Rule Out Tuberculosis

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Objectives

1. Brief review of current TB epidemiology
2. Review some clinical features of TB
   - Pulmonary
   - Miliary
   - Pleural
3. Discuss appropriate work up
<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Rate*</th>
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<tbody>
<tr>
<td>2007</td>
<td>13,282</td>
<td>4.4</td>
</tr>
<tr>
<td>2008</td>
<td>12,895</td>
<td>4.2</td>
</tr>
<tr>
<td>2009</td>
<td>11,520</td>
<td>3.8</td>
</tr>
<tr>
<td>2010</td>
<td>11,163</td>
<td>3.6</td>
</tr>
<tr>
<td>2011</td>
<td>10,517</td>
<td>3.4</td>
</tr>
<tr>
<td>2012</td>
<td>9,945</td>
<td>3.2</td>
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*Cases per 100,000. Updated as of June 10, 2013.
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2012*

*Updated as of June 10, 2013
U.S. and Ohio TB Case Rates 1993-2013

Rate per 100,000 Population

Year


Ohio Rate
U.S. Rate
Country of Origin for Foreign Born TB Cases in Ohio, 2013

- **India**: 17%
- **Bhutan**: 8%
- **Ethiopia**: 8%
- **Somalia**: 7%
- **Nepal**: 6%
- **Other***: 54%

*26 Other Countries
“Rule out Tuberculosis”

• Review the next 3 films and decide which patient has tuberculosis.
Who Has Tuberculosis?

A. X-ray #1
B. X-ray #2
C. X-ray #3
Next some clinical information.
37 yo with no PMHx with symptoms of cough, diarrhea, nausea and vomiting for 1 week. + fever. WBC=18 with 50% bands

Note dense consolidation, air bronchograms, ?hilar fullness.
26yo college student from Korea with 22 mm PPD and complaints of fatigue

Note patchy nodular infiltrate, localized to RUL
42 yo man, born in Greece, emigrated 20 years ago c/o lumbosacral back pain for 1 month. Episode of fever 1 week ago. Treated with azithromycin. No respiratory symptoms now. This CXR is unchanged from 1 week ago.

Note right hilar fullness, thickening right paratracheal stipe, patchy opacity under clavicle
Who Has Tuberculosis?

A. X-ray #1
B. X-ray #2
C. X-ray #3
Radiographic Clues to Pulmonary TB

• Infiltrates tend to be patchy rather than densely consolidated
• Presence of cavitation is helpful, but not diagnostic
• Hilar adenopathy represents new (primary) infection and is uncommon in adults with tuberculosis (unless immunocompromised)
Clinical clues to tuberculosis

• Duration of symptoms weeks to months
• Association of weight loss, fatigue
• May not be febrile at presentation (40-80% febrile at hospitalization for TB)
• Labs typically are normal or nonspecific (anemia, normal or slightly elevated WBC)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Medical risk factors of TB</th>
</tr>
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<tbody>
<tr>
<td>Born in endemic region</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Homeless</td>
<td>ESRD</td>
</tr>
<tr>
<td>Incarceration</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>Prior exposure to TB</td>
<td>HIV infection</td>
</tr>
</tbody>
</table>
Admitted and placed in respiratory isolation..now what?

• Sputum for AFB (do we really need 3?)
  – Rule in v. rule out
    – RULE IN: 3 chosen because it maximizes sensitivity of test
    – RULE OUT: 1 negative smear has NPV 98% (in US study)
Admitted and placed in respiratory isolation..now what?

• Sputum for AFB

• Nucleic Acid Amplification
  – PCR done directly on a clinical specimen
  – Performs best on smear + specimens
  – Results within 24 hours
  – Available at State Labs, reference labs and larger hospitals and health systems
Admitted and placed in respiratory isolation..now what?

- Sputum for AFB
- Nucleic Acid Amplification
- PPD or IGRA or both
What are IGRAs and should I be using them?

• Interferon Gamma Release Assays (quantiferon and t spot)
• Can be used in all situations that we have traditionally used a TST (PPD)
• Similar to the TST, its sensitivity decreases in the immunosuppressed
Summary w/u pulmonary TB

• Use clinical and x ray data to determine likelihood of TB
• Sputum for AFB still important (rule in v. rule out)
• NAA useful in specific situations
• IGRA or TST (not both)
Case Presentation

• HPI: 20 y/o male college student presents to urgent care clinic with persistent cough.
• Initially had flu like illness in 2 months prior
• Symptoms lingered with persistent cough
• Seen by PCP – Treated with Azithromycin
• Due to persistent symptoms he presented to urgent care and a chest xray was performed.
More History

- No constitutional symptoms
- No history of tuberculosis exposure
- Had a PPD several years ago that was negative
- US born, Korean family. Travelled to Korea for 3 months last summer
- College in Cleveland, born and raised in Chicago
- Physical examination and vitals are all normal
What would you do next?

