Tuberculous Lymphadenitis

and the role of *M. bovis*
The King’s Evil
Introduction

- TB lymphadenitis refers to involvement of lymph nodes by members of the *M. tuberculosis* complex which include *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti* and *M. caprae*.
- It may be associated with pulmonary TB or other organ involvement but is usually an isolated finding-20% of all TB cases are extrapulmonary TB
Case 1

- 32 year old female who emigrated from Vietnam in 1994 was being treated for Hepatitis B with Lamivudine when she developed painful swelling in her right supraclavicular region in January 09.

- She underwent a lymph node biopsy in February 09 which revealed caseating necrosis and cultures were positive for *M. tuberculosis*.
Case 1 - 3/11/09
Epidemiology

- In the US, non-tuberculous mycobacteria are the most common cause of mycobacterial lymphadenitis in children
- Per the CDC 2000 surveillance, extrapulmonary TB (EPTB) rates have not declined in the US like Pulmonary TB (PTB) - 0.9% Vs 4%
- HIV positive patients with MTB are more likely to have EPTB than HIV negative patients – 45-70% Vs 15%
Epidemiology

- In HIV positive patients TBLN is associated with CD4 < 300 (usually <100)
- A US based study in Houston revealed the following characteristics in HIV negative patients:
  - Predictive factors: Female (OR 2.6), birth in Africa/SE Asia (OR 4.6/33.7)
  - Protective factors: White Race (OR 0.1) and Diabetes Mellitus (OR 0.3)
## Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Extrathoracic TBLN</th>
<th>PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Asian &gt; African</td>
<td>Africa &gt; Asia</td>
</tr>
<tr>
<td><strong>Drug Resistance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>10%</td>
<td>10-11% Non US born</td>
</tr>
<tr>
<td>MDR</td>
<td>1.4%</td>
<td>1-2%</td>
</tr>
<tr>
<td>XDR</td>
<td>rare</td>
<td>Rare</td>
</tr>
<tr>
<td>BCG vaccinated</td>
<td>37%</td>
<td>21%</td>
</tr>
<tr>
<td>HIV positive</td>
<td>&lt;1% - 5%</td>
<td>12% positive</td>
</tr>
</tbody>
</table>
Pathogenesis

- 3 suspected routes:
  1) Reactivation of PTB or hilar extension is most common
  2) Deep cervical involvement from laryngeal infection
  3) Hematogenous
Histo-pathology

4 distinct cytological patterns noted on aspirate, ranging from

- Pattern 1: occasional granulomas with early epitheloid cells, extensive necrosis and foam cells, numerous AFB- seen in HIV positive patients with TBLN

- Pattern 4: Numerous granulomata with most epitheloid cells and minimal necrosis + absence of AFB mostly- seen in HIV negative patients with TBLN
Clinical features

- Pediatric TBLN is mostly an isolated infection in the anterior cervical chain.
- Adult infection is similar with 70% anterior cervical chain - 58% of which is in the jugulodigastric region.
- HIV co-infection is associated with a more severe/disseminated disease.
# Clinical Differences between TBLN and Pulmonary TB

<table>
<thead>
<tr>
<th></th>
<th>TBLN</th>
<th>PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum culture</td>
<td>12%</td>
<td>64%</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough &gt; 2 weeks</td>
<td>26%</td>
<td>50-66% in reactivation</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever &gt; 2 weeks</td>
<td>19%</td>
<td>70% in Primary, 50% in Reactivation TB</td>
</tr>
<tr>
<td>Wt loss</td>
<td>17%</td>
<td>43%</td>
</tr>
<tr>
<td>Night sweats &gt; 2 weeks</td>
<td>19%</td>
<td>72%</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>49%</td>
<td>65% in primary TB and 80-90% in secondary TB</td>
</tr>
</tbody>
</table>
Clinical Features

- Abnormal CXR did not correlate with sputum positivity but wt loss did (OR 4.3)
- Disease associations: Chronic granulomatous disease, lymphoma, HIV
- Diabetes, Renal Insufficiency and Alcoholism and low iron and Vitamin D levels are also associated with MTB
Diagnosis

- About 20% have positive sputum cultures but only 9-15% had positive AFB sputum smears.

- Biopsy is the gold standard for diagnosis

- FNA biopsy lead to TB diagnosis in 79% of cases compared to surgical biopsy in 83%

- Histology more sensitive than culture (OR 11.9)
Diagnosis

- Nucleic acid amplification tests for TB lymphadenitis are rapid but yield variable and inconsistent results.

- Immune based blood tests include T cell based cellular response (IGRA- Interferon Gamma Release Assay) and humoral antibody response.
Treatment

- Drug resistance in 13% of 147 cases of TBLN in Manitoba – only in foreign born
- Standard per British Thoracic Society for uncomplicated TBLN – Rifampin+ Isoniazid+ Ethambutol for 2 months followed by Isonizid and Ethambutol for 6 months
- Standard abbreviations include: S = streptomycin, H or INH= isoniazid, R or RFM= Rifampin, Z or PZA= Pyrazinamide, E = Ethambutol
Treatment

- Extend to 6-12 months if LN persists, rebiopsy and place on a CAT II regimen: 2 months of SHRZE then 1 month of RHZE followed by 5 months of RHE
- Alternate regimen is 4RHZE + 2 RH: 5 year remission rate was 89%
- Steroids not recommended by IDSA currently (Evidence DIII) however has had anecdotal benefit
Treatment

- Steroids decrease pain and discomfort anecdotally though these outcomes have not been studied in larger trials.

