Case 1 and Case 2

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Case 1

27 yo Indian woman came to the US to join her husband three months prior to clinic visit. She initially saw an ob/gyn for an infertility workup and was found to have mild hypothyroidism and a 2 cm X 3 cm lymph node was palpated in the right neck. Pt referred for a lymph node biopsy which showed necrotic debris on path, and a positive AFB smear.

Case 1

On evaluation in TB clinic, pt denied cough, fever or night sweats. Denied previous history of TB, but reported lymph node enlargement after an episode of typhoid fever a year before. Reports taking daily meds for the lymph node enlargements for one year, with serial monitoring by CT. During treatment pt gained about 4kg and noted neck nodes enlarged while on treatment.

Case 1

PMH/PSH unremarkable

PE: Well-appearing young woman with multiple enlarged, firm anterior cervical nodes bilaterally; PE otherwise negative

CXR normal

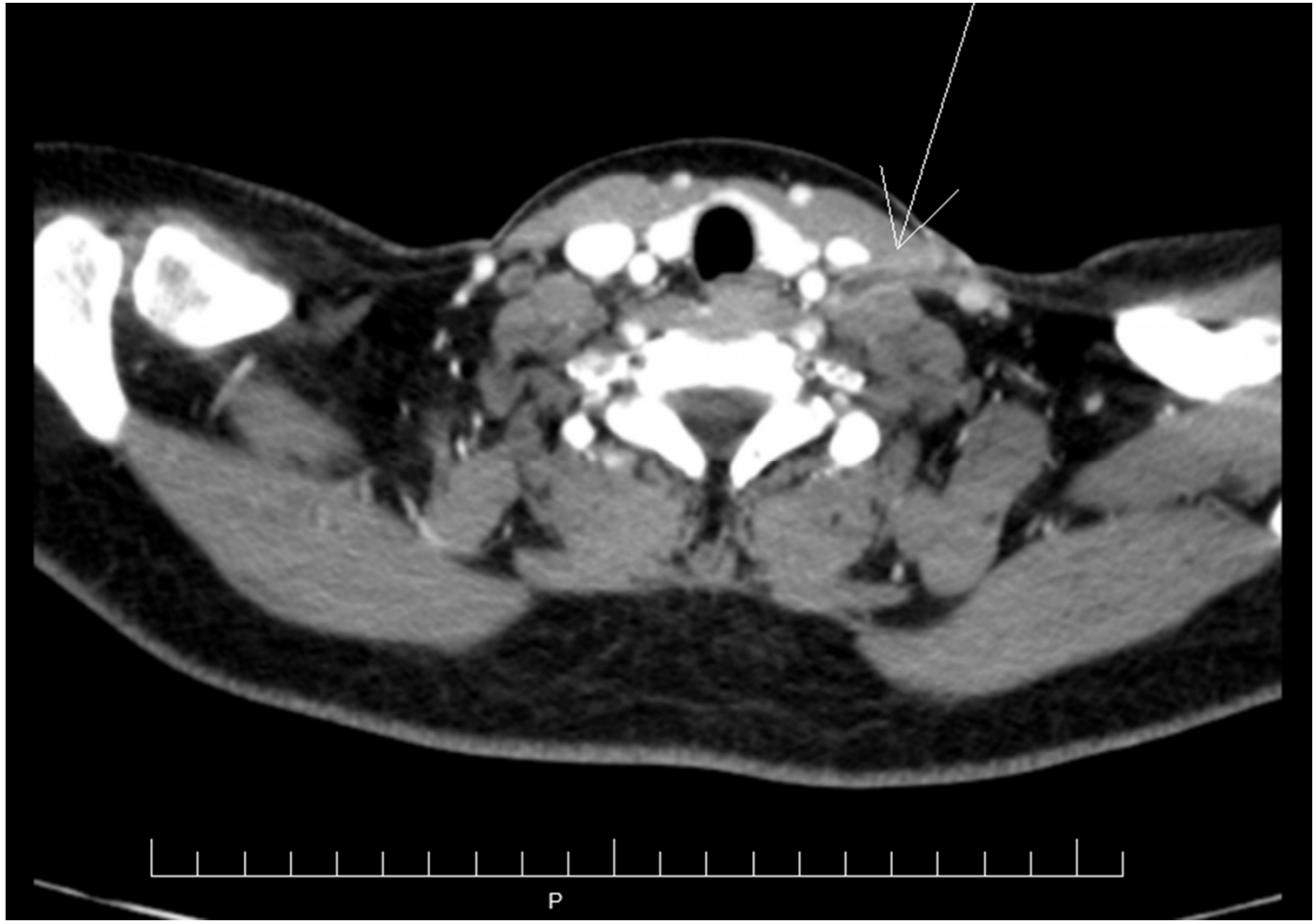
A Google search of the names of the medications she took for a year reveal them to be Isoniazid, Rifampin and Ethambutol

Question 1

What are the factors concerning for multidrug-resistant TB in this patient?