A. Admit to respiratory isolation for further work up.
B. Place a PPD and refer to Tuberculosis Clinic for evaluation.
C. Call your medical school classmate who is a pulmonologist and ask her to see the patient this week.
D. Prescribe a course of moxifloxacin and schedule a f/u visit in 2 weeks with a specialist of your choosing.
Does he have TB?

A. Yes  
B. No
Follow up

• Referred to TB Program
• PPD and quantiferon were both negative
• 3 sputum for AFB negative
• CT scan performed
• Pulmonary referral for bronchoscopy
What is the diagnosis?

A. Mycobacterium Avium
B. Tuberculosis
C. Blastomycosis
D. Histoplasmosis
E. Testicular cancer with mets
F. Wegener’s
MetroHealth and Case Western Reserve University, affiliated since 1914, partners in advancing patient care through research and teaching.
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TBBX

- NECROTIZING GRANULOMATOUS INFLAMMATION INVOLVING ALVEOLATED PULMONARY PARENCHYMA

- GMS stain demonstrates large spherical bodies associated with the necrotizing granuloma.
Culture grows: Blastomycoses

Broad Based budding yeast
Differential upper lobe infiltrates

- Bacterial pneumonia
- Tuberculosis
- Non Tuberculous mycobacteria (MAC, Kansasii) often in pre-existing lung disease (COPD, previous TB)
- Atypical bacterial pathogens (nocardia, actinomycyes)
- Endemic mycoses (histoplasmosis, blastomycosis)
- Cancer: primary lung, lymphoma, metastatic disease
- Wegener’s, BOOP, Eosinophilic pneumonias, sarcoidosis
Mobile Chest X-ray Unit
Case

• 68 yo man who emigrated from Nepal about 3 years ago. Medical history of DM and HTN. Presents to ED with complaints of weight loss, malaise, poor appetite for 3 months. Recently has had some emesis.

• PPD status unknown.

• Weight at presentation was 98 lbs (baseline around 130 lbs)
Note diffuse, monotonous, micronodular pattern. Classic miliary tuberculosis.
Miliary Tuberculosis

- “Unchecked hematogenous dissemination”
- Can occur during primary infection or as a form of reactivation
- Varied presentation (subacute febrile wasting illness to ARDS and multisystem organ failure)
- Peak ages: infants, adolescents, elderly
- Immunosuppressed
- Liver involvement is common (elevated alk phos and hepatomegaly)
- Miliary pattern on CXR occurs in over one half of patients (normal cxr in 20-30%)
Miliary TB continued

- CBC often normal
- PPD/IGRA can be negative
- AFB: lung, liver, and bone marrow
- Treatment—treat early—treat aggressively
- Mortality=20% (unchanged since the introduction of INH)
Case

• 32 yo woman with history of Crohn’s disease. Started on infliximab about 3 months ago. Now presents with SOB and fever for about a weeks duration. PPD was negative prior to starting infliximab.

• Demographics: born and raised in suburban Cleveland, works as graphic designer. Denies tuberculosis exposure

• On admit was febrile to 101, 92% on RA, vitals otherwise stable. Faint crackles diffusely on lung exam (heard after cxr reviewed). Otherwise normal exam
Work Up

• Admitted to medical floor, isolation bed.
• 3 sputums negative for AFB
• Bronchoscopy with transbronchial biopsy arranged.
• Additional labs sent
What’s her diagnosis?

A. Miliary Tuberculosis
B. Non tuberculous mycobacterial infection
C. Influenza pneumonia
D. Disseminated histoplasmosis
E. Pneumocystis
Results

• Transbronchial biopsy showed caseating granuloma with fungal forms
• Urine histo antigen was positive.
• Differential diagnosis of miliary pattern includes:
  – TB
  – Histo/ other fungal pneumonia
  – Lymphangitic spread of cancer
  – Other diagnoses including: atypical pneumonia, ARDS, pneumocystis pneumonia, Langherhans Cell Histiocytosis
Case

- 26 yo former heroin abuser who presents to the ED with complaints of SOB. Mildly hypoxic at 92%. Otherwise looks well. Reports history of PE 2 years ago still on coumadin.
- CT PE performed
- CBCD and LFTs normal
- Never had a PPD
- Recent moldy basement exposure
What’s his diagnosis?

