Extra-pulmonary forms of Tuberculosis 2010-2013

ד"ר בן דיין דני איל
מחלקת ריותות שחפת
ב"ח שעמואל הרופא
Patient 1

- A 35 Israeli young man
- Treated by Humera for 6 months (Ankylosing Spondylitis)
- PPD: 11 mm. No preventive treatment
- Presenting symptoms: prolonged fever, diarrhea, abdominal pain, weight loss, sweating,
- Abdominal CT: Lymphadenopathy and thickening of terminal ileum
- Colonoscopy and Biopsy:

Non Caseiting Granuloma
Patient 1

- **Crohn disease**: Prednisone and Imuran
- Decreased fever for 2 weeks - slight improvement
- **Symptom rebound**: Fever, pain and diarrhea
- **MTB culture from ileum biopsy**
Patient 1

- **At presentation**: General deterioration with fever, chilling, profuse diarrhea and vomiting

- **Physical examination**: Sensitive abdominal distension, ascites

- **Laboratory**: Severe malabsorption: hypo-albuminemia- (1.6 mg), anemia (HB: 8.5 g/dl) Chol: 80mg-, TG: 92

- **Abdominal Xray**: partial obstruction

- **Chest CT**: LUL cavitation

- **Sputum**: Genexpert +
Patient 1

- TPN
- Anti TB treatment low and progressive doses.
- Clinical improvement (decreased fever)
- Laboratory improvement
- Discharge

Dg: Abdominal (ileocaecal) and pulmonary TB
    Anti-TNF treatment
Patient 2

- Young Erythrea patient
- HIV negative
- Fever, abdominal pain, sweating, weight loss for 3 months
- Physical examination: abdominal distension, ascites
  Swollen mass RT abdomen
Patient 2

- **Ascites**: fluid: LY, ADA +, smear negative - Genexpert negative
- **Abdominal mass**: drainage under US: purulent fluid
  No diagnostic (AFB, Genexpert, Culture negative)
- **Chest Xray**: normal. Negative sputum
- **ATT treatment** with progressive improvement (after few weeks the fever decreased, decrease amount of ascites ...)
- Repeated mass drainage because pain and local pressure

- **Dg**: Isolated Abdominal TB with RT abscess
  (No pulmonary infection)
Extra pulmonary TB: Risk factors

- Frequent in immuno-compromised patients (41% vs 20%)
- Frequent in females - young people - foreign born
- EPTB increased (7.6% - 20% in USA)
Distribution of EPTB:

Shmuel Harofe hospital (2010-2013) 121 pts (15%)

- Pleura: 47%
- Abdominal: 35%
- Bone: 14%
- CNS: 4%
- Soft tissue: 6%
<table>
<thead>
<tr>
<th>Characteristics (2010-2013)</th>
<th>Pleural</th>
<th>Abdominal</th>
<th>Bone</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56 (46%)</td>
<td>42 (34%)</td>
<td>18 (14%)</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

**Origin:**
- Israel: 3 (60%)
- FSU: 1 (20%)
- Ethiopia: 2 (40%)
- African refugee: 50 (89%)

**Age:**
- <40: 47 (85%)

**Gender**
- F/M: 16/40

**HIV status**
- Positive: No

**Immunosuppression:**
- No
➢ Which factors are associated with extra pulmonary dissemination?

➢ Which factors are associated with a special organ involvement?

Host Pathogen Interaction
Molecular characterization of MTB has revealed 4 lineages of MTB
Genetic diversity may be relevant to clinical disease
*M tuberculosis* has a clonal genetic population structure that is geographically constrained. Evidence suggests strain specific differences in virulence and immunogenicity in light of this global phylogeography.
The Beijing family

Appears to be more virulent, more transmissible & associated with MDR

Global dissemination of the *Mycobacterium tuberculosis* W-Beijing family strains

Pablo J. Bifani, Barun Mathema, Natalia E. Kurepina and Barry N. Kreiswirth

A large, genetically related group of *Mycobacterium tuberculosis* strains, variously called W or Beijing, is distinguished by specific molecular markers and referred to as the W-Beijing family strains. Molecular epidemiological studies suggest that these strains are highly prevalent throughout Asia and the countries of the former Soviet Union and they have also been reported in several other geographical regions, including North America. Although the spread of W-Beijing family strains in diverse populations is well documented, the underlying host-pathogen factors accounting for their continued dissemination and burden of disease have yet to be determined.