A. Birth outside of the US
B. Prior treatment with TB medications
C. Self-administration of TB medications without DOT
D. All of the above

Case 1: CT imaging



Case 1

Chest CT negative for intrathoracic lymphademopathy or lung parenchymal abnormalities

Induced sputums AFB smear negative X 3

HIV negative

CBC with slightly low Hgb, normal CMP, slightly elevated TSH with normal free T4

Pt started on RIF 600, INH 300, PZA 1500, EMB 1200 and vit B6 50

Case 1

After nearly six weeks, M. tb cultures grew from both the lymph node and the initial induced sputum.

Resistant to RIF, INH, PZA, EMB and Streptomycin

TB meds held and samples sent for MDDR

Case 1

In addition to mutations for the first line drugs, a gyrA mutation encoding quinolone resistance was detected. No mutations associated with the injectables were detected.

Question 2

How would you most accurately describe this patient's disease?

A. Polydrug-resistant TB
B. Multidrug-resistant TB (MDR-TB)
C. Pre-extensively drug-resistant TB (Pre-XDR-TB)
D. Extensively drug-resistant TB (XDR-TB)

Case 1: PreXDR

DEFINITIONS

- Multidrug-resistant (MDR) refers to TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* that is **resistant to at least isoniazid (INH) and rifampin (RIF).**

- Pre-extensively drug-resistant (Pre-XDR) refers to MDR-TB that is **also resistant to *either* a fluoroquinolone *or* a second-line injectable anti-TB drug (kanamycin, capreomycin, or amikacin), but not both.**

- Extensively drug-resistant (XDR) refers to MDR-TB that is **also resistant to *both* a fluoroquinolone and a second-line injectable anti-TB drug.**

Case 1: Pre-XDR

What are our treatment options?

RIF, INH, PZA, EMB, Streptomycin
Moxifloxacin
Kanamycin/Capreomycin/Amikacin
Ethionamide
Para-aminosalicylate (PAS)
Cycloserine
Linezolid
Clofazimine
Carbapenems
Amox/Clav, Clarithromycin
Bedaquiline

Question 3

Which of these TB medicines prolong the QT interval?

A. Moxifloxacin
B. Linezolid
C. Clofazimine
D. Bedaquilline
E. A, C and D
F. All of the above

QT Prolongation

Bedaquiline, Moxifloxacin and Clofazamine all are known to prolong the QT interval, which increases the risk of *torsade de pointes*.

EKG monitoring recommended if treating with bedaquiline plus another drug that prolongs QT

No consensus guidelines on the concomittant use of bedaquiline along with moxifloxacin and/or clofazimine

Case 1: Pre-XDR

Pt hospitalized for PICC placement and initiated on DR-TB medication regimen:

- Amikacin 550mg IV qd
- Bedaquilline 400mg po qd
- Cycloserine 250mg po bid
- Para-aminosalicylate 4g po bid
- Clofazimine 200mg po qd
- Vit B6 100mg po qd

Clofazimine tx in DR-TB

- Originally developed for TB treatment in 1954; discarded in favor of better TB drugs
- Currently indicated for treating leprosy
- Mechanism of action unclear
- Is a component of the Bangledesh regimen
  - A 9-month regimen shown to be effective in MDR-TB treatment using 4 months of kanamycin, prothionamide and INH and 9 months of a quinolone, clofazimine and PZA

Clofazimine tx in DR-TB

Main side effect: skin discoloration

Requires investigational new drug (IND) application to FDA for use outside of leprosy

Case 1: Pre-XDR

Final phenotypic susceptibilites confirmed resistance to first line agents and quinolones.

Sensitive to Kanamycin, Amikacin, Capreomycin Ethionamide, PAS, Linezolid, Clofazimine

No further sputum cultures grew after initial culture.

Case 1: Pre-XDR

Pt tolerated regimen well, with minor, tolerable side effects, including moderate even skin darkening and initial lymph node swelling and drainage.

QTc 384 (baseline) --> 462 (peak)

After the 6-month intensive phase, IV amikacin and bedaquiline were discontinued. Low dose linezolid (300mg qd) was added to her continuation phase regimen of PAS, cycloserine and clofazimine.

Case 1: Pre-XDR

After one year on TB meds, pt came in to clinic for a sick visit reporting intermittent abdominal cramps X 10 days. Pt noted clumps of blood when she urinates. No dysuria, normal BMs. LMP was 3 weeks prior.

Exam was negative for abdominal tenderness, organomegaly or CVA tenderness.

Urine pregnancy test negative, UA trace blood

Question 4

What would be your next step?

A. Hold all meds
B. Hold clofazimine
C. Hold linezolid
D. Hold cycloserine
E. Hold PAS
F. None of the above

Case 1: Pre-XDR

Holding clofazimine for two weeks did not improve symptoms.

CT abdomen to check for nephrolithiasis revealed no evidence of stones, hydronephrosis or hydroureter. Fat containing masses, likely dermoids, seen in adnexa bilaterally.

Upon consultation with SNTC, etiology determined to be hormonal disruption due to PAS.

Case 1: Pre-XDR

Followed up with GYN and started OCPs with resolution of symptoms.

