Differentiating between CAP and tuberculosis

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Case 1

• A 20-year-old female patients
• 10 day history of tiredness, headache, sore throat, low-grade fever, and dry cough.
• Pneumonia told and sent her home with a prescription for amoxicillin
• 2 days later visit Emergency Department
  – worse with shortness of breath on exertion
  – pleuritic chest pain bilaterally.
  – temperature of 38°C,
  – mild dyspnea
Laboratory data

- Hgb 11.8 g/dl
- WBC 6.2 X 10⁹/l
- Blood gases (Room Air):
  - pH 7.48
  - pO₂ 105 mm Hg
  - pCO₂ 34 mm Hg
  - HCO₃ 22 mm/L
- Serology test
  - Mycoplasmal IgM, 1:128
Mycoplasmal Pneumonia

- Moxifloxacin 400 mg IV QD
- Fever subsided on the 3rd day
- No fever under oral Moxifloxacin
- Received a total 10 days moxifloxacin therapy
Case 2

- A 50-year-old male presented with fever, dyspnea and cough.
- Vital signs:
  - temperature 38.5°C, heart rate 125/min,
  - respiratory rate 22 breaths/min,
- Physical examination: no cyanosis; no orthopnea; no signs of respiratory distress.
- Diabetes under oral hyperglycemic agents for 5 years.
Laboratory findings

- white blood cell count 10.2 x 10⁹/L
- neutrophils 75%,
- Hb 10.8 g/dL
- Gram smear:
  - GPC rare
  - GNB 1+
Inpatient treatment

- The patient was treated empirically with 400 mg qd IV moxifloxacin
- Fever intermittently for 5 days
- Cough and dyspnoea persisted
- The patient is pale and appears unwell
Laboratory findings

- C-reactive protein 63 mg/L
- WBC count 10,620/µL
- Serology:
  - negative for HIV,
  - negative IgM for *Mycoplasma* spp.
- Urinary antigen test: negative for *Legionella* spp
- Sputum
  - Gram stain: no bacteria observed
  - Ziehl–Nielsen: positive for acid-fast bacilli

1 week later
INH, RIF, PZA, EMB for 1 wk

Anti-TB for 8 wk
CAP: Incidence and Outcomes

- The 6th leading cause of death in United States
- 2-3 million cases/year
- 500,000 admissions/year
- 45,000 deaths/year
- Mortality
  - Outpatient < 1%
  - Admit (ward) 10%-14%
  - ICU 30%-40%

Issues in CAP

**Diagnosis:**
- failure to differentiate etiology clinically and radiologically
- No study has reliably shown a correlation between clinical symptoms and/or chest radiograph and etiology.

**Etiology:**
- Not defined in 50% of patients
<table>
<thead>
<tr>
<th></th>
<th>Typical Pneumonia (Lobar pneumonia)</th>
<th>Atypical Pneumonia (Interstitial/infiltrative pneumonia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequent symptoms</strong></td>
<td>Fever/Chillness/Productive cough/Pleuritic chest pain</td>
<td>Fever/less chest pain or chillness/non-productive cough/headache/myalgia</td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
<td>Leukocytosis/may find pathogens in sputum culture</td>
<td>May or may not leukocytosis/Less frequent to find pathogen in sputum culture</td>
</tr>
<tr>
<td><strong>Pathogens</strong></td>
<td>Streptococcus pneumoniae H. Influenza M. Catarrhalis Gram negative bacilli</td>
<td>Chlamydia pneumoniae Mycoplasma pneumoniae Legionella pneumoniae Virus</td>
</tr>
</tbody>
</table>
Typical Pneumonia
( Lobar pneumonia )

Atypical Pneumonia
( Interstitial/infiltrative pneumonia )
The graph illustrates the percentage of cases of hospital-acquired community-acquired pneumonia (CAP) caused by various organisms. The most common causative agent is Streptococcus pneumoniae, followed by Chlamydia pneumoniae, Viral, Mycoplasma pneumoniae, Legionella spp., Haemophilus influenzae, Group B-ve enterobacteria, Coxiella burnetii, Staphylococcus aureus, Moraxella catarrhalis, and Other.

