Extrapulmonary tuberculosis: a challenging diagnosis?

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Definitions

- **Definite case of TB:**
  - A patient with *M. tuberculosis (MTB)* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay
  - In countries that lack the laboratory capacity to routinely identify MTB, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli

Ref: WHO, 2010
Definitions

- **Extrapulmonary tuberculosis (EPTB):**
  - Isolated occurrence of TB at body sites other than the lung

- **Extrapulmonary tuberculosis (EPTB) diagnosis:**
  - At least one specimen with confirmed M. tuberculosis or histological or strong clinical evidence consistent with active EPTB
  - Case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease
  - A patient with both PTB and EPTB should be classified as PTB

Ref: WHO, 2010
Epidemiology I

- EPTB prevalence in HIV-uninfected individuals

Ref: Sharma, Indian J Med Res 2004

EPTB prevalence 15-20%
Epidemiology II

- EPTB prevalence in HIV-infected individuals

Ref: Sharma, Indian J Med Res 2004

EPTB prevalence 70%
Pathogenesis I

HIV
Cancer
Immunosuppressive Rx
Anti-TNF treatment
Very young/old

IMMUNE SYSTEM

Cellular immunity
Pathogenesis II

Ref: Kaufmann, Nature Med 2011

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Pathogenesis III

(a) Mycobacterium tuberculosis
- Multivesicular bodies
- TLRs 2/6 (MACD)
- TLRs
- TNFα
- IL-1
- IL-6
- COX2
- IL-12
- IFNγ

(b) T_1_ lymphocyte
- TNFα
- IL-1
- IL-6
- IFNγ
- AP-1
- NFκB
- STAT1
- PPAR
- TNFα
- IL-12
- IFNγ
- TLR
- Noninfected macrophage
- Infected macrophage
- Foam cell
- Granuloma
- Infected macrophage

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Manifestations of EPTB

- EPTB involves organs other than the lungs:
  - Pleura
  - Lymph nodes
  - Abdomen
  - Genitourinary
  - Skin
  - Joints and bones
  - Meninges
  - Other: skin, eye
TB lymphadenitis
TB lymphadenitis

- King’s Evil or scrofula
TB lymphadenitis

- **Pathogenesis:**
  - MTB enters the body via the respiratory tract
  - Haematogenous and lymphatic dissemination
  - Hilar and mediastinal lymph nodes initially involved
  - Tonsil could also be an portal of entry with lymphatic spread to draining cervical lymph nodes
TB lymphadenitis

- **Staging:**
  - Stage 1: enlarged, firm mobile discrete nodes showing non-specific reactive hyperplasia
  - Stage 2: large rubbery nodes fixed to surrounding tissue owing to periadenitis
  - Stage 3: central softening due to abscess formation
  - Stage 4: collar-stud abscess formation
  - Stage 5: sinus tract formation
TB lymphadenitis

Stage 1-2

Stage 3
TB lymphadenitis

Stage 4

Stage 5

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Upper abdominal and mediastinal lymph nodes may cause
- Thoracic duct obstruction and chylothorax, chylous ascites or chyluria
- Obstructive jaundice
TB lymphadenitis

- **Diagnosis:**
  - FNA: smear microscopy, TB culture, histology, GeneXpert
  - Radiological findings
## TB lymphadenitis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FNA Xpert</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All culture positive cases</td>
<td>139/150 92.7 (86.9 – 96.1)</td>
<td>172/195 88.2 (82.3 – 96.1)*</td>
</tr>
<tr>
<td>CD4 &lt; 100</td>
<td>69/70 98.6 (91.2 – 99.9)</td>
<td>35/45 77.8 (62.5 – 88.3)</td>
</tr>
<tr>
<td>CD4 100 - 250</td>
<td>35/38 92.1 (77.5 – 97.9)</td>
<td>52/59 88.1 (76.5 – 94.7)</td>
</tr>
<tr>
<td>CD4 &gt; 250</td>
<td>20/24 83.3 (61.8 – 94.5)</td>
<td>63/64 98.4 (90.5 – 99.9)</td>
</tr>
<tr>
<td><strong>FNA auramine smear microscopy for AFB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All culture positive cases</td>
<td>59/147 40.1 (32.2 – 48.6)</td>
<td>188/193 97.5 (93.7 – 99.0)</td>
</tr>
<tr>
<td>CD4 &lt; 100</td>
<td>39/70 55.7 (43.4 – 67.4)</td>
<td>43/45 95.6 (83.6 – 99.2)</td>
</tr>
<tr>
<td>CD4 100 – 250</td>
<td>9/36 25.0 (12.7 – 42.6)</td>
<td>58/59 98.3 (89.7 – 99.9)</td>
</tr>
<tr>
<td>CD4 &gt; 250</td>
<td>4/23 17.4 (5.7 – 39.5)</td>
<td>63/64 98.4 (90.5 – 99.9)</td>
</tr>
<tr>
<td><strong>FNA cytology</strong></td>
<td></td>
<td></td>
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<tr>
<td>All culture positive cases</td>
<td>130/146 89.0 (82.5 – 93.4)</td>
<td>122/173 70.5 (63.0 – 77.1)</td>
</tr>
<tr>
<td>CD4 &lt; 100</td>
<td>62/69 89.9 (79.6 – 95.5)</td>
<td>19/37 51.4 (34.7 – 67.8)</td>
</tr>
<tr>
<td>CD4 100 – 250</td>
<td>30/35 85.7 (69.0 – 94.6)</td>
<td>42/54 77.8 (64.1 – 87.5)</td>
</tr>
<tr>
<td>CD4 &gt; 250</td>
<td>22/24 91.7 (71.5 – 98.5)</td>
<td>47/57 82.5 (69.6 – 90.8)</td>
</tr>
</tbody>
</table>

