or not TB
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- Bronchiectasis Surprise...
- TB & old guys...

Okay, just one more...

What's This...?

20 yo Chinese M w/ 20 d h/o fever (HIV+)

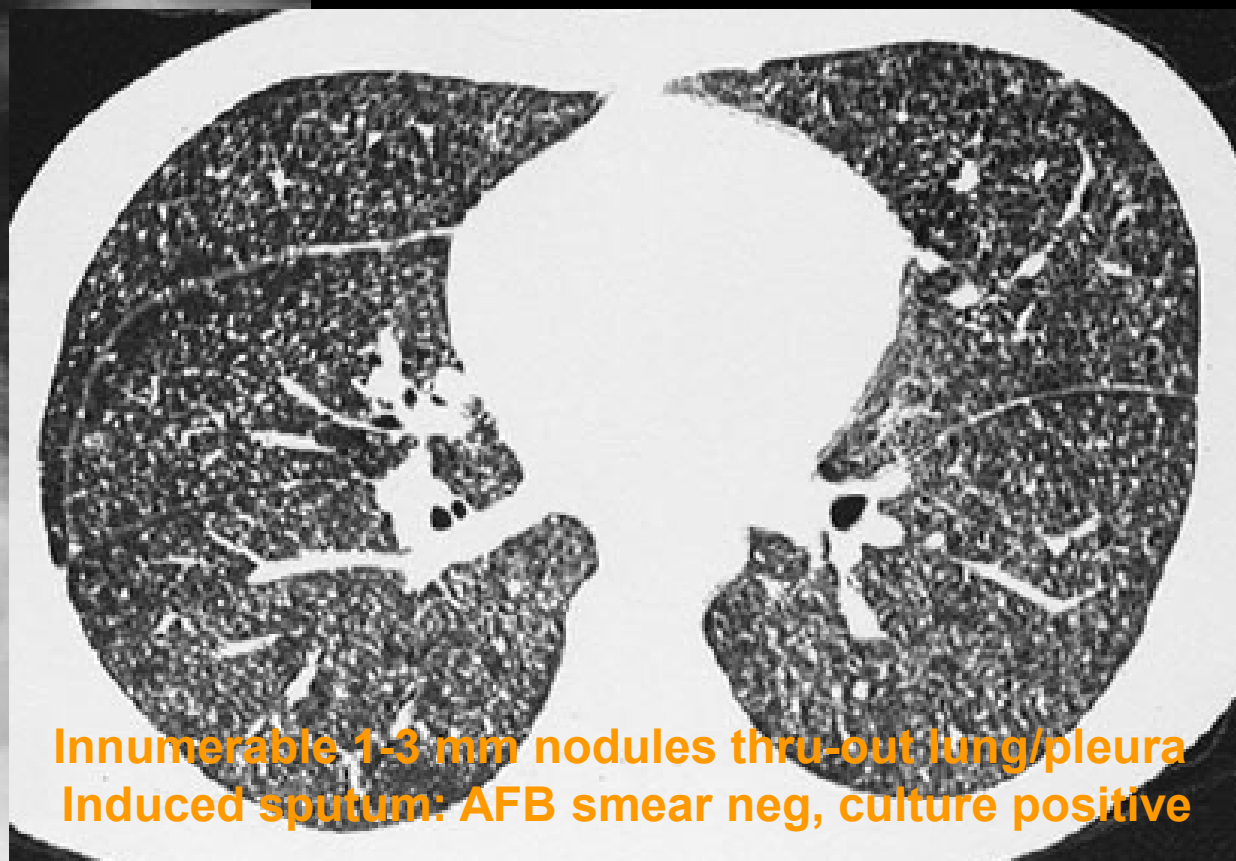
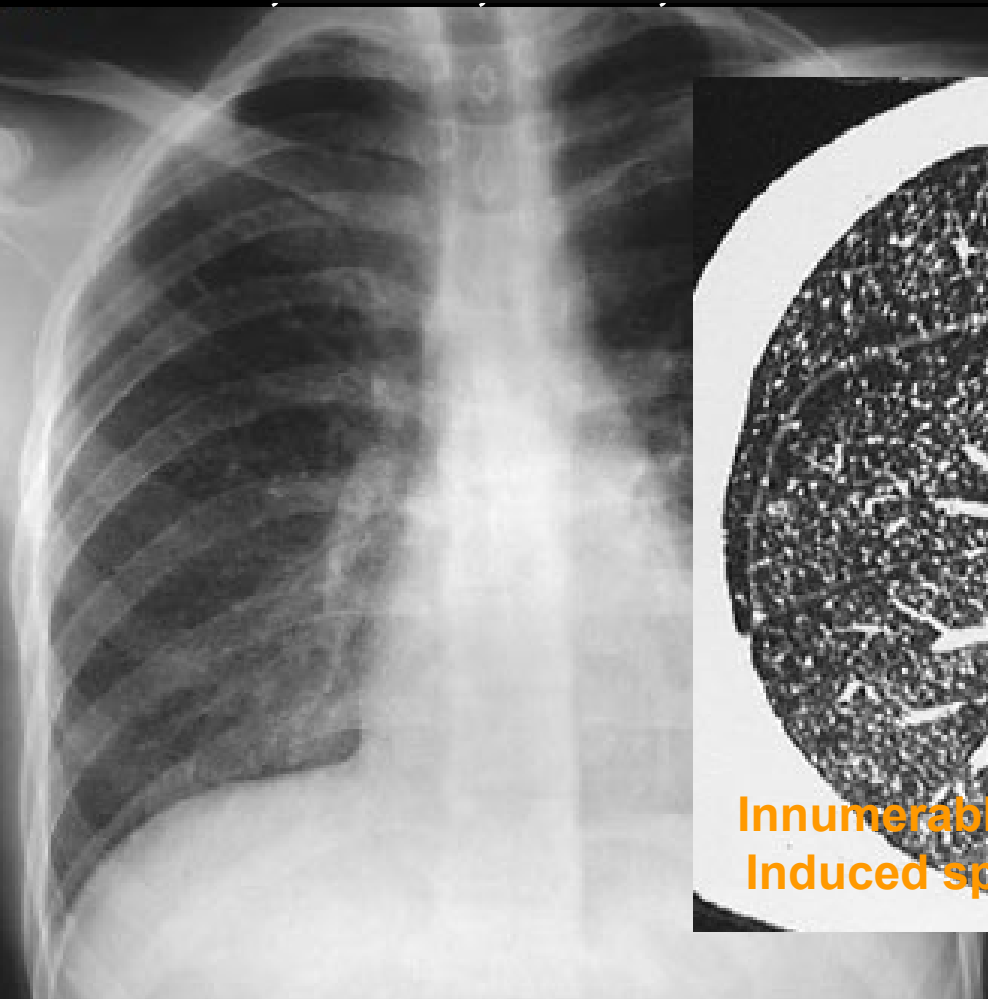
"Normal" CXR