Pulmonary TB Presenting as CAP

Liam, CK, et al. Respirology. 2006;11:786–792
### Pulmonary TB Presenting as CAP

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom &gt;14 days</td>
<td>25.1</td>
<td>4.63-136.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Night sweats</td>
<td>5.45</td>
<td>1.1-26.79</td>
<td>.038</td>
</tr>
<tr>
<td>Upper lobe lesion</td>
<td>8.23</td>
<td>1.59-42.53</td>
<td>.012</td>
</tr>
<tr>
<td>Cavitary lesion</td>
<td>19.41</td>
<td>2.94-128.2</td>
<td>.002</td>
</tr>
<tr>
<td>WBC &lt;12000 /dl</td>
<td>6.28</td>
<td>1.21-32.52</td>
<td>.029</td>
</tr>
<tr>
<td>Lymphopenemia</td>
<td>4.73</td>
<td>1.08-20.85</td>
<td>.04</td>
</tr>
</tbody>
</table>

Liam, CK, et al. Respirology. 2006;11:786–792
The scope of tuberculosis

• Over 2 billion people (1/3 population) in the world are infected with *M. tuberculosis*
  – 10-15 million active tuberculosis cases
  – 3 million deaths each year.

• 22 countries carry 80% of world’s TB burden

• 54% of TB cases occur in Africa and Asia
Burden of Tuberculosis

WHO: Global health report 2009, fact sheet (per 100,000 persons)
Estimated TB incidence rate, 2006
New cases per 100,000 population

Estimated new TB cases (all forms) per 100,000 population:
- No estimate
- 0-24
- 25-49
- 50-99
- 100-299
- 300 or more
Micro-organism

- Mycobacterium tuberculosis
  - Slow-growing organism
  - Obligate aerobic
  - 4 ~ 8 weeks on solid medium
  - Remain stain after decoloration with acid alcohol
  - acid-fast stain
TB: Classic Clinical Presentation

- Insidious onset and chronic course
- Chest symptoms
  - Cough (usually productive)
  - Hemoptysis
  - Chest pain (usually pleuritic)
- Constitutional symptoms
  - Fever
  - Chills/sweats
  - Fatigue/malaise
  - Anorexia
  - Weight loss
Radiographic Presentations of Primary TB

- Middle and lower lobe infiltrates
- Ipsilateral adenopathy
- Pleural effusion
- Rare with cavitation
Radiographic Presentations of Reactivated TB

• 85% upper lobe infiltrates
• Often with cavitation
• Rare with adenopathy
The Predictive Value of CXR in Diagnosis of TB

<table>
<thead>
<tr>
<th>Score of the reader</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Highly consistent for TB</td>
<td>68 (64–72)</td>
<td>90 (87–93)</td>
<td>0.90 (0.87–0.93)</td>
<td>0.69 (0.65–0.72)</td>
</tr>
<tr>
<td>b) Consistent for TB</td>
<td>23 (19–26)</td>
<td>77 (73–80)</td>
<td>0.55 (0.49–0.62)</td>
<td>0.44 (0.40–0.47)</td>
</tr>
<tr>
<td>c) Pathology, but no TB</td>
<td>2 (0–3)</td>
<td>96 (94–98)</td>
<td>0.33 (0.16–0.51)</td>
<td>0.43 (0.40–0.46)</td>
</tr>
<tr>
<td>&quot;TB&quot; (a+b)</td>
<td>91 (88–93)</td>
<td>67 (62–71)</td>
<td>0.78 (0.74–0.81)</td>
<td>0.84 (0.81–0.88)</td>
</tr>
</tbody>
</table>

n=998

Infectious Diseases 2005, 5:111
X-ray-based evaluation causes over-diagnosis of TB

NTI, Ind J Tuberc, 1974
Sputum Examination

• AFB Smears
  – Ziehl-Nielsen, auramine-rhodamine
  – Rapid, ~50-70% sensitive, nonspecific (NTM)

• Culture
  – Sensitive and specific, but slow
  – Up to 20% “culture negative” TB

• Molecular methods
  – PCR of DNA or RNA

*Chest 1969;95:1193*
Sensitivity of Positive Results

- **Sputum smear:**
  - 5-10x10³ bacilli/ml
- **Sputum culture**
  - 10-100 bacilli/ml
- **TB PCR**
  - <10 bacilli/ml