Pt completed 18 months of therapy with resolution of palpable lymphadenopathy.

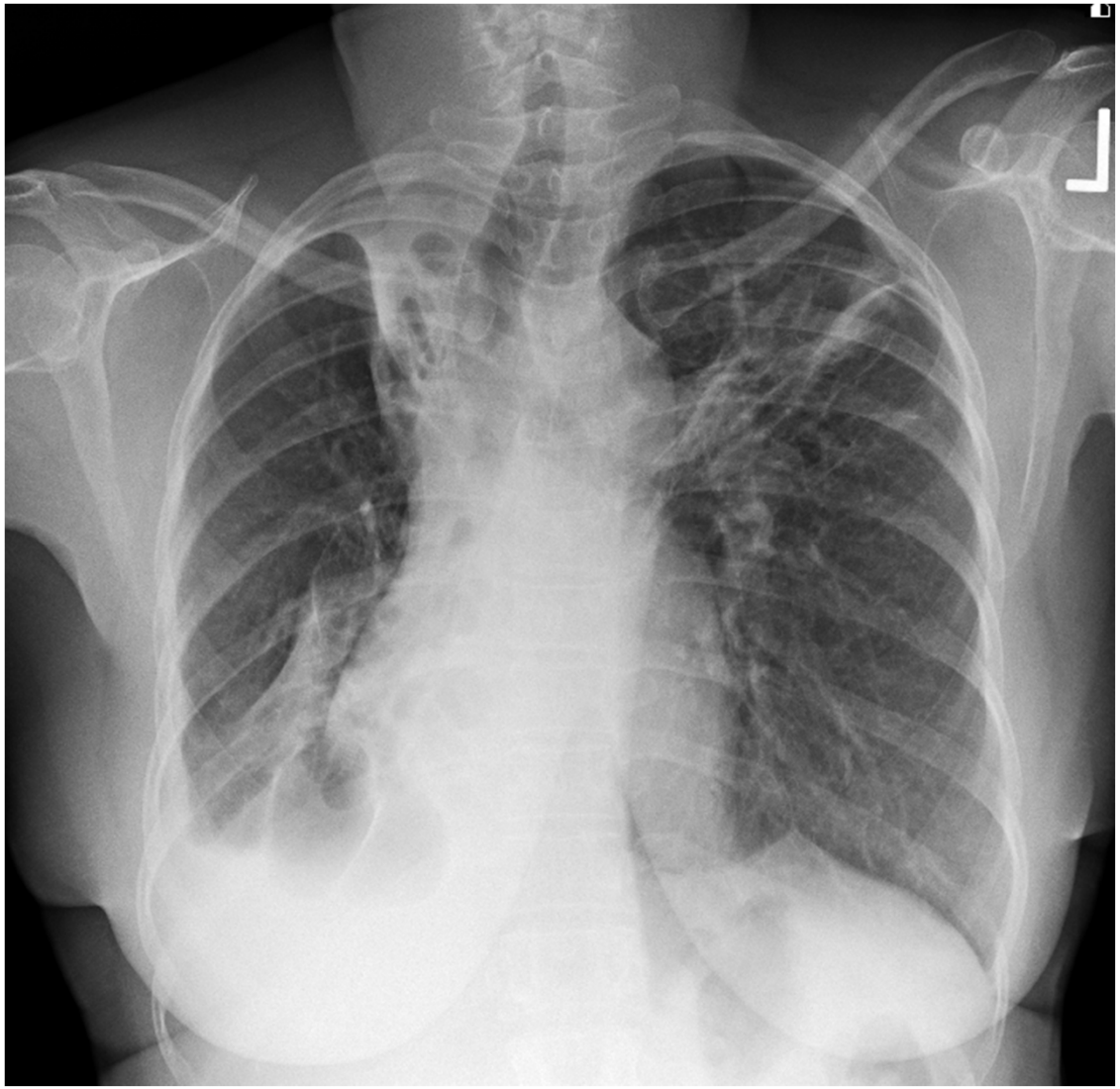
Will follow up q6 months for two years to evaluate for relapse.

Case 2

47 yo Nigerian woman came to Nashville to visit family. Within two days, was seen in a clinic for hearing issues, and endorsed wet cough for ‘a couple of weeks’ with inability to bring up sputum. Also reported night sweats, fatigue and weight loss of an unknown amount. Was treated with Z-pack and told to go to the TB clinic.

Chest X-ray obtained.

Case 2



Case 2

Upon further questioning, the patient admitted to having been treated for TB on two occasions: in 2011 for eight months and in late 2014 for one month, after which she developed hearing loss and discontinued treatment.

PMH: DM2

PE: Thin woman, NAD, no palpable LAD, decreased BS in R base

Sputums and labs obtained

Question 5

How would you proceed?