Fever persists

More SOB

Miliary TB

Chest CT:



Innumerable 1-3 mm nodules thru-out lung/pleura
Induced sputum: AFB smear neg, culture positive

I know how it will all end for me...

**One of my kids will unplug my
life support
to charge their phone...**

Be Happy...



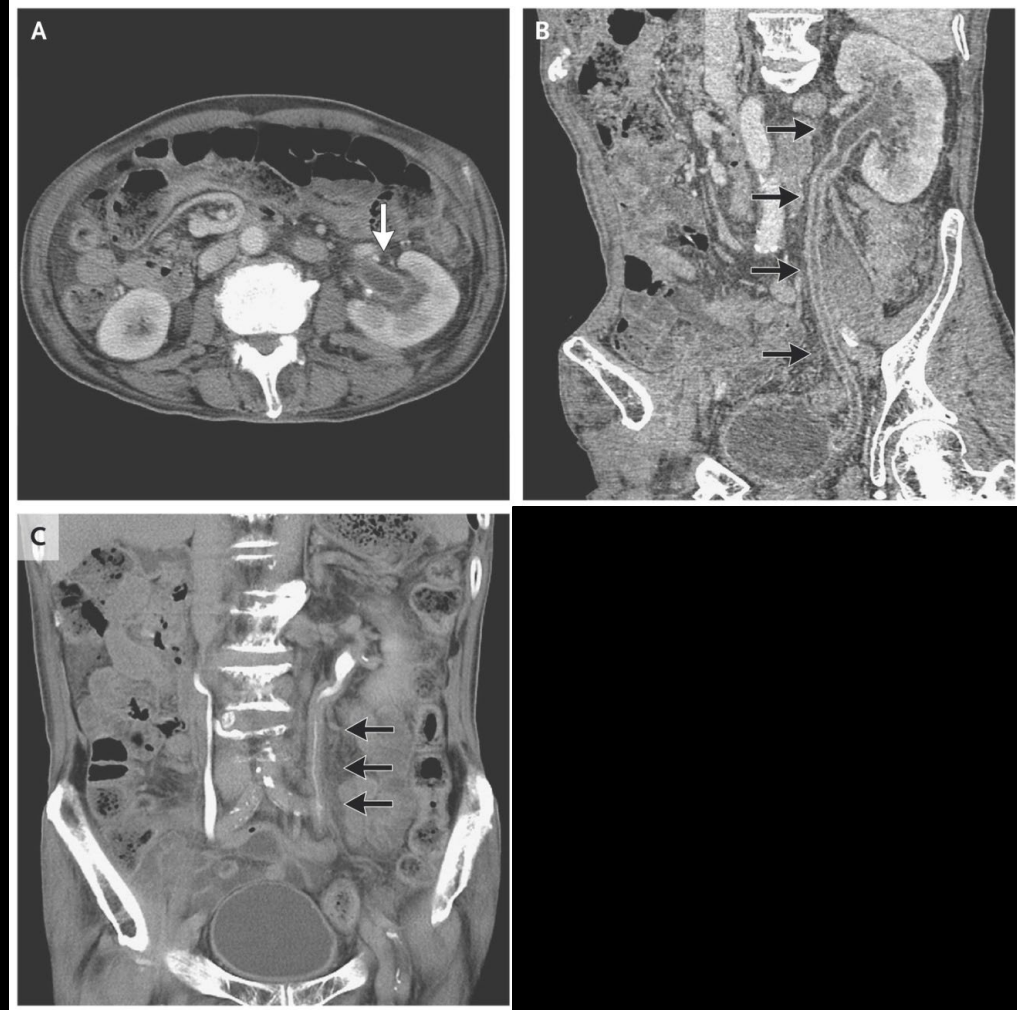
The End!

Plumbing Difficulties...

76 yo male, fever/fatigue
PMH: DM II
CXR: Med Adenopathy x2 yrs
Lab: hematuria, pyuria (culture neg)
Abd CT: Dilated L renal pelvis
Narrow/thick L ureter wall

Abx Rx -> Fever, pyuria persist

Urinary AFB pos, PCR -> TB
HRZE: resolved all symptoms



Urinary TB -> Sterile pyuria

Complications: Ureteral stricture, oligospermia, vaginal bleed

Can You See TB?