TRENDS in Microbiology
Vol.10 No.1 January 2002
45-52
There is a relation between lineage and site of disease, (not attributable to host nutrition status, HIV infection or BCG vaccination)
Host pathogen interaction

Strains of *M. tuberculosis* commonly found in Europe and America are less likely to cause tuberculous meningitis in Vietnamese adults than strains predominantly found in Asia.

<table>
<thead>
<tr>
<th>Group</th>
<th>All isolates (%)</th>
<th>Pulmonary tuberculosis (%)</th>
<th>TBM (%)</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>OR [95% CI]$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asian (RD105 deleted)</td>
<td>168 (39.9)</td>
<td>87 (37.2)</td>
<td>81 (43.3)</td>
<td>1.631</td>
<td>0.20</td>
<td>1.29 [0.87-1.91]</td>
</tr>
<tr>
<td>Indo-Oceanic (RD239 deleted)</td>
<td>192 (45.6)</td>
<td>104 (44.4)</td>
<td>88 (47.1)</td>
<td>0.286</td>
<td>0.598</td>
<td>1.11 [0.76-1.63]</td>
</tr>
<tr>
<td>Euro-American (pks 15/1 047 bp)</td>
<td>43 (10.2)</td>
<td>32 (13.7)</td>
<td>11 (5.9)</td>
<td>6.88</td>
<td>0.009</td>
<td>0.40 [0.19-0.81]</td>
</tr>
<tr>
<td>Undefined$^a$</td>
<td>18 (4.3)</td>
<td>11 (4.7)</td>
<td>7 (3.7)</td>
<td>0.232</td>
<td>0.629</td>
<td>0.79 [0.30-2.08]</td>
</tr>
<tr>
<td>Total</td>
<td>421 (100)</td>
<td>234 (100)</td>
<td>187 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Undefined isolates failed to generate a product on repeated PCR for one of the two RD regions despite generating product for other PCRs; it is likely these isolates carried additional deletions or mutations in the primer region.

$^b$ Odds ratio was calculated comparing the meningeal and pulmonary proportions for each lineage.

doi:10.1371/journal.ppat.1000341.t003

Physiologic response to *M. tuberculosis* increases the risk to develop disseminated Disease
Black race, sex, and extrapulmonary tuberculosis risk: an observational study

*BMC Infect Dis. 2010; 10: 16*

Increased risk of EPTB in black people compared to non-blacks (may be due to incidence 8-fold higher in U.S.-born blacks than U.S.-born whites and HIV)
Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis

Y. Gonzalez,* G. Adams,† L. D. Teeter,† T. T. Bui,† J. M. Musser,†‡ E. A. Graviss*†

INT J TUBERC LUNG DIS 2003 7(12):1178-1185

- 4-year cohort of EPTB patients was compared with PTB cases. EPTB 28.6% /1878 cases. The most common: lymph nodes (43%) and pleura (23%).

- 5-fold increase in rates of extrapulmonary TB in blacks compared to whites (6.5 vs 1.3 per 100,000 population)

- This ethnic group may have increased susceptibility to tuberculosis, indicating an interaction between genetics, immunity, and environment in the pathogenesis of TB.