A. Start standard 4-drug regimen (RIF, INH, PZA and EMB)
B. Start standard 4-drug regimen plus injectable
C. Start standard 4-drug regimen plus injectable and moxifloxacin
D. Wait to start meds until results of genotypic resistance testing obtained

Case 2

Induced sputum: AFB smear POS (10+)

GeneXpert:

- M.tb DNA **Detected**
- rpoB mutation **Detected**

HIV negative

Normal CBC; creatinine 1.52 (eGFR 47); Hep panel Neg; Normal LFTs, Normal TSH, Hgb A1c 7.8

Case 2

Results for Molecular Detection of Drug Resistance (Sanger Sequencing, complete panel); Conventional Drug Susceptibility Test in progress.

Locus (region) examined*	Result	Interpretation (based on in-house evaluation of 550 clinical isolates)
rpoB (RRDR)	**Mutation:** GAC>GTC; Asp516Val	Rifampin resistant. (100% of isolates in our in-house evaluation of 550 clinical isolates with this mutation are RMP-R.)
inhA (promoter)	No mutation	Cannot rule out INH resistance. (89% of INH-R isolates in our in-house evaluation of 254 clinical isolates have a mutation at one or both of these loci.)
katG (ser315 codon)	No mutation	
embB (Met306,Gly406)	**Mutation:** TTC>TGC; Phe398Cys	Effect of this mutation on ethambutol resistance is unknown. Cannot rule out ethambutol resistance.
pncA (promoter, coding region)	**Mutation:** nt399 'T' deleted	Likely pyrazinamide resistant.
gyrA (QRDR)	No mutation	Cannot rule out fluoroquinolone resistance. (50% of FQ-R isolates in our in-house evaluation of 550 clinical isolates have a mutation at this locus.)
rrs (1400 region)	No mutation	Cannot rule out resistance to injectable drugs (kanamycin, capreomycin, amikacin). (In our in-house evaluation of 550 clinical isolates: • 91% of AMK-R isolates have a mutation in the rrs locus; • 87% of KAN-R isolates have a mutation in either the rrs locus or the eis locus; • 55% of CAP-R isolates have a mutation in either the rrs locus or the tlyA locus.)
eis (promoter)	No mutation	
tlyA (entire ORF)	No mutation	

*A negative results (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

MDDR assays were developed and the performance characteristics determined by the DTBE Reference Laboratory. They have not been cleared or approved by the Food and Drug Administration.

Case 2

How to treat? Considerations:

- Diabetes
- Renal insufficiency
- Hearing loss
- INH???

Case 2

Pt hospitalized to initiate DR-TB regimen of:

- Amikacin IV at 10-15mg/kg
- Moxifloxacin 400mg qd
- EMB 1200mg qd
- PAS 4g bid
- INH 300mg qd

Case 2

Peaks and troughs of AMK obtained and titrated in hospital.

- Peaks up to 45 initially (goal in 20s – 30s)
- Changed to q48h dosing
- Creatinine rose to 2.2

Pt developed significant nausea, vomitting and diarrhea

Question 6

Which of these medications may cause significant gastrointestinal adverse effects?

A. Ethionamide
B. PAS
C. Clofazimine
D. A and B
E. All of the above

Case 2

Transaminases normal. PAS discontinued due to GI side effects. Linezolid 600mg po qd started.

Pt discharged to home on AMK 650mg IV q48h, moxifloxacin, EMB, INH and linezolid

Within one week of discharge, pt developed acute on chronic renal failure with a peak creatinine of 5.8

Case 2

Amikacin discontinued. All meds held.

After supportive treatment and rehydration, pt's creatinine returned to baseline of 1.69 after several days.

Phenotypic susceptibilities resulted.

Case 2

Susceptibility Testing Method: Indirect agar proportion, 7H10 medium; Susceptibility is defined as < 1% resistance compared to colonies that develop on drug-free media

RESULTS:

	Percent Resistance	***Interpretation***		***Percent Resistance***	***Interpretation***
Isoniazid 0.2 ug/ml	100	R	Kanamycin 5.0 ug/ml	0	S
Isoniazid 1.0 ug/ml	100	R	Ethionamide 10.0 ug/ml	0	S
Isoniazid 5.0 ug/ml	100	R	Capreomycin 10.0 ug/ml	0	S
Rifampin 1.0 ug/ml	100	R	PAS 2.0 ug/ml	0	S
Ethambutol 5.0 ug/ml	37.50	R	Ofloxacin 2.0 ug/ml	0	S
Streptomycin 2.0 ug/ml	50	R	Amikacin 4.0 ug/ml	0	S
Streptomycin 10.0 ug/ml	5	R			
Rifabutin 2.0 ug/ml	0	S			
Ciprofloxacin 2.0 ug/ml	0	S			

Susceptibility Testing Method: MGIT 960

Pyrazinamide 100 ug/ml : Resistant

Case 2

Additional susceptibilites from National Jewish

- Sensitive to Linezolid and Cycloserine

EKG QTc 442

Case 2

Pt restarted on DR-TB treatment with:

- Bedaquiline 400mg qd X 2 weeks, then 200mg q M,W,F
- Moxifloxacin 400mg qd
- Linezolid 600mg qd
- Cycloserine 250mg bid
- Ethionamide 250mg bid
- Vit B6 150mg po qd