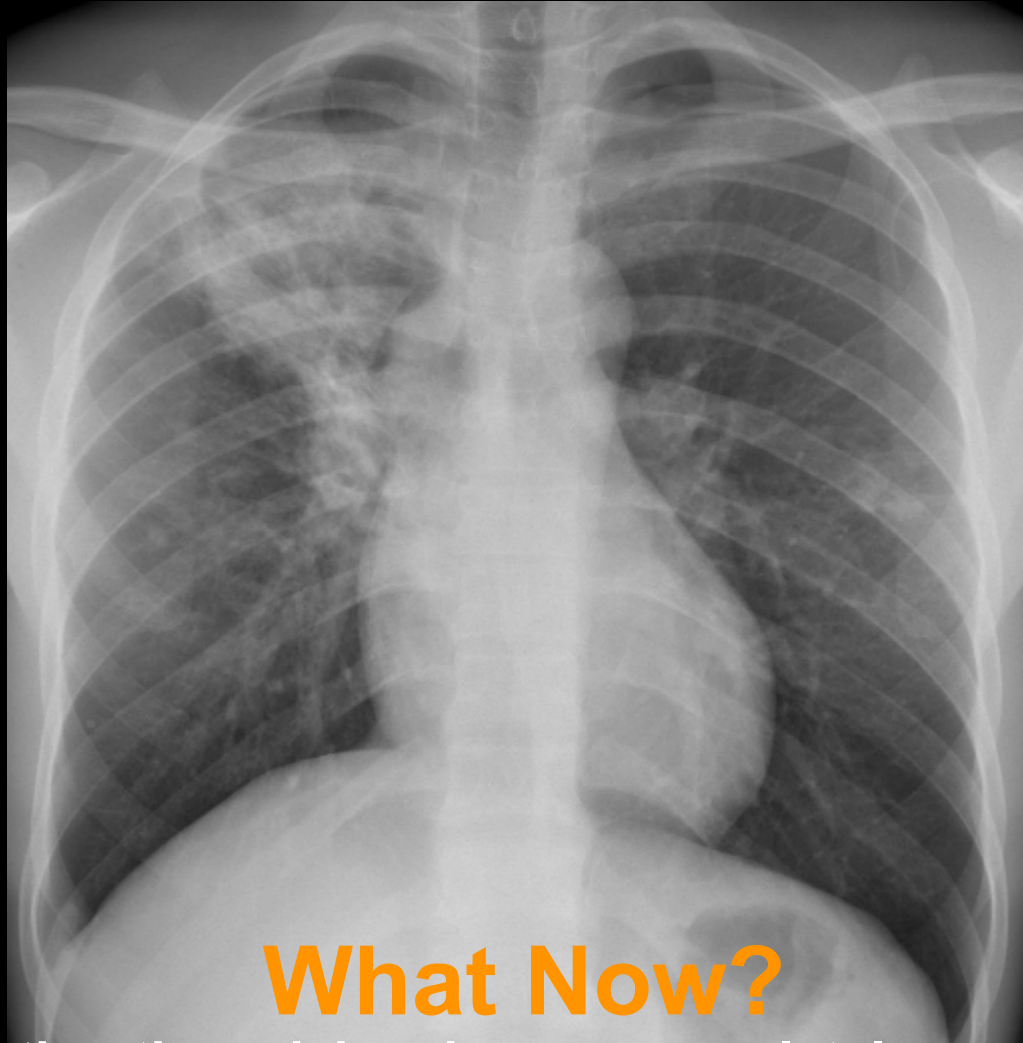
28 yo M w painless vision loss x2 weeks

Ophthalmology: Posterior uveitis OD > OS

Suspect infectious etiology (ie, TB)

- PMH: None
- SH: Ugandan working on IA farm for 6 mos
Agricultural exchange student Visa x 1yr
Denied prior TB or exposure
- Lab: QFT-G 6.2; Negative: HIV, Syphilis
- Radiograph...

This CXR Got People's Attention...



What Now?

Recall other than vision, he was completely asymptomatic

Sputa x 8 (one induced) over 12 days were AFB smear negative

1 of 3 Xpert: TB and *rpoB* mutation positive

CDC reported insufficient DNA for Molecular Detection Drug Resistance

Next Steps

- CDC asked: Delta Ct for the positive Xpert?
- Based on the answer, suggest RIF resistance false pos.
- How would you proceed now...
 - Initiate HRZE?
 - Initiate treatment for MDRTB?
 - Wait longer, bronchoscopy, other ideas?
- MDRTB Rx started
- Lab reported sl. growth in 1st samples (AFB +)
- 2 weeks later adequate growth, MDDR no mutations
- Treatment reverted to HRZE

