Extrapulmonary Tuberculosis

Tuberculosis Clinical Intensive
October 11th, 2018

Michelle Haas, M.D.
Associate Director
Denver Metro Tuberculosis Program
Denver Public Health

DISCLOSURES

• I have no disclosures or conflicts of interest to report
• Off-label uses: NAAT on extrapulmonary specimens
Objectives

• At the end of this presentation you will be able to:
  • List at least 4 extrapulmonary manifestations of TB and potential approaches to confirm the diagnosis
  • Explain the importance to evaluate for concomitant pulmonary TB
  • Describe differences in treatment where applicable to patients with extrapulmonary TB compared to pulmonary TB

Sites of Involvement

Clinical Presentation: Site of Disease

CDC Reported TB Cases by Form of Disease United States, 2016

- Pulmonary (70%)
- Extrapulmonary (20%)
- Both (10%)
- Pleural (18%)
- Lymphatic (37%)
- Other (23%)
- Bone/joint (9%)
- Peritoneal (8%)
- Genitourinary (5%)
- Meningeal (4%)

Pulmonary Involvement in EPTB

- 72 EPTB cases, 2003-2004
- CXR abnormal: 35 (49%)
- Sputum collected (spont-or-induced): 57 (79%)
  - AFB smear positive: 5 (9%)
  - AFB culture positive: 12 (21%)
  - CXR abnormal-vs-normal: 23% vs 19%
  - HIV negative, CXR normal: 2/24 culture positive
- Sputum examinations in EPTB patients…may identify potentially infectious cases of TB

### EPTB Key Aspects of Treatment

#### Diagnosis of pulmonary vs EPTB
- **Bacillary load**: Often high, Usually low
- **Imaging**
  - Pulmonary: Plain radiography, Chest CT
  - Extrapulmonary: CT, MRI
- **Diagnostic specimens**
  - Pulmonary: Sputum, Induced sputum, BAL, Post bronchoscopy, Gastric aspirate
  - Extrapulmonary: FNA, Bx: core/needle, excisional/surgical, Serous cavity fluids, Joint fluids, CSF
- **Sampling**: Usually multiple, Usually single
- **Tests**
  - Pulmonary: AFB smear/culture, Nucleic acid amplification
  - Extrapulmonary: AFB smear/culture, NAAT, Cytology/histopathology, Cell count & diff, Protein (+/- LDH), glucose, ADA, gamma-interferon
- **Smear/culture pos**: Smear+: 50-70%, Culture+: 90%
- **Treatment duration**: 6-9 months usually, Bone & joint: 6-9 months, Brain: 9-12 months, Others: 6 months
- **Corticosteroids**: No, Meningitis, Some pericarditis
- **IRIS/paradoxical worsening**: Rare, Not uncommon
- **Response**: Mycobacteriology, clinical, imaging, Clinical, imaging
<table>
<thead>
<tr>
<th>Issue</th>
<th>Pulmonary</th>
<th>Extrapulmonary</th>
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<tbody>
<tr>
<td>Bacillary load</td>
<td>Often high</td>
<td>Usually low</td>
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<tr>
<td>Imaging</td>
<td>Plain radiography</td>
<td>CT</td>
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<td>Chest CT</td>
<td>MRI</td>
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<td>Diagnostic specimens</td>
<td>Sputum</td>
<td>FNA</td>
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<td></td>
<td>Induce sputum</td>
<td>Bx: core/needle, excisional/surgical</td>
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<td>BAL</td>
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<td>Post bronchoscopy</td>
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<td>Gastric aspirate</td>
<td>CSF</td>
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<tr>
<td>Sampling</td>
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<td>Usually single</td>
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<tr>
<td>Tests</td>
<td>AFB smear/culture</td>
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<tr>
<td></td>
<td>Nucleic acid amplification</td>
<td>NAAT</td>
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<td><em>ATS/IDSA/CDC 2017 Dx Guidelines</em></td>
<td>Cell count &amp; diff</td>
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<td><em>At present, NAAT testing on specimens other than sputum is an off-label use of the test.</em></td>
<td>Protein (+/- LDH), glucose</td>
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<td>ADA, gamma-interferon</td>
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<tr>
<td>Smear/culture pos</td>
<td>Smear+: 50-70%; Culture+:90%</td>
<td>Smear+: 25-50%; Culture+:80-70%</td>
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<tr>
<td>Treatment duration</td>
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<td>Bone &amp; joint: 6-9 months</td>
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<td>Brain: 9-12 months</td>
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<td>Others: 6 months</td>
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<tr>
<td>Corticosteroids</td>
<td>Severe respiratory failure</td>
<td>Meningitis</td>
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<td></td>
<td></td>
<td>Some pericarditis</td>
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<tr>
<td>IRIS/paradoxical</td>
<td>Rare</td>
<td>Not uncommon</td>
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<tr>
<td>worsening</td>
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<tr>
<td>Response</td>
<td>Mycobacteriology, clinical, imaging</td>
<td>Clinical, imaging</td>
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</table>