A. Miliary Tuberculosis
B. Disseminated Histo
C. Talc lung
D. Hypersensitivity pneumonitis
E. None of the above

Extensive foreign body emboli with granulomatus inflammation of pulmonary vasculature.

There is extensive deposition of polarizable foreign material consistent with tablet filler components microcrystalline cellulose consistent with the intravenous injection of crushed pharmaceutical tablets.
Summary Miliary TB

• Very old, very young AND immunosuppressed
• Abnormal CXR not always present
• Usually subacute febrile wasting illness
• Differential dx (you will think about much more than you see it)
• Make the diagnosis
Early tent colony
Pleural Disease

• 30 yo Spanish speaking man presented to ED with complaints of fever and RUQ abdominal pain for 1 week duration. Onset of symptoms was fairly abrupt
  – +nausea and vomiting
  – No diarrhea
  – Loss of appetite.
• Vitals: 102.1, 99, 128/70, 18
• Non toxic appearing, uncomfortable, holding right upper abdomen, slightly diminished breath sounds right lower lung field, benign abdominal exam
• ED labs with WBC 6,000, Hb 14
• CT abdomen/pelvis notable for large right pleural effusion with infiltrate v. atelectasis
Case continued

• Following CT abdomen a chest x-ray was performed.
Note loculated effusion right side, no definite infiltrate or adenopathy
Additional history and course

- Admitted to the hospital for CAP v. PE
- Started on lovenox and antibiotics overnight
- Born in Honduras, in US for 7 years. Denies TB exposure. No prior TB testing
- Pleural fluid ultimately obtained after lovenox wore off:
  - pH 7.5, LDH 1000, glucose 40, Cell count: 2073 41% neutrophils, 42% lymphs, 15% monos
  - Pigtail catheter placed at time of thoracentesis due to concern for loculated parapneumonic effusion
Case continued

• Patient remained febrile for 5 additional days
• PPD placed and ultimately returned positive (17 mm)
• ID and pulmonary involved. Antibiotics changed around. Chest tube removed and replaced.
• 7 days after admit I return to the service, found out he was still there and still febrile and initiated antituberculosis treatment (ATT)
• ADA returned at 65mg/dl that same day
Pleural Tuberculosis

• Relatively common presentation of tuberculosis. 3-5% of all TB cases in US. Up to 30% in sub-Saharan Africa

• Classically considered a manifestation of post primary tuberculosis (within 2 years of exposure)
  – Rupture sub pleural focus into pleural space
  – Effusion largely as a result of the immune response to the TB antigen rather than significant uncontrolled infection. (culture yield low: 10-47%)

• Can occur as manifestation of reactivation disease with similar pathogenesis
## Pleural Fluid Characteristics

<table>
<thead>
<tr>
<th>Test</th>
<th>Usual Result</th>
<th>Our patient</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>&gt;500 IU/L</td>
<td>1000 IU/L</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>&gt;4 gm/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Normal</td>
<td>40 mg/dl</td>
<td>Can be low in 20% patients</td>
</tr>
<tr>
<td>pH</td>
<td>&gt;7.3</td>
<td>7.5</td>
<td>Can be low in 20% patients</td>
</tr>
<tr>
<td>Cell Count</td>
<td>&lt;5000/uL</td>
<td>2073</td>
<td></td>
</tr>
<tr>
<td>Differential</td>
<td>&gt;90% lymphocytes</td>
<td>41% neutrophils 42% lymphs</td>
<td>Early on can have more neutrophils</td>
</tr>
<tr>
<td>Adenosine deaminase (ADA)</td>
<td>&gt;47 UL</td>
<td>65mg/dl</td>
<td>Use remains controversial</td>
</tr>
</tbody>
</table>
Adenosine Deaminase

Fig. 1. – Total adenosine deaminase activity (ADA) in pleura fluid. Tra: transudates; TB: tuberculous; Neo: neoplasics; Par: parapneumonics; Emp: empyema; Mis: miscellaneous.
Lessons from case

• Demographics are important
• Clinical presentation (series 49 patients TB pleurisy 1964-70, Mt. Sinai, NY)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Abrupt onset</td>
<td>63%</td>
</tr>
<tr>
<td>Cough</td>
<td>93%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>73%</td>
</tr>
<tr>
<td>Fever</td>
<td>86%</td>
</tr>
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</table>

Summary

• Reviewed some radiographic and clinical Characteristics of Tuberculosis in the hospitalized patient
• New Tests helpful, but don’t replace clinical acumen
  – Nucleic acid amplification (NAA)
  – Interferon gamma release assays (IGRA)
• As TB rates continue to fall a high index of suspicion will be needed to make the diagnosis