Case 2

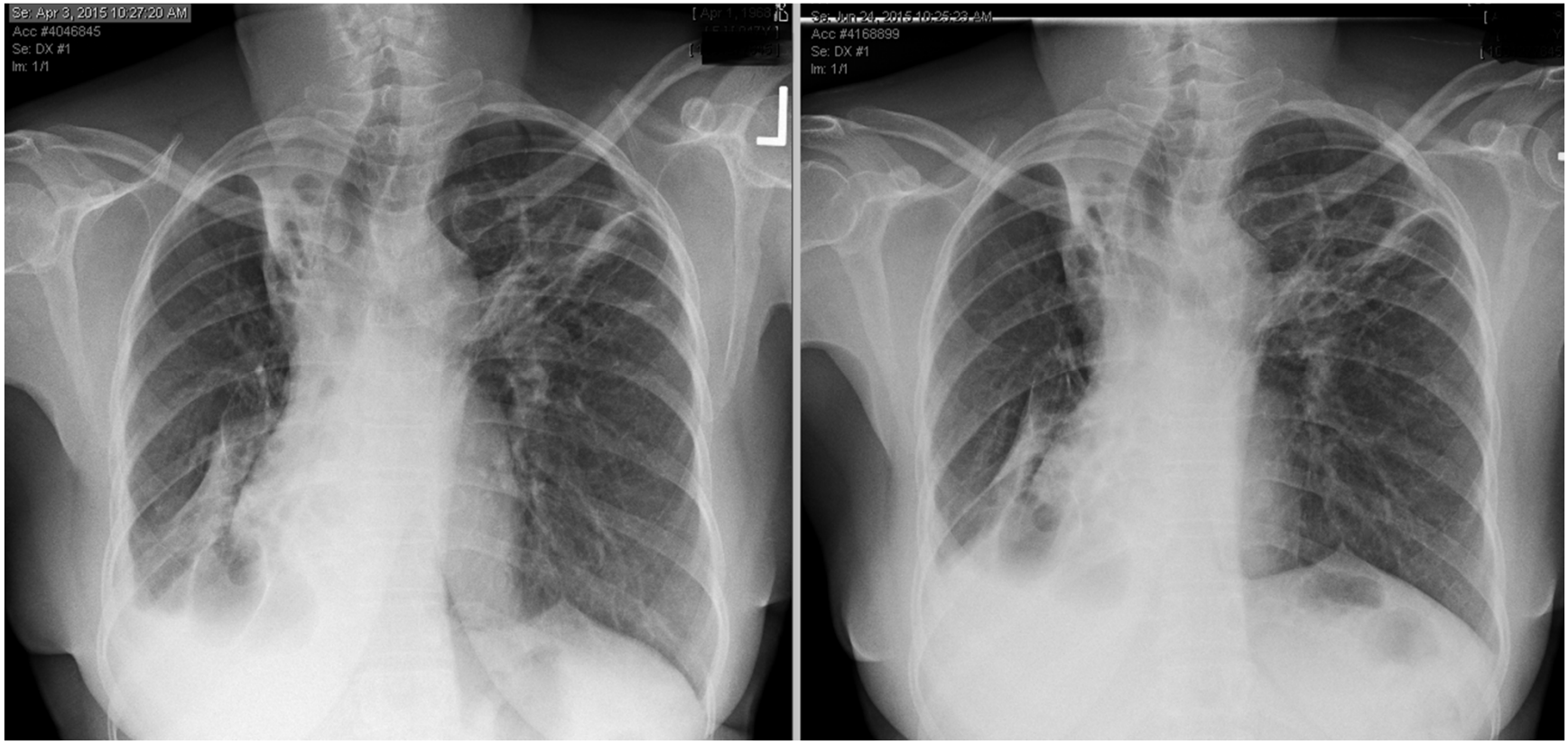
Pt tolerated new regimen with symptomatic treatment for nausea.

LFTs normal, Cell counts stable

QTc 420s – 460s

Sputum cultures converted to negative at one month of initial treatment.

Case 2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Case 2

At about month 5 of DR-TB treatment, pt experienced abrupt onset of witnessed visual hallucinations.

Question 7

What should be your next step?

A. Hold all meds
B. Hold cycloserine
C. Start haloperidol (Haldol) 2mg po bid
D. Add citalopram (Celexa) 20mg po qd
E. None of the above

Case 2

Cycloserine was held with rapid resolution of psychotic symptoms.

After consultation and discussion with patient and family, cycloserine restarted at lower dose (250mg po qd). Pt is tolerating it without issues.

Case 2

Pt currently on continuation phase therapy with

- Moxifloxacin 400mg qd,
- Cycloserine 250mg qd,
- Linezolid 600mg qd and
- Ethionamide 250mg bid
- Vit B6 150mg qd

Has completed 11 of 18 months of MDR-TB treatment.