- Bellamy et al. (cohort from western Africa) found a significant increase in the frequency of natural resistance-associated macrophage protein 1 (Nramp 1) polymorphism among patients with EPTB.
EPTB

- MTB genotype influences TB phenotype

- Different lineages of tuberculosis have different clinical site, different pathogenicity, response to drug therapy

- Host susceptibility

- Studies on host susceptibility and pathogen virulence- vaccine
### Distribution of EPTB

**Table 2 Distribution of extrapulmonary tuberculosis cases by site of disease**

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Number of persons (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary$^a$</td>
<td>564 (100.0)</td>
</tr>
<tr>
<td>Lymphatic$^b$</td>
<td>183 (32.4)</td>
</tr>
<tr>
<td>Pleural</td>
<td>153 (27.1)</td>
</tr>
<tr>
<td>Bone</td>
<td>63 (11.2)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>31 (5.5)</td>
</tr>
<tr>
<td>Miliary</td>
<td>31 (5.5)</td>
</tr>
<tr>
<td>Meningeal</td>
<td>24 (4.2)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>17 (3.0)</td>
</tr>
<tr>
<td>Other</td>
<td>78 (13.8)</td>
</tr>
</tbody>
</table>

$^a$Extrapulmonary = extrapulmonary only or extrapulmonary + pulmonary

$^b$Proportion of extrapulmonary cases
Abdominal TB: Epidemiology

- Abdominal tuberculosis was common in the United States early in the 20th century. (Most common cause of small intestinal obstruction and stricture)

- By the middle of the 20th century, all forms of tuberculosis had declined dramatically. (Increased standard of living, pasteurization of milk, control of bovine tuberculosis, and introduction of antituberculous treatment)

- 1960s: “rare” or Third World disease.

- 1985: AIDS increased high occurrence of abdominal tuberculosis was high proportion of extrapulmonary disease (25%)
Pathogenesis of abdominal TB

Ingestion of contaminated milk products

Hematogenous spread from pulmonary focus

Mode of infection

Direct spread from adjacent organs

Swallowing of infected sputum
Abdominal TB: characteristics

Abdominal TB

- Peritoneal
- Intestinal
- Nodal
- Solid/Visceral
## Abdominal TB: Location and Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>AFB</th>
<th>GENXPERT</th>
<th>ADA</th>
<th>MTB</th>
<th>Granuloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peritonitis</strong> <em>(60% (Ascites))</em></td>
<td>5%</td>
<td>No</td>
<td>40%</td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Lymph nodes</strong> <em>(80%)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Abscess</strong> <em>(40%)</em></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>20%</td>
<td>No</td>
</tr>
<tr>
<td><strong>Ileo Caecum</strong> <em>(16%)</em></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>50%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Kidney</strong> <em>(4%)</em></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes <em>(50%)</em></td>
</tr>
</tbody>
</table>
Abdominal TB: characteristics

- Pulmonary: 61%
- Diarrhea: 42%
- Abdominal distention: 50%
- Weight loss: 52%
- Ascites: 60%
- Fever: 76%
- Abdominal pain: 80%
Abdominal TB - problems:

- **Diagnosis challenge**
  - Mimic other disease
  - Non specific clinical presentation

- **Complications (diagnosis delay):**
  - Perforation
  - Obstruction
  - Bleeding
  - Malabsorption

- **Role of surgery?**
Peritonitis TB: Diagnosis

- **Ascites**: smear, PCR and culture have extremely low sensitivity (<5% in most studies)
  - Lymphocytic exudate usually present
  - Adenosine Deaminase elevated in ascites
  - In one meta-analysis, ADA levels showed high sensitivity (100%) and specificity (97%)
- **CA 125** may be elevated (mimicking ovarian CA)

- **Tissue biopsy usually needed**
  - Omentum or lymph nodes
  - Granulomas (usually caseating)
  - Thickened peritoneum with tubercles
Intestinal TB: Diagnosis

- The ileocecal region is the most common area of involvement in the GIT due to the abundance of lymphoid tissue

- **Colonoscopy:**
  - **Nodules (hypertrophic):** Most common in caecum especially near IC valve
  - **Ulcers:** Located between the nodules (Transversely oriented / circumferential contrast to Crohns)
  - **Strictures:** Healing of these ‘girdle ulcers’
### Table II. Relationship between localization of extrapulmonary tuberculosis and diagnostic procedure