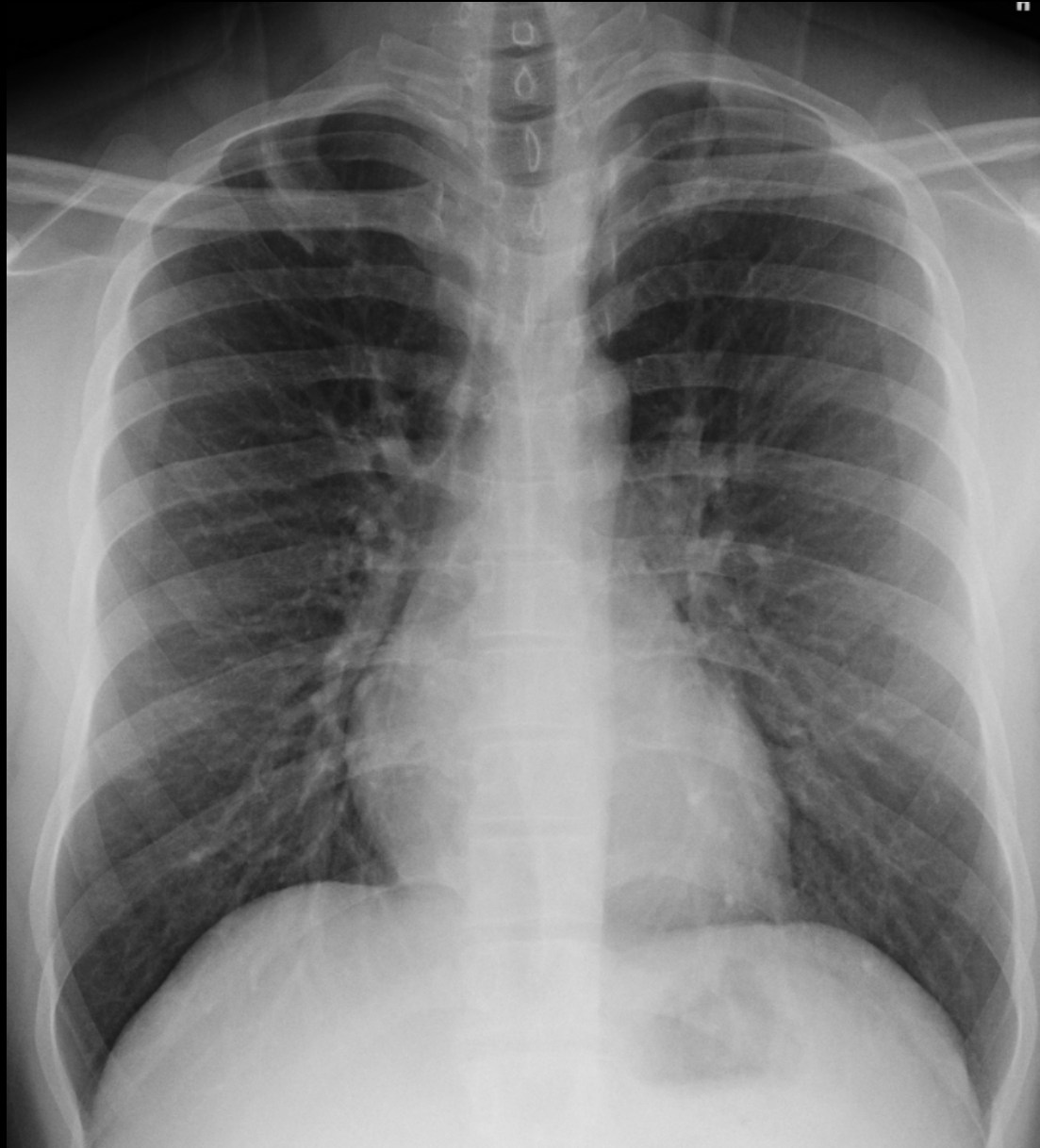
Delta Ct...?

- Gene Xpert by a non-expert...
 - Ct = Cycle Threshold
 - # PCR cycles to amplify MTB DNA to detectable level
 - DNA load low, PCR cycle # higher (eg, Hi Ct<16, Vy Low >28)
 - Overlapping PCR probes (A-E) target 81 bp Rifampin Resistance Determining Region (RRDR) of *rpoB* gene
 - No mutation: Ct matching for all 5 probes
 - Ct difference hi & low probes >4 identifies mutation
- False RIF resistant when bacterial load low (smear neg)
 - Ct may vary (ie, D & E prone to hi Ct vs B & C $\Rightarrow$ Delta Ct >4)
 - In this case: Delta Ct 4.4 (35.0-30.6)
 - Also occurs in HIV, pediatric, extra-pulmonary samples
- Xpert Ultra (more sensitive & specific)...Low TB load?

TB or not TB #3...

19 yo student from Indonesia. Healthy,
asymptomatic, denies HIV risk factors
PMHx negative; No medications
FH: Brother had active TB 2 years ago
Student Health screen: TST+, IGRA+
Chest x-ray...

Radiologist Report: Scarring RUL...Rule out TB



What now?

Chest CT?

#J209797120090708

ME

Apical Lordotic view provides further confirmation

Repeat CXR 5 days later after requesting re-do with shirt & neck ornamentation removed

...Not Active TB

- Inactive TB Infection treated
- Abnormal X-ray report suggests TB?
...Review film yourself (or with trusted clinician)
- Don't rush to Chest CT in *uncertain* TB cases
...Consider *Apical Lordotic* option
 - Demonstrates Posterior/Apical Lung Segments
 - Easily Done, Less Radiation, Less Costly
- TB/Chest CT Rule: Chest CT adds to w/u of active TB
...Most useful for smear negative TB work-up
(If Apical Lordotic view fails to clarify TB diagnosis)