**Response**

Mycobacteriology, clinical, imaging

Clinical, imaging
Radiographic Findings in EPTB

- Lympadenopathy with central attenuation, septation (neck, chest, abdomen, pelvis)
- Effusions
- Diskitis, osteomyelitis +/- paraspinous abscess
- Enhancement of meninges, peritoneum, pericardium
- Ring enhancing CNS lesions
- Omental stranding, mesenteric adenopathy
- Bowel wall thickening +/- abscess
- Urinary collecting system obstruction +/- renal parenchymal destruction
- Adnexal mass

Typical Findings Extrapulmonary Specimens

- AFB smear: 10-50% sensitive
- AFB culture: 60-90% sensitive
- NAAT 50-75% sensitive
- Necrotizing granulomata
- Protein elevated
  - Pleural/peritoneal (>4-5gm/dL)
  - CSF (>100-500mg/dL)
- Moderately decreased glucose (~40-50mg/dL)
- Pleocytosis
  - Pleural (1,000-5,000 WBC/uL)
  - CSF (100-500/uL)
  - Lymphocyte predominant differential
Patient #1

- 28 year old woman, originally from Mexico, presented to her primary care provider with cough for 2 months
- Urgent care visit 3 days after that visit
  - Continued cough, CXR obtained...
  - Given azithromycin and discharged from the ED.

Patient #1

- 5 months later: repeat PCP visit:
  - Continued cough, no relief with albuterol
  - 8 lb. weight loss: BMI 18.6.
- 8 visits later...
Patient #1

- Family took her to another hospital
  - Somnolence, confusion
  - Continued nausea/vomiting
- 9/6: MRI/brain: diffuse focal flair hyperintensity; diffuse leptomeningeal enhancement compatible with meningitis.
- LP: WBC 149, t prot 152, glucose 14
  - *M. tuberculosis* PCR positive

Typical Findings CSF in TB Meningitis

- **Protein elevated:** 100-500mg/dL (may be higher in spinal block)
- **Moderately decreased glucose:** (~25-50mg/dL)
- **Pleocytosis:** 100-500/uL
- **Lymphocyte predominant,** but can be mixed or neutrophilic early in presentation

- **TB PCR sensitivity:** ~50% (range 40-75%)
- **AFB smear sensitivity:** ~10% (higher for tissue biopsy and CSF pellicle)
- **AFB culture sensitivity:** ~50%
### TBM Clinical Presentation

<table>
<thead>
<tr>
<th>Stage I</th>
<th>headache and fever only</th>
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<tbody>
<tr>
<td></td>
<td>Non-specific symptoms</td>
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<td>Stage II</td>
<td>Meningismus</td>
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<tr>
<td></td>
<td>Drowsiness/lethargy</td>
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<td></td>
<td>Focal neurologic deficits</td>
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<tr>
<td>Stage III</td>
<td>Stupor/coma/seizures</td>
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<td>Gross paresis/paralysis</td>
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#### Typical Complications TB Meningitis

