Tuberculosis/HIV infection

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HIV and TB

- TB is the most common opportunistic infection in HIV infection and the first cause of mortality in HIV infected (10-30%)

- 10 millions patients co infected in the world.
  11% in children (85% in SubSaharan Africa)

- Immunosuppression induced by HIV modifies the clinical presentation of TB:
  1. Subnormal clinical and roentgen presentation
  2. High rate of MDR/XDR
  3. High rate of treatment failure and relapse (5% vs < 1% in HIV - )
Case 1

- A 33 year old woman, Ukraine origin

Presenting symptoms:
1. Fever 39°-40° 1 month
2. Dry cough - abdominal pain

In the past:
1. 10 years ago: “pleuritis”, pleural punctation
2. Intra venous drug addict
3. HIV test negative 6 years ago

Physical examination:
1. Febrile, left pulmonary ronchus
2. Enlarged liver firm, non tender (7cm below the Rt costal margin)
### Laboratory Results

<table>
<thead>
<tr>
<th>ESR</th>
<th>Hb</th>
<th>WBC</th>
<th>PMN</th>
<th>LY</th>
<th>PLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>9 g/dl</td>
<td>7200</td>
<td>81 %</td>
<td>7%</td>
<td>291.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$10^3/\mu\text{L}$</td>
<td></td>
<td></td>
<td>$10^3/\mu\text{L}$</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Natrium</th>
<th>Potassium</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Protein</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>131 meq/L</td>
<td>3.8 meq/L</td>
<td>29 mg</td>
<td>0.6 mg</td>
<td>6.9 gr</td>
<td>2.9 gr</td>
</tr>
<tr>
<td>(135-145)</td>
<td>(3.5–5.1)</td>
<td>(10-45)</td>
<td>(0.7-1.2)</td>
<td>(6-8)</td>
<td>(3.5-5.5)</td>
</tr>
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<tr>
<th>Alkal Phosph</th>
<th>γ GT</th>
<th>SGOT</th>
<th>SGPT</th>
<th>Bilirubine</th>
<th>PT-PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980 IU</td>
<td>1138 IU</td>
<td>42 IU</td>
<td>78 IU</td>
<td>1 mg</td>
<td>N</td>
</tr>
<tr>
<td>(100-290)</td>
<td>(11-39)</td>
<td>(9-37)</td>
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Case 1
Case 1

Abdominal CT: diffuse hepatic infiltration
Needle Core Biopsy: granulomas hepatitis
### Case 1

<table>
<thead>
<tr>
<th>HIV (Elisa +WB)</th>
<th>CD4 Cells / µL</th>
<th>VL</th>
<th>HBs Ag</th>
<th>HCV Ab</th>
<th>VDRL IGg</th>
<th>Blood culture</th>
<th>Sputum</th>
</tr>
</thead>
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<tr>
<td>+</td>
<td>495 (15%)</td>
<td>&gt;100.000</td>
<td>negative</td>
<td>+</td>
<td>+</td>
<td>negative</td>
<td>AFB+Gene probe: negative</td>
</tr>
</tbody>
</table>

Liver granuloma and FUO in HIV positive patient

???????
# Granulomatous Hepatitis: 2-15% liver Bx

*Uta Drebber et al. liver international 2008: 828-834*
*Gaya DR et al. J Clin Patho 2003: 850-3*
*Dourakis SP et al. Euro J Gastroentrology Hepatol 2007:101-106*

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<tr>
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<th>German 442/12161</th>
<th>Greece 66/1768</th>
<th>N Ireland 63/1662</th>
<th>Saudi Arabia</th>
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<tr>
<td><strong>Primary Biliary Cirrhosis</strong></td>
<td><strong>48.6%</strong></td>
<td><strong>68%</strong></td>
<td><strong>23%</strong></td>
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<tr>
<td><strong>Sarcoidosis</strong></td>
<td>8.3%</td>
<td>7.6%</td>
<td>11%</td>
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<tr>
<td><strong>infectious</strong></td>
<td><strong>3.9%</strong></td>
<td></td>
<td></td>
<td>55/59</td>
</tr>
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<td>TB: 3 cases</td>
<td></td>
<td></td>
<td></td>
<td>TB: 19 cases</td>
</tr>
<tr>
<td><strong>Chronic HCV</strong></td>
<td></td>
<td>7.5%</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>2.4%</td>
<td></td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>36%</td>
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HIV and Hepatic Granuloma

- Literature: *Tb responsible for most of the cases*

1. **retrospective study 1985-1997**
   - Evaluate etiology 93 pts with HIV, FUO and HG.
   - *TB responsible for all the cases (78% with other site TB)*