Ref: Van Rie, submitted
Pleural TB

- **Pathogenesis:**
  - Small subpleural focus ruptures into the pleural space
  - Interaction between tubercle bacilli or their specific components inducing a delayed hypersensitivity reaction
  - Rupture of a cavity into the pleural space results in empyema thoracis
Pleural TB

- Clinical features:
  - Acute illness, symptoms for few days – weeks
  - Pleuritic chest pain
  - Non-productive cough
  - Dyspnoea
  - Fever
Pleural TB

- **Physical examination:**
  - Digital clubbing
  - Decreased air entry
  - Dull percussion of chest
  - Friction rub
Pleural TB

- Diagnosis:
  - Imaging (CXR, sonar, CT-scan)
  - Pleural tap
    - Differential white cell counts
    - Total protein, LDH, glucose
    - Adenosine deaminase (ADA)
    - Smear microscopy, TB culture
    - (GeneXpert)
  - Pleural biopsy, thoracoscopy
**Pleural TB: ADA**

*ADA cut-off 40 U/L*
*In low TB prevalence setting lymphocyte proportion + ADA*

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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>Mean</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>CTPE</td>
<td>56.7</td>
<td>28.2</td>
<td>62.0</td>
<td>28.9</td>
</tr>
<tr>
<td>PTPE</td>
<td>64.2</td>
<td>16.2</td>
<td>63.1</td>
<td>16.0</td>
</tr>
<tr>
<td>CPE</td>
<td>64.8</td>
<td>42.3</td>
<td>71.6</td>
<td>62.1</td>
</tr>
<tr>
<td>UPE</td>
<td>21.8</td>
<td>10.5</td>
<td>14.2</td>
<td>7.7</td>
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<tr>
<td>Malignant</td>
<td>21.4</td>
<td>23.7</td>
<td>14.9</td>
<td>8.5</td>
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<tr>
<td>Miscellaneous</td>
<td>19.5</td>
<td>18.9</td>
<td>20.6</td>
<td>41.6</td>
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<tr>
<td>Transudative</td>
<td>9.7</td>
<td>5.3</td>
<td>6.2</td>
<td>2.7</td>
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<tr>
<td>Undiagnosed</td>
<td>19.0</td>
<td>8.5</td>
<td>12.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Total</td>
<td>28.4</td>
<td>26.9</td>
<td>31.2</td>
<td>32.4</td>
</tr>
</tbody>
</table>


CTPE: confirmed pleural tuberculosis; PTPE: probable pleural tuberculosis; CPE: complicated parapneumonic effusion; UPE: uncomplicated parapneumonic effusion.

Ref: Garcia-Zamalloa, PLoS One 2012
### Pleural TB: Xpert MTB/RIF

#### Diagnostic accuracy of assays used on samples from 20 TB and 5 non-TB patients

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of samples that were:</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Not done</td>
</tr>
<tr>
<td>Pleural fluid ADA</td>
<td>22</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pleural biopsy specimen histology/ZN microscopy/liquid culture</td>
<td>18</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Sputum smear microscopy</td>
<td>6</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Pleural fluid liquid culture</td>
<td>9</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pleural fluid Xpert assay</td>
<td>5</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Ref: Friedrich, JCM 2011
Abdominal TB

- TB of the gastrointestinal tract, peritoneum, omentum, mesentery, and its nodes and other solid intra-abdominal organs such as liver, spleen and pancreas