- Pressure of exudate $\rightarrow$ cranial nerve palsies (e.g., IV, VI, VII), deafness, visual disturbances, other paresis/paralysis
- Hydrocephalus
- Occlusive vasculitis
- SIADH
- Mass effect
- Paradoxical worsening/IRIS
Corticosteroids in TB Meningitis

- RCT, double-blinded, age>14, N=542
- Dexamethasone vs placebo
- RR death 0.69 (0.52-0.92), p=0.01
- Severe disability: 18% vs 13% (NS; p=0.27)
- Adverse effects: 9% vs 20% (p=0.02)


Corticosteroids in TB Meningitis

- Recommended by ATS/IDSA TB treatment guidelines
- Less clear role in tuberculoma or spinal TBM
- Dexamethasone 0.4mg/kg/d split qid or prednisone 1mg/kg/d
  - 4 weeks at full dose then 4-week taper
Patient #1

• Bronchoalveolar lavage AFB smear +, probe + *Mycobacterium tuberculosis*.

• Started on TB treatment with isoniazid, rifampin, pyrazinamide and ethambutol and steroids

• *Completed 12 months of treatment and made a full recovery*

Patient #2

33 year old woman, prior residence in the Philippines presented with right sided neck swelling. Some subjective fevers, no other symptoms

Partial improvement with amoxicillin-clavulanate

QFT+, HIV negative

Excisional Biopsy of right supraclavicular node: caseating granulomas

Sputum AFB smear+
Patient #2 clinical course

- Started on HRZE
- Converted her sputum cultures at one month
- LN swelling slowly improved
- Completed 6 month course of treatment.

LN TB: Paradoxical Worsening

- Enlarging, new, or draining LNs
- 20-25% of HIV-negative LN cases
- Median onset: 46 days (IQ: 34-111 days)
- Granulomata, AFB+, culture-negative
- Median duration: 69 days
- Robust response to MTB with treatment and release of antigens
- NSAIDs, corticosteroids, aspiration (none evidence based)

Patient #3

• 60 year old man with cryptogenic cirrhosis, associated TIPS placement is admitted July 2016 with fevers, cough chronic right sided effusion and decompensated cirrhosis (MELD 24)
  – Started on vancomycin and cefepime for presumed HCAP
  – New murmur identified, TTE with possible mitral valve vegetation
  – Multiple blood cultures negative
  – ID consulted to assist with the evaluation of culture negative endocarditis

Patient #3

• ID spends the next few days pouring through his records
  – Originally from Mexico, living in the US for 18 years
  – Prior admission 2 months prior with sepsis and pneumonia. Found to have exudative pleural fluid, negative cultures
  – Remote history of presenting to TB clinic several years prior, IGRA testing done at that time was negative
**Patient #3**

**Jan 2016 – GI bleeding**

**May 2016 - Sepsis**

Pleural fluid –
- RBC 48,000
- WBC 1,800 (73% L)
- Prot 2.2
- LDH 279 (serum 422)
- Procalcitonin < 0.05

*Discharged on Levofloxacin, symptoms improve*
Patient #3

Pleural fluid – July 2016
pH 7.35
Gluc 138
RBC 46,000
WBC 1,749 (78% L)
Prot 2.5
LDH 215 (serum 421)
ADA 2.1

AFB cultures not sent on pleural fluid 😞

Patient #3 continued

• CBC
  • WBC 3.0
  • Hct 24.8
  • Platelets 68
• INR 2.5
• Cr 0.94

• LFTs
  • Total Bilirubin 5.0, direct 2.0
  • AST 50
  • ALT 28
  • Alb 1.2

Sputum 1+ AFB; Xpert (+) TB and Rifampin resistant
What regimen would you recommend?

Any additional testing?