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My patients and their families

Selected References

- Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2008: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition*
- Hwang et al. *Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies.* BMJ Open. 2014;4:e004143
- Yoo, JW et al. *Clinical experience of using clofazimine to treat multidrug-resistant tuberculosis.* Int J Tuberc Lung Dis. 2013 Sep;17(9):1243-4

Case 3

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Nashville TB Symposium
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Case 3

- 56 year-old Male from Mexico with hypertension, diabetes, prior deep venous thrombosis, left below-knee amputation, blind left eye, kidney transplant in 2000
- Chronic CellCept® and prednisone 5 mg daily
- History of pulmonary TB ~20 years prior treated in Mexico
- Baseline creatinine 2 mg/dL, albumin 2 g/dL, A1c 9.8%, HIV negative

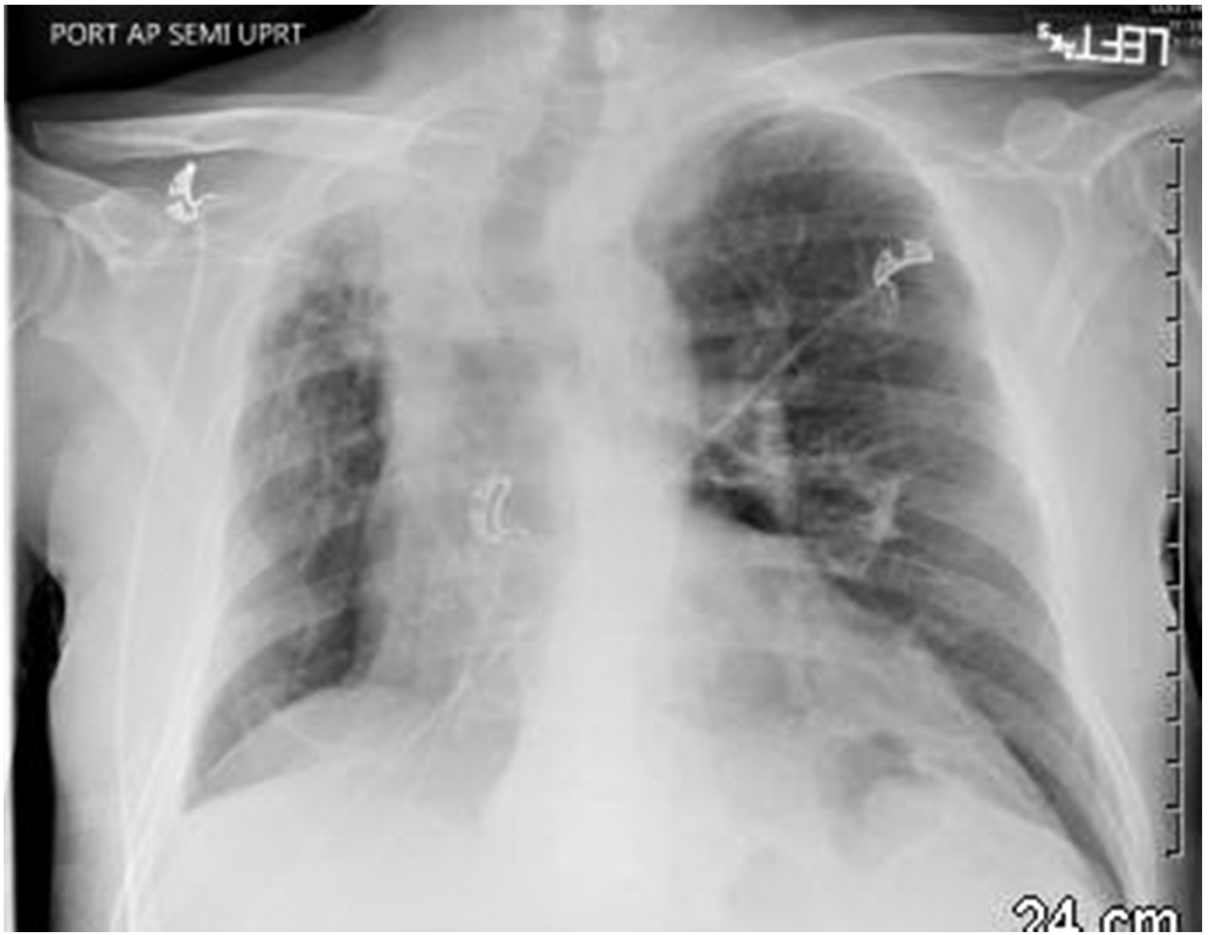
Case 3

- The patient visited the US in 2014 and was diagnosed with pulmonary TB (MTB rifampin resistance and low-level isoniazid resistance) and T11-T12 Pott's disease
- Consultation with SNTC
- Final TB regimen included isoniazid 900 mg 2X/week, linezolid 300 mg po qdaily, moxifloxacin 400 mg po qdaily and pyrazinamide 1,500 mg po qdaily
- Plan for 18 months of TB treatment