- **Pathogenesis:**
  - Haematogenous spread from primary lung focus in childhood, with later reactivation
  - Ingestion of bacilli in sputum
  - Direct spread from adjacent organs
  - Lymphatic spread
Abdominal TB

❖ **Clinical manifestations:**
  ❖ Non-specific, anorexia, fever, night sweats, pain, diarrhoea, jaundice

❖ **Diagnosis:**
  ❖ Imaging (CXR, plain X-ray abdomen, barium enema, sonar, CT abdomen
  ❖ Colonoscopy
  ❖ Laparoscopy
  ❖ Ascites
Abdominal TB

- **Sonar findings in gastro-intestinal and peritoneal TB**
  - Free or loculated intra-abdominal fluid
  - “Sliced bread sign”
  - Lymphadenopathy (mixed, heterogeneous)
  - Bowel wall thickening
  - Pseudokidney sign

Ref: Kedar, Clin Radiol 1994
Abdominal TB

- Prospective study
- 32 HIV-infected patients with prolonged fever
- High-resolution sonar multiple splenic microabcesses
- NB. Conventional sonar no splenic abnormalities
- Diagnoses:
  - 14 TB
  - 7 visceral leishmaniasis
  - 5 disseminated *M. avium*
  - 2 Salmonella spp. Sepsis
  - 2 lymphoma
  - other

Ref: Bernabeu-Wittel, Eur J Clin Microbiol Infect Dis 1999
Multiple Lesions of the Spleen: Differential Diagnosis of Cystic and Solid Lesions

Aya Kamaya, MD, Stefanie Weinstein, MD, and Terry S. Desser, MD
Neurological TB

- Classified in three clinico-pathological categories
  - TB meningitis (TBM) (70-80% of cases)
  - Tuberculoma (5-10%)
  - Arachnoiditis (5-10%)

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TB meningitis

Critical event is the rupture of a subependymally located tubercle (Rich focus) resulting in the release of infectious material into the subarachnoid space.
TB meningitis

- Highest incidence in the first three years of life
- Gradual disease over 2-6 weeks
- Vague ill-health, apathy, behavioral changes, anorexia
- Later headache, vomiting and fever
- Focal neurological symptoms or seizures (20-30%)
TB meningitis

- **Diagnosis:**
  - Imaging
  - CSF investigation
    - Differential cell count, protein, glucose, ADA
    - TB microscopy/culture
    - (GeneXpert MTB/RIF)
Yield TB work-up body fluids

Table IV. Yield of various tissues and body fluid specimens by the conventional smear and culture methods in patients with extrapulmonary tuberculosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pleural fluid</th>
<th>Pericardial fluid</th>
<th>Cerebrospinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear microscopy</td>
<td>&lt; 10%</td>
<td>&lt; 1%</td>
<td>5-37%</td>
</tr>
<tr>
<td>Mycobacterial culture</td>
<td>12-70%</td>
<td>25-60%</td>
<td>40-80%</td>
</tr>
</tbody>
</table>

Data derived from references 71-75, 84-86, 88, 104, 113, 115, 117, 180

Ref: Sharma, Indian J Med Res 2004
Better tools?
GeneXpert MTB/RIF

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Urine LAM assay

- Urine dipstick test, test result in 25 minutes
- Antigen detection based on lipoarabinomannan (LAM)
- Major lipopolysaccharide component of MTB cell wall
- Sensitivity 13-93%, specificity 87-99% (overall)
- Sensitivity better in HIV+ with advance immunosuppression
- Most studies in pulmonary TB

Ref: Lawn, Lancet 2011
Urine LAM assay
Treatment

Recommendation 1.1
New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR

(Strong/High grade of evidence)

Remark a: Recommendation 1.1 also applies to extrapulmonary TB except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy (see Chapter 8).

Ref: WHO, 2010
Pulmonary and extrapulmonary disease should be treated with the same regimens (see Chapter 3). Note that some experts recommend 9–12 months of treatment for TB meningitis (2, 3) given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response (3). Unless drug resistance is suspected, adjuvant corticosteroid treatment...

Although many fewer treatment studies have examined treatment of extrapulmonary tuberculosis, compared with pulmonary disease, increasing evidence, including some randomized controlled trials, suggests that 6- to 9-month regimens that include INH and RIF are effective (2–16). Therefore, among patients...
Treatment monitoring

- Clinically
- Weight
- X-ray changes are poor indicator of clinical response
- If poor response to treatment:
  - Alternative diagnosis?
  - Drug-resistant TB?
Take home messages

- Making EPTB diagnosis can be challenging
- Don’t be satisfied with a probable TB diagnosis
- Always collect a sputum specimen
- Rapid diagnostic tests (Xpert, LAM) are on the move
Thank you