Patient #3

• Treatment started with levofloxacin, amikacin, EMB, linezolid and imipenem
  – Imipenem discontinued after two weeks
  – QTc stable at 500
• MDDR-no INH resistance
• Phenotypic susceptibilities—rifampin and pyrazinamide resistance
Pleural disease evaluation

<table>
<thead>
<tr>
<th>Specimen Cultured</th>
<th>AFB Culture Sensitivity</th>
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<tbody>
<tr>
<td>Sputum only</td>
<td>48%</td>
</tr>
<tr>
<td>Fluid only</td>
<td>63%</td>
</tr>
<tr>
<td>Sputum + Fluid</td>
<td>79%</td>
</tr>
</tbody>
</table>

- Pleural Biopsy
  - Closed
    - Up to 40% of specimens contain no pleural tissue
    - Image guided gaining favor
    - Sensitivity (pathology + culture): 80-90%
- Thoracoscopy/VATS: sensitivity approaches 100%


Pleural Fluid ADA
Low Incidence Setting

- N=338 patients
- Lymphocytic exudative
- 7 pleural TB cases
- Typical cut-off: >40
- Sensitivity: 85%
- Specificity: 90%
- PPV: 85%
- NPV: 99%

ADA Limitations

- False negatives
  - Early disease
  - Advanced age
  - Smokers
- False positives
  - Non-TB empyema, parapneumonic effusions
  - Mesothelioma, lung and hematologic malignancies
  - Rheumatologic conditions


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<thead>
<tr>
<th>Other Serous Compartment TB</th>
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<thead>
<tr>
<th></th>
<th>Pericardial</th>
<th>Peritoneal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Chest pain</td>
<td>Abdominal pain, distension, anorexia</td>
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<tr>
<td></td>
<td>Dyspnea</td>
<td></td>
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<td></td>
<td>Narrowed pulse pressure</td>
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<tr>
<td>Radiography</td>
<td>Enlarged cardiac shadow</td>
<td>Ascites, fat stranding, adenopathy, studding</td>
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<tr>
<td></td>
<td>Effusion (US/CT)</td>
<td></td>
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<tr>
<td>Specimens</td>
<td>Pericardiocentesis</td>
<td>Paracentesis</td>
</tr>
<tr>
<td></td>
<td><em>PCR, AFB smear/culture, cell count/diff, chemistry, ADA</em></td>
<td>Peritoneal biopsy</td>
</tr>
<tr>
<td>Regimen</td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Sometimes</td>
<td>No</td>
</tr>
</tbody>
</table>
Corticosteroids in TB Pericarditis

- RCT, 2/3 HIV-positive, N=1400 adults
- 2x2 design: prednisolone vs. placebo
- Prednisolone
  120mg/dx7d→90→60→30→15→5mg/d
- No difference in death+tamponade+constrictive pericarditis
  - HR 0.95 (0.77-1.81; 24% vs 26%; p=0.66)
  - Constrictive pericarditis reduced: 4.4% vs 7.8%; HR 0.56 (0.36-0.87; p=0.04)
  - Hospitalization reduced: 21% vs 25%; HR 0.79 (0.63-0.99; p=0.04)

Routine administration not endorsed by IDSA/ATS guidelines

Patient #4

- 49 year old man with newly diagnosed type II diabetes who presented to an outside hospital with back pain and numbness/tingling in his legs bilaterally
  - No fever/chills
  - No weight loss
  - Vitals stable, afebrile
  - Exam without neurologic deficits

MRI report:
- "likely metastatic disease"
- Pathologic 80% vertebral body fracture at T3, mass-like lesion with epidural extension of presumed tumor and retropulsion → severe canal stenosis
Patient #4

- Lived for years in Mexico, has been in the US since 2003
- No health insurance
- TST reportedly negative; HIV negative
- Underwent biopsy of T3:
  - Fibroadipose tissue and fragments of bone with prominent granulomatous inflammation
  - No evidence of malignancy, no AFB or fungal organisms
- Discharged home on the following:
  - Dexamethasone
  - Metformin