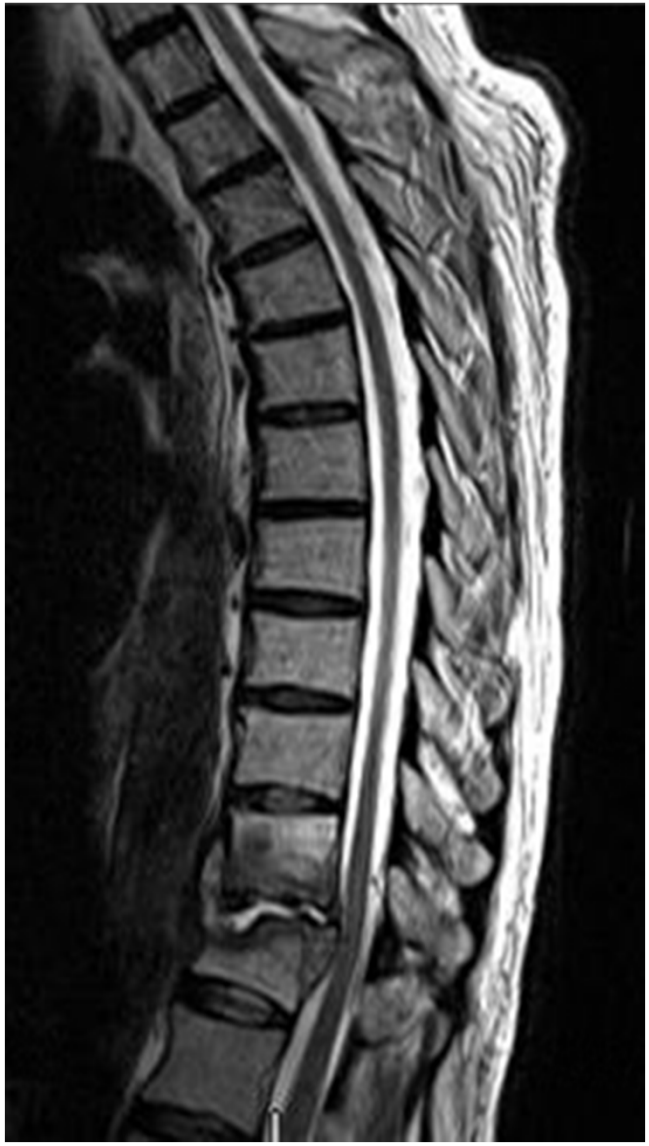
Case 3

- TB treatment stopped in Mexico at 4 months
- Six months later pt developed worsening back pain and decided to come back to the US
- MRI: worsening T11-T12 Pott's disease with paraspinal phlegmon, mild cord compression
- Neuro exam without focal deficit
- Neurosurgery said no surgical intervention
- IR guided biopsy was performed

CXR



T-spine MRI



Case 3

- Consultation with SNTC
- Restarted isoniazid, moxifloxacin, linezolid and pyrazinamide
- T11-T12 smear positive, culture grew MTB with same susceptibility pattern as 2014 sputum MTB isolate
- Sputum MTB PCR & AFB stain/cx x 3 negative
- Discharged on same TB meds and brace

Question 8

- Would you check serum levels of all his TB medications?
  a) Yes
  b) No
  c) I am not sure

Drug levels

Drug	Level (mcg/mL)	Goal (mcg/mL)
Isoniazid 900 mg 2X/w	P: 12.15	9 – 15
Linezolid 300 mg QD	P: 10.72 , T: 6.05	P: 12 – 26, T: 3 – 9
Pyrazinamide 1,500 mg QD	P: 38.05	20 – 60
Moxifloxacin 400 mg QD	P: 0.77 → 0.82	3 – 5