<table>
<thead>
<tr>
<th>Localization</th>
<th>n</th>
<th>Culture</th>
<th>Smear</th>
<th>Path.</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node, peripheral</td>
<td>15</td>
<td>10 (2)</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9</td>
<td>7 (1)</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Psoas abscess</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node, retroperitoneal</td>
<td>3</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lymph node, mesenterial</td>
<td>3</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lymph node, mediastinal</td>
<td>4</td>
<td>3</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3</td>
<td>3 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Articular and osteogenic</td>
<td>3</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>35</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Some samples were both culture and polymerase chain reaction (PCR) positive; numbers shown in parentheses. Path., pathology.
Abdominal TB-diagnosis

- Abdominal TB diagnosis
  - Pulm
  - Ascites
  - Colonoscopy
  - Laparoscopy
Prognosis of ATB

- Good response to treatment

- Median hospitalization time: 1 month

- 1 death from perforation (heart transplant patient)

- Treatment for 1 y
CNS-TB

- The most severe and lethal complications
  5-10% of extra pulmonary TB cases
  Due to the hematogenous spread of the bacilli.

- Epidemiology:
  - Infants
  - Immunosuppressed: 10-20% AIDS-TB
  - Miliary tuberculosis

- Neurological sequels are common
- Mortality rate remains high
- Not specific clinical presentation and radiological features
Hematogenous spread of the tubercles bacilli

Tubercules (Rich Foci) brain and spinal cord (1st infection)

Rupture
(subarachnoid space - ventricular region)

Enlarge (into the brain)

Meningitis

Tuberculomas Abscess
CNS-TB: characteristics

- Patients (2005-2014): 24
- HIV Infection (60%)
- Females (60%)
- Origin: FSU: 4
  - African: 14
  - Other: 2
Presenting symptoms: 80% Fever- headache
10% CNS TB appeared during the first months of pulmonary TB treatment (IRIS)
25% no evidence of Pulmonary TB
Frequent Rx features: cavitation and diffuse infiltrates
3 pts with miliary TB ....
MRI gadolinium-enhanced:
Factors associated with mortality (35%)
Treatment and Outcome

- Anti-tuberculosis treatment period of 12 months with adjunctive dexamethasone (2 months)

- No neurosurgical therapy was performed, not even in cases of increased intra cerebral pressure

- 38% with neurological sequels i.e. gait abnormality hemiparesis and cranial nerve palsy
EPTB

- **Diagnostic challenge** - High index of suspicion specially in foreign workers
  Inaccessible site and small no of bacilli
  More sensitive laboratory tools: AFB and culture negative

- **Treatment delay** - Variety of presentations and insidious onset - complications

- **Lack of association with HIV** except for CNS-TB

- High frequency in *African Refugees* - other screening of foreign workers and HIV infection
Case 1

- 27 old year man - Erythrea
- Active Pulmonary Tuberculosis
- DST: INH and Strepto resistant

- HIV + CD4=150 cells
- Anti TB therapy 9 months (outpatient clinic)
- Negative sputum culture - no HAART
Case 1

- 10 months later: general convulsions.
- Hemiplegia and aphasia
- No new change in Chest CT
- Brain biopsy: tuberculomas positive PCR
- Genotype:
Case 1

- Anti TB, high dose steroids HAART
- Physiotherapy
- Clinical stabilization

- 2 months later, neurological deterioration - stupor
- Brain CT: edemas, new lesions
- Neurosurgeon: non invasive therapy - no additional brain biopsy, no surgery
- Other opportunistic infection treatment
- CD4: 100 cells Suspected resistance to EFV that was changed to kaletra
- High dose mannitol
- Coma and death
Case 2

- 36 young woman, FSU
- HIV not treated CD4 : 50 cells
- Denied any risk factors
- Fever in the last month. No cough
- General seizure- no coma
- CSF: no meningitis
- Brain CT
Case 2

- Brain biopsy: granuloma - positive gene expert
- Resistance to RFP ------ MDR-TB
- Treatment: anti MDR-TB treatment
  - Steroids
  - Antiepileptic therapy
- After TB stabilisation- HAART
Comparison by ethnicity

- **Foreign-born**
  - CNS-TB cases
  - PTB cases

- **Canadian Aboriginal**
  - CNS-TB cases
  - PTB cases

- **Canadian non-Aboriginal**
  - CNS-TB cases
  - PTB cases

Year of diagnosis:
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000