- Surgery has no role for MTB unlike non TB mycobacteria (Evidence BIII per IDSA)

- Interferon gamma and GCSF are under investigation
Paradoxical Response (PR)

- Defined as development of enlarging nodes or new nodes during treatment; seen in 23-30%
- Among HIV negative patients: Baseline peripheral monocytosis is a significant predictor for PR but NOT age, sex, node size, low Vitamin D, AFB smear/culture positive, ANC or ALC.
Case 1 0 4/2/09
Paradoxical Response

- Among HIV positive patients: PRs noted in 7% not on HAART Vs 36% on HAART.

- Steroid use did not change duration of PRs.

- Aspiration, I&D and excision were associated with a shorter duration of PR but not significantly so (p=0.1).
Outcomes

- Cure rates vary from 81% - 95% with surgery + Anti TB regimen for 12-18 months
- Relapse rates noted to be 8.1 per 1000 person yrs of follow up
- Residual palpable adenopathy in 5-30% of cases
- Spontaneous drainage in 17%
Implications

- TBLN even in the absence of pulmonary symptoms carries an infection risk as they may have Pulmonary TB and should be placed under respiratory precautions till pulmonary TB is ruled out.

- Caution: Risk of transmission is 13% in smear negative but sputum culture positive patients
An alternate pathogen

The BCG vaccine, which has been derived from *M. bovis* has also been associated with infection in immunocompromised patients—especially children with Chronic Granulomatous Disease.
**M. bovis**

- *M. bovis* is associated with bovine TB and spreads to humans via infected dairy products and direct droplet spread.
- A study in San Diego revealed a rise in incidence of *M. bovis* from 5 to 11% from 1994-2005.
- *M. bovis* is more commonly associated with TBLN than with pulmonary TB (16% of all TBLN cases vs 4% of all pulmonary TB cases).
**M. bovis**

- Clinically: it is indistinguishable from *M. tuberculosis* however is more frequently associated with TBLN and with treatment failures.

- Diagnosis: The commonly used MTB probe cannot distinguish between different variants of MTB and it is often underdiagnosed. It has an intrinsic resistance to Pyrazinamide (PZA) and should be suspected whenever sensitivity results reveal a mono-resistance to PZA.
M. bovis and HIV

- HIV positive patients with *M. bovis* were more likely to have lymphadenitis (63%) compared to their HIV negative cohort (50%)
- HIV positive patients had a PPD reaction that was 1/10 that of the cut off for MTB (≥5 mm)
Treatment for M. bovis

- Due to its intrinsic resistance to PZA, the standard 6 month regimen for MTB is not feasible.
- Standard treatment includes Isoniazid (INH), Rifampin (RFM) and Ethambutol for 2 months followed by INH + RFM for seven months.
- Streptomycin can been added instead of PZA.
Prognosis and Implications

- Persons with *M. bovis* are 2.55 times as likely to die during treatment than those with *M. tuberculosis*
- An outbreak of *M. bovis* in patients with advanced HIV in 1994 had a 100% case fatality
Summary and Recommendations

- Test all patients with peripheral lymphadenopathy and TB risk factors for MTB: PPD, FNA, CXR and HIV test if positive for MTB
- If histology consistent with TB then start treatment pending cultures
- If cultures negative then perform excisional biopsy
- If persistent paradoxical response, repeat FNA and extend treatment
- Consider steroids for symptomatic relief
- Standard treatment regimens are of 6 months but often extended to 18 months based on clinical response.
Special Thanks to
Dr. Ford Von Reyn
Dr. Elizabeth Talbot
Dr. J F Fontanilla
Dr. J Parsonnet
for both past and ongoing input


   *Int J Tuberc Lung Dis* 2006, 10:1117-1122


Sridhar CB, Kini U, Subhash K. Comparative cytological study of lymph node tuberculosis in HIV-infected individuals and in patients with diabetes in a developing country. Diagn Cytopathol 2002;26:75-80


Hofmeyr A, Eddie Lau WF, Slavin MA. Mycobacterium tuberculosis infection in patients with cancer, the role of 18-fluorodeoxyglucose positron emission tomography for diagnosis and monitoring treatment response. Tuberculosis (Edinb). 2007 Jul 11


Rodwell TC; Moore M; Moser KS; Brodine SK; Strathdee SA Tuberculosis from Mycobacterium bovis in binational communities, United States. Emerg Infect Dis. 2008 Jun;14(6):909-16.

Guerrero A; Cobo J; Fortun J; Navas E; Quereda C; Asensio A; Canon J; Blazquez J; Gomez-Mampaso E Nosocomial transmission of Mycobacterium bovis resistant to 11 drugs in people with advanced HIV-1 infection. SOLanct. 1997 Dec 13;350(9093):1738-42.