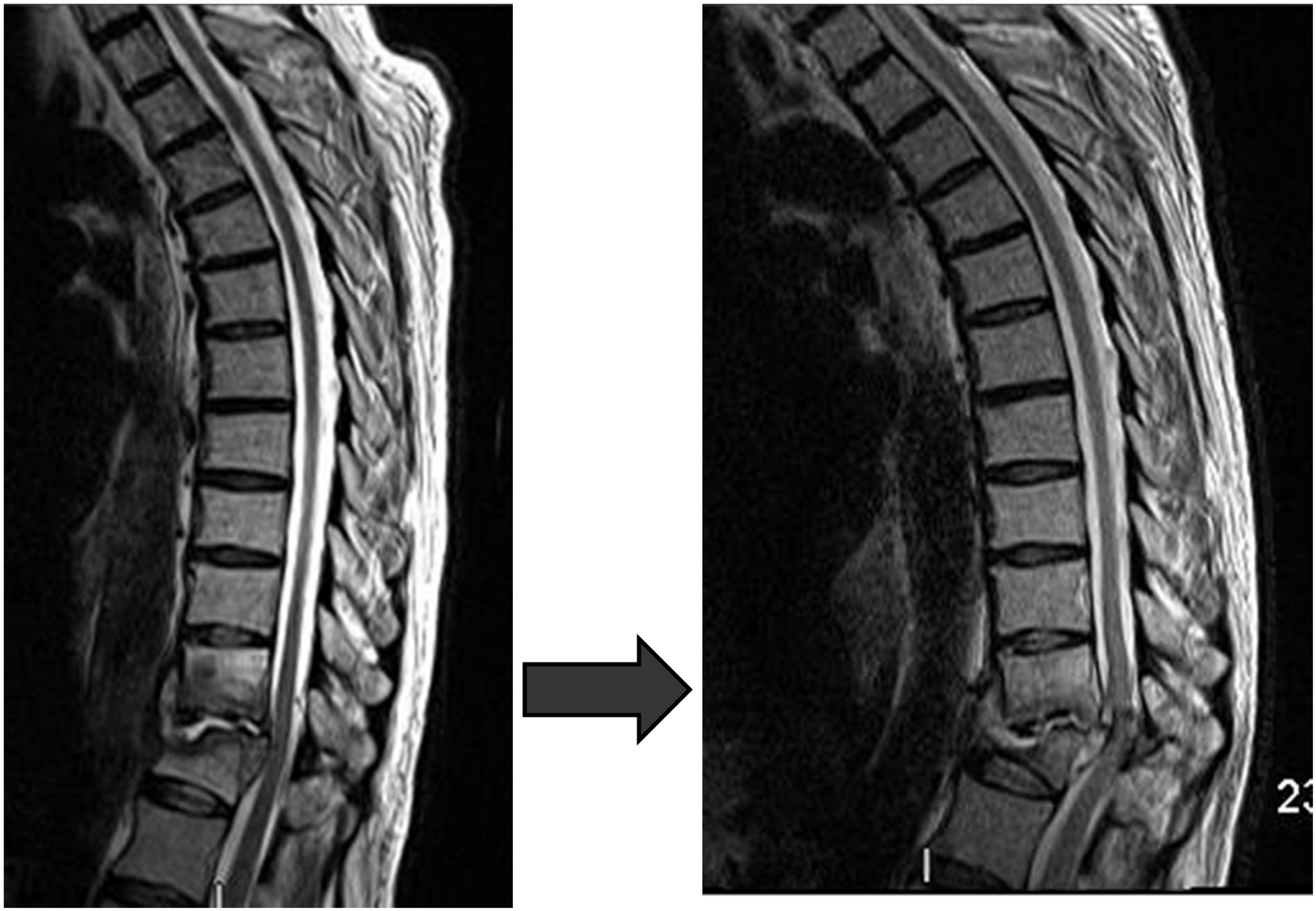
Question 9

- Which are potential side effects of linezolid?
  a) Pancytopenia
  b) Optic neuropathy
  c) Serotonin syndrome
  d) Peripheral neuropathy
  e) All of the above
  f) None of the above

Case 3

- 8/2015: MDR Pseudomonas UTI & septicemia
- 1/2016 (6 months TB treatment): worsening back pain and new onset leg weakness
- MRI: worsening T11-T12 kyphosis, progression of T12 fracture, edema and cord compression

T-spine MRI



Question 10

- What would you do next?
  a) Consult neurosurgery
  b) Consult neurosurgery and stop current TB regimen
  c) Consult neurosurgery and continue current TB regimen
  d) Other

Case 3

- TB medications continued
- Neurosurgery decided to offer spinal decompression and stabilization to protect neurologic function
- Surgery was performed without immediate major complications, patient was extubated next day, left chest tube placed
- Vertebral tissue & bone AFB stain negative
- Vertebral bone MTB PCR positive

Question 11

- Does this positive MTB PCR mean that the patient has active TB disease?
  a) Yes
  b) No
  c) We do not know

Case 3

- Spinal tissue & bone cultures finalized negative at 6 weeks

Molecular tests in vertebral bone	July 2015	Feb 2016
MTB PCR	Positive	Positive
Hain test	rpoB(+) KatG(-) inhA (-)	rpoB(+) KatG(-) inhA (-)
MDDR	rpoB(+) All others (-)	Unable to amplify

Case 3

- BAL AFB stain, MTB PCR, culture negative
- Chest tube fluid AFB stain, MTB PCR, culture negative

Case 3

- Patient developed multiple complications after post-operative day 5
  - ESBL E. coli pneumonia /aspiration
  - MDR Pseudomonas pneumonia x 2
  - NSTEMI
  - Prolonged respiratory failure requiring trach
  - Graft failure requiring renal replacement therapy
  - Multifactorial shock (septic, cardiogenic, adrenal)
- After 6 weeks in the ICU the patient expired

Question 12

- What are common challenges of TB disease after transplant?
  a) Higher incidence than in the general population
  b) Extrapulmonary TB disease is more frequent
  c) Higher mortality rate
  d) Risk factors include old age, diabetes, history of rejection and maintenance therapy with steroids
  e) Multiple medication interactions
  f) All of the above

Question 13

- What would you tell transplant teams about TB prevention in transplant patients?
  a) TB screening should start right after transplant
  b) TB screening should start prior to transplant
  c) TB disease is not preventable in transplant recipients due to lifelong immunosuppression
  d) A person with latent TB infection should never receive a transplant, even if previously treated

Acknowledgements

- Kentucky TB Prevention & Control Program
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