JOURNAL OF CLINICAL MICROBIOLOGY. 2004,1012–1015
The Diagnosis for TB in Sputum-negative Patients

- Sputum induction
  - 3% saline inhalation
- Bronchoscopy
- CT-guided biopsy
- Open lung biopsy
Endobronchial Ultrasound (EBUS)

EBUS Improved TB Diagnostic Yield for Pulmonary TB

• 121 patients with active pulmonary TB
  – Negative-sputum AFB smear
  – Lack of spontaneous sputum

• Bronchoalveolar lavage:
  – AFB smear and culture for *M. tuberculosis*
  – Trans-bronchial lung biopsy (TBLB)

# The Yield of EBUS-guided Bronchial Lavage and Biopsy for Pulmonary TB

<table>
<thead>
<tr>
<th>Result</th>
<th>Without EBUS n=48</th>
<th>With EBUS n=73</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive BALF smear</td>
<td>6/48 (12.5%)</td>
<td>23/73 (31.5%)</td>
<td>.018</td>
</tr>
<tr>
<td>Positive BALF culture</td>
<td>23/48 (47.9%)</td>
<td>49/73 (67.1%)</td>
<td>.040</td>
</tr>
<tr>
<td>Positive TBLB</td>
<td>2/16 (12.5%)</td>
<td>24/49 (49.0%)</td>
<td>.017</td>
</tr>
<tr>
<td>Positive BALF smear, culture, or TBLB</td>
<td>29/48 (60.4%)</td>
<td>59/73 (80.8%)</td>
<td>.020</td>
</tr>
</tbody>
</table>

EBUS: Endobronchial ultrasound  
BALF: Bronchoalveolar lavage fluid  
TBLB: Trans-bronchial lung biopsy  

The first available results for diagnosis of pulmonary TB

• 99 patients with a positive culture for *M. tuberculosis* in their sputum or BALF
  – negative-sputum AFB smear
  – lack of spontaneous sputum

• Bronchoalveolar lavage:
  – AFB smear and culture for *M. tuberculosis*
  – Amplified Mycobacterium Tuberculosis Direct test, (Gen-Probe, USA)

Lin, SM. J Thorac Cardiovasc Surg 2010;139:1554-60
**EBUS Improved TB PCR Diagnostic Yield for Pulmonary TB**

<table>
<thead>
<tr>
<th>Test</th>
<th>With EBUS N=56</th>
<th>Without EBUS N=43</th>
<th>O.R.</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive BALF AMTD</td>
<td>50(89.3%)</td>
<td>28(65.1%)</td>
<td>4.46</td>
<td>1.56-12.81</td>
<td>.006</td>
</tr>
<tr>
<td>Positive AFB smear of BALF</td>
<td>17(30.4%)</td>
<td>4(9.3%)</td>
<td>4.25</td>
<td>1.31-13.78</td>
<td>.013</td>
</tr>
<tr>
<td>Positive BALF M. tuberculosis culture</td>
<td>38(67.9%)</td>
<td>20(46.5%)</td>
<td>2.43</td>
<td>1.07-5.53</td>
<td>.041</td>
</tr>
<tr>
<td>Positive sputum M. tuberculosis culture</td>
<td>24(42.9%)</td>
<td>24(55.8%)</td>
<td>0.59</td>
<td>0.27-1.32</td>
<td>.228</td>
</tr>
</tbody>
</table>

EBUS: Endobronchial ultrasound  
BALF: Bronchoalveolar lavage fluid  
AMTD: Amplified Mycobacterium Tuberculosis Direct test

EBUS Improved TB PCR Diagnostic Yield for Pulmonary TB

Culture positive
n=99

BAL without EBUS
N=43 (43.4%)
- BAL smear positive
  N=4 (9.3%)
- BALF PCR positive
  n=28 (65.1%)
- Only culture positive
  N=14 (32.6%)

BAL with EBUS
N=56 (56.6%)
- BAL smear positive
  N=17 (30.4%)
- BALF PCR positive
  n=50 (89.3%)
- Only culture positive
  N=5 (8.9%)

Summary

• Pulmonary TB may present as CAP
• Think TB if “high-risk” profile
• Sputum smear are negative in 50% of TB cases
• New TB diagnostic tests may improve on the sensitivity and specificity of TB diagnosis