



Virginia is for TUBERCULOSIS

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Background

- 27 yo female from Viet Nam
- History of pulmonary TB treated in Viet Nam ~5 years ago
- Treated with RIPE
- 3/2013: presents with cough for 3 weeks



Background

- In US on a 2-year "compassion" visa that is about to expire
- Down's Syndrome
- Mute
- Understands Vietnamese when spoken to by family
- Lives with father, mother, two brothers (ages 19 and 23) and 10-yo sister



Background

- Initially seen by local pediatrician
- Given prescription for azithromycin x 5 days
- No improvement
- CXR obtained 4/5/13



Background

- Referred to local health department
- 3 sputum smears obtained → positive for AFB
- 5/4/13 Started RIPE
- Sputums become negative within a few weeks of starting therapy
- Patient seems to be doing well
- Monitoring weight—very small in stature and approximately 75 lbs

Then..

- 7/3/2013: Official result of high-level INH resistance received. Susceptible to other first-line medications by traditional testing
- Local HD discussed with State TB control:
 - INH stopped
 - moxifloxacin 400 mg po daily added to rifampin, ethambutol, pyrazinamide

8/2013

- Family reports vomiting after medications
- Apparently this has been going on for some time and occurs a few hours after patient takes her TB medications (after the nurse has left)
- No phone in the house so nurse/outreach worker has to use cell phone for translation (remote area so poor cell coverage)
- Brother does speak English and has a cell phone but usually at work
- Father insistent that the patient does not like American food and wants her to eat Vietnamese food
- Patient was previously thought to be doing well but not gaining weight (still about 75 lbs)

8/17/2013

- Hematemesis reported
- Sputum smear obtained found to be positive
- Patient sent to local ER and admitted



Case

- State TB consultant contacted due to concern for N/V with medications
- Due to worsening CXR and sputum smear positive, concern for drug resistance
- Recommended that once sample grew, to be sent to CDC for molecular based resistance testing

Case

- Patient's N/V in the hospital controlled with protonix and zofran
- Ate well → observed eating a whole plate of lasagna
- Unclear if worsening CXR and sputum smear positivity due to:
 - resistance
 - not actually receiving enough medication (due to vomiting)
- Continued on current regimen

Case

- Continues to do generally well
- Sputum smears become negative
- Molecular testing returns

Molecular Results from 8/18/13 Sample

Mutation	Interpretation
rpoB	Low-level but likely clinically relevant rifampin resistance
inhA, katG	INH resistance
embB	Ethambutol resistance
pncA	Cannot rule out PZA resistance
gyrA (no mutation)	Cannot rule out fluoroquinolone resistance

Case

- All medications stopped
- Request made to do new drug susceptibilities on most recent specimen
- Call placed to SNTC to decide next drug regimen
- Particular concerns: N/V with prior medications, small stature (33 kg), use of aminoglycosides in setting of mutism

Case

- Recommendation:
 - place picc line for IV medication
 - place PEG tube to help prevent N/V with second-line drugs
 - send initial isolate from April to CDC to see if same molecular resistance pattern on current panel was present from beginning of therapy and not detected by traditional DST
 - repeat susceptibilities on most recent isolates pending due to concern for patient receiving PZA, moxifloxacin essentially alone in setting of resistance to other medications

Case

- Medications to be started once Picc/PEG placed: (33.1 kg)
 1. Capreomycin 500 mg IV MWF
 2. PAS 4 g once daily
 3. Cycloserine 250 mg once daily
 4. Moxifloxacin 400 mg once daily
 5. Linezolid 300 mg once daily
 6. Pyrazinamide 750 mg once daily
 7. B6 100 mg once daily
- Conferred with SNTC to ensure that medications could all be crushed, mixed with water into a "slurry" and administered down the PEG tube

Case

- Local health department attempts to have patient admitted to local hospital for picc/PEG placement and initiation of second-line TB medications
- Both local hospitals in the area refuse patient
- Arrangements made for admission to tertiary care center approximately one hour away from patient's home

Admission CXR 10/4/13



1. Persistent rounded area of abnormal opacity right lung base. Findings may relate to parenchymal consolidation/pneumonia/TB although appearance alone does not allow exclusion of a mass. 2. Persistent left perihilar abnormal opacity. This is slightly improved since most recent prior exam. 3. No edema, pneumothorax or new areas of parenchymal abnormality.