Patient #4

- Presents again 3 weeks later with:
  - Continued numbness and tingling of the entire bilateral LE's as well as unsteady gait
  - Worsening right sided upper back pain
  - IGRA positive
  - PSA 4.76 (>4 abnormal)
Patient #4

Transferred to a referral center and admitted to neurosurgery

Concern for malignancy, PET scan ordered

• Underwent debulking with T3 corpectomy, T1-T5 spinal fusion, T2-4 decompression

Patient #4

• Intense FDG activity in the following:
  • Soft tissues around the site of the T3 corpectomy
  • left lateral sixth rib lesion with likely pathologic fracture
  • Prostate
  • Right scrotum
Patient #4

- Excisional biopsy of left rib mass, and fluid sampling for culture
  - Blood and fibroadipose tissue.
- 2nd Rib biopsy:
  - Bone and bone marrow with extensive infiltration by non-caseating granulomas
  - No mycobacterial or fungal elements noted by AFB and GMS staining

- Prostate, right medial, right lateral, left medial and left lateral core biopsies:
  - Benign prostatic tissue with acute and chronic inflammation, foreign body giant cell reaction and abundant non-caseating granulomas

Patient #4

- Patient was initiated on isoniazid, rifampin, pyrazinamide and ethambutol
- PCR for *Mycobacterium tuberculosis (Mtb)* was positive from spinal mass/abscess fluid a few days later.
  - Culture positive, pan-susceptible
- Rib biopsy cultures negative for *Mtb*
- Urine culture negative for *Mtb*
- Sputum cultures negative for *Mtb*
## Other Sites of EPTB

<table>
<thead>
<tr>
<th>Site</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>Urine AFB culture</td>
<td>Standard</td>
<td>Flank pain+fever</td>
</tr>
<tr>
<td></td>
<td>Urine PCR</td>
<td></td>
<td>Hematuria</td>
</tr>
<tr>
<td></td>
<td>Biopsy specimens</td>
<td></td>
<td>Sterile pyuria</td>
</tr>
<tr>
<td>Genital tract</td>
<td>Biopsy specimens</td>
<td>Standard</td>
<td>Female&gt;male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tubes, ovaries, Epididymis</td>
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<tr>
<td>Liver/spleen</td>
<td>LFTs: mild cholestatic profile</td>
<td>Standard</td>
<td>Not uncommon in disseminated* TB</td>
</tr>
<tr>
<td></td>
<td>Biopsy (rare)</td>
<td></td>
<td>TB, especially miliary</td>
</tr>
<tr>
<td>Ocular</td>
<td>Exam</td>
<td>“Standard”</td>
<td>Anterior uveitis</td>
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<tr>
<td></td>
<td>Positive TST/IGRA</td>
<td>+/‐ ophthalmic corticosteroids</td>
<td>Pan uveitis/choroiditis</td>
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<td>Exclusion of other causes</td>
<td></td>
<td>TB bacilli or hypersensitivity</td>
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<tr>
<td></td>
<td>Aqueous/vitreous fluid (rare)</td>
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<td>Choroidal nodules</td>
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<tr>
<td>Erythema induratum</td>
<td>Biopsy: panniculitis</td>
<td>??</td>
<td>Hypersensitivity (not disease)</td>
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<td></td>
<td></td>
<td></td>
<td>Some PCR+</td>
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<tr>
<td></td>
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<td>No organisms</td>
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*disseminated = involvement of two anatomically non-contiguous sites

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**Extra pulmonary TB summary**

- LN, pleura most common; any site can be affected
- CNS TB can be a medical/surgical emergency
- Look for concurrent pulmonary TB
- Dx: imaging → sampling → mycobacteriology+
- Rx: CNS 9-12months, bone 6-9months, others 6months
- Corticosteroids: TB Meningitis
Questions?