Case

- PEG placed in ENDO suite by GI
- Interventional radiology without airborne facility → picc placed at bedside
- Father spending every day/night with patient in the hospital
- Language line used for communication
- One hospitalist spoke Vietnamese which was helpful

January 2014

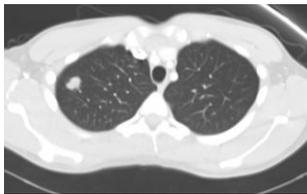
Fast forward to today

- Due to conflicting PZA susceptibilities, ethionamide added to regimen
- Loses weight initially with this medication (down to 69 lbs)
- Ensure started

- Sputum culture negative since 2/13/14
- Initial sputum culture: RIPE – R, FQN - S
- Gaining weight: > 90 lbs
- N/V resolved
- Capreomycin discontinued 9/12/14
- Immigration status still pending
- Contact Investigation
 - Mother completing course of Avelox
 - Father, older brother and sister remain IGRA neg
 - Younger brother.....

The Diagnosis Case #2

- 6th T-SPOT: pos
- Asymptomatic
- CXR abnormal
- CT scan
- Sputum
 - smear (-)
- Needle guided biopsy
 - smear and culture positive
 - Tissue block to CDC
- College student



Centers for Disease Control and Prevention
 National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)
 Division of High-Consequence Pathogens & Pathology (DHCPP)
Infectious Diseases Pathology Branch (IDPB)
Pathology Report

IDPB Number: 2914-0936
 Receipt Date: 07/01/2014
 Sign-out Date: 07/29/2014
 Patient Name: [REDACTED]
 Submitter/Outside # (s): M-14-02643
 Case Origin: VA, USA
 Specimen(s) Received: 1 block
 Submitted By: Lian B Galkovich, M.D.
 Infectious Disease Specialist
 Sentara Norfolk General Hospital
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IDPB #	ACID #	RT #	Panel #	BIOSAT #	Other #'s	Specimen
2014732108	NONE/VE3					

Diagnosis:
 Lung, core needle biopsy: Minute fragments of lung parenchyma with no definitive granulomas (see comment).
 *Positive molecular evidence of Mycobacterium tuberculosis complex species.
 See comments and footnotes, as applicable.

Comments:
 The block was received with a minute amount of tissue. Necrotizing granulomas were described prior to submission, however granulomas were not seen on sections prepared at the CDC, suggesting that the area of interest was cut through. The presence of Mycobacterium tuberculosis complex species DNA was detected by PCR and sequencing.

Infectious Diseases Pathology Branch Pathology Report Continued
 IDPB No. 2014-0936
 Centers for Disease Control and Prevention

Microscopic Examination:
 The block is received with a minute amount of tissue. H&E stained sections of the lung core needle biopsy prepared at the CDC show minute fragments of lung parenchyma and blood; no definitive granulomas are seen.

Specimen	Yeast	Result
6th Imp CT-guided core biopsy (06/03/14)	Mycobacterium spp. (0440)	Indeterminate
6th Imp CT-guided core biopsy (06/03/14)	Mycobacterium genus	Positive for Mycobacterium tuberculosis complex species

LABORATORY DEVELOPED TESTS: Histochanical stains, immunohistochemistry, toxic, and molecular assays, if applicable, were developed and their performance characteristics determined by the Infectious Diseases Pathology Branch laboratory. They have not been cleared or approved by the U.S. Food and Drug Administration. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. The sensitivities of these assays have not been fully determined and negative results do not exclude infection by the specific tested for. Urines always reported all bacteriological, immunohistochemical and molecular results as separate.

ISG Footnotes:
 *ACID/RT/BIOSAT/RT/BIOSAT testing using an immunofluorescence technique was performed with appropriate positive and negative controls.
 *PCR/VE: immunostaining present with the target antigen(s) having appropriate antigen distribution and localization.
 *ACID/VE: no specific immunostaining present.
 *IMMUNOFLUORESCENCE (See Comment): immunostaining present (as indicated) is known to cross react with non-target pathogens (see footnote).
 *ACID/RT/BIOSAT: immunostaining is cytoplasmic to non-responder distribution and/or localization for target antigen(s).
 *ACID/RT/BIOSAT: incorporate an equivalent tissue for evaluation.
 Information on the specific antibody including relevant references (in sections) or primary antibody production (ACID/RT/BIOSAT) is described below.
 *Mycobacterium spp. (0440): This color gelatinized method reacts with several Mycobacterium spp., including M. bovis, M. chelonae, M. fortuitum, and M. goodii. It does not react with Rapid growers: Rhodococcus, Nocardia spp. and Corynebacterium spp.

PCR Footnotes:
 *Sensitivity or specificity of assay (immunofluorescence) were confirmed on coded tissue. The quality of labeled nucleic acids was assessed by a housekeeping gene assay for every test.
 *PCR/VE: amplification of specific gene target sequence.
 *ACID/RT/BIOSAT: amplification of specific gene target sequence, but the presence of amplifiable nucleic acids in the sample is assessed by housekeeping gene PCR assay.
 *INDETERMINATE: presence of specific gene target sequence could not be confirmed.
 *NONE/VE/ACID: gene target is not detectable using specific assay.
 Information on the specific assay including relevant references (as indicated) is described below.
 *Mycobacterium genus: DNA extracted from tissue was used as a template for a Mycobacterium genus specific, multi-PCR assay targeting the IS6110 gene. Positive amplification (100%) by 1579 bp region(s) of IS6110 was observed in Mycobacterium tuberculosis. Housekeeping genes for the assay are IS6110 and IS6111.

DCLS Conventional Susceptibilities- case #2

Drug	Susceptibility	Date Released: 07/29/2014
1st Line MGIT TB		
Ethambutol 5.0 ug/mL	RESISTANT	Amended: 09/13/2014 Previously reported: 07/29/2014
PREVIOUS: Ethambutol 5.0 ug/mL	: PENDING	
Isoniazid 0.1 ug/mL	RESISTANT	Amended: 09/13/2014 Previously reported: 07/29/2014
PREVIOUS: Isoniazid 0.1 ug/mL	: PENDING	
Pyrazinamide 100 ug/mL	SENSITIVE	
Rifampin 1.0 ug/mL	RESISTANT	
Streptomycin 1.0 ug/mL	RESISTANT	
PREVIOUS: Streptomycin 1.0 ug/mL	: PENDING	
2nd Line MGIT TB		Amended: 09/13/2014 Previously reported: 07/29/2014
Capreomycin 3.0 ug/mL	SENSITIVE	
Ofloxacin 1.5 ug/mL	SENSITIVE	
Ethionamide 5.0 ug/mL	SENSITIVE	
Isoniazid 0.4 ug/mL	PENDING	

Summary: CDC Results

	MDDR Mutation	Interpretation	Conventional (11/15/13)
RIF	rpoB	Low-level, clinically relevant rifampin resistance	Sensitive
INH	inhA, katG	INH resistance	Resistant
EMB	embB	Ethambutol resistance	Resistant
PZA	pncA	Cannot rule out PZA resistance	Sensitive
FQN	gyrA (no mutation)	Cannot rule out fluoroquinolone resistance	Sensitive