1. **Liver specimen obtained from 171 pts with AIDS**
   - Significant microscopic abnormalities in 58%
   - 70 pts with TB (35 with anatomical TB lesions)

   *Vidal F et al. Int Conf AIDS 1998 12:288*
   *Lanjewar DN. HIV 2004:253-7*

- Hepatic tuberculosis is associated with 90% cases of miliary TB

- Tubercule bacilli reach the liver by way of hematogenous dissemination: Hepatic artery in case of miliary tuberculosis
  Portal vein in case of focal liver tuberculosis
Case 1

- Antituberculosis treatment (INH, RFP, PZA ETB) progressive elevated doses

- Fever decreased dramatically and abdominal pain improved

- Progressive improvement in liver function
  \( (\text{Alk phosph decreased from 1980 IU to 200 IU}) \)

- Positive Tuberculosis Cultures: sputum and urine

- Non Caseiting granuloma in liver

- **Dg: Generalized Tuberculosis and AIDS**
  (reactivation of old untreated TB)
Tuberculosis Treatment and HAART

- **Active TB is an AIDS-defining disease**

- **Begin anti TB treatment immediately**
  
  **Duration of Anti TB treatment** 9 months to 1 year

- **HAART Timing**: no consensus
  
  >200 cells/mm: defer until complete TB treatment
  >50 cells/mm and < 200 cells/mm: wait until induction phase
  < 50 cells/mm: start as soon as possible

- **Problems**:

  - Drug toxicities (skin rash, hepatotoxicity)
  - Drug interaction RFP decreases level of ARV drug-resistance
  - Immune restoration induced by HAART may be associated with IRIS

**Use of HAART results in marked decreases of death and other opportunistic infection**
Anti Retroviral Treatment

- A retrospective series from England:
- 188 patients: 85% no antiretroviral-therapy when TB was diagnosed
- 45% began HIV therapy during TB treatment (median of 2 months after TB diagnosis).
- 3.5%: new AIDS-defining illnesses (*compared with 24% in those not treated*).
- 50% Adverse Events (. peripheral neuropathy, rash, hepatitis, and GI)
- 30% either changed or interrupted TB or HIV treatment.
- **16 coinfected patients who died did not receive antiretrovirals**

*Dean GL et al. AIDS. 2002;16:75-83*
Anti Retroviral treatment

- **Reverse Transcriptase inhibitor**: interferes with the reverse transcription that converts HIV RNA to HIV DNA
  1. NRTI nucleoside analogue (AZT, lamivudine)
  2. NNRTI non nucleoside analogue (Nevirapine)

- **Pi: Protease Inhibitor**
  prevents maturation of virion capable of infecting other cells
  (Indinavir, Ritonavir)

- **Treatment combination (HAART)**
  2NRTI AND NNRTI (EFV or NVP) 1st line
  3 NRTI -alternative 1st line
  2NRTI and PIr (SQV/r or LPV/r and RTV – 2nd line

- Since the use of HAART, mortality from HIV has declined dramatically in the developed world.
HAART and TB: PROBLEMS

- **Toxicities:**
  - 14-20% of HIV+ pts starting ARV have elevation in Liver function tests
  - 2-10% need to interrupt ART because of significant hepatotoxicity
  - CNS (EFV)
  - Skin rash (NVR)

- **Drug interaction:**
  - Regimen including **Rifampicin** reduce the therapeutic activity of NNRTI and PI through the cytochrome P450 enzyme
  - Lead to HIV resistance

**WHO recommendation: regimen containing EFV (2NRTI AND NNRTI)**

- **Immune reconstitution syndrome (IRIS)**
  1. TB IRIS is characterized by clinical worsening soon after initiation of ART
  2. Occurs in 10-30% of patients commencing ART
  3. Cause: recovery of the immune system after HAART institution with reconstitution of antigen-specific T cell-mediated immunity

**Important to differentiate from treatment failure**
Case 1

- After 2 months of anti TB treatment, new test for CD4: we begun on HAART *(CD4 fall from 495 to 35 cells/μL)*
- No hepatotoxicity, Mild gastrointestinal troubles
- Few weeks after ARV treatment:
  - Fever 39
  - Blood culture negative
  - Xray: no change
- IRIS  Steroid treatment for 1 month: improvement
- The pt is ongoing with both treatment
Conclusion (Case 1)

- In HIV positive patient with fever, liver infiltration and Hepatic Granuloma, *Tuberculosis infection is highly suspected*
- *Anti TB treatment should be institute rapidly* as the diagnosis may be delayed
- *Actually, HAART and anti TB is safe* and reduces mortality especially if EFV regimen used
- *IRIS is frequent*
Case 2

- 33 year old man born in Ethiopia
- One year ago, hospitalized because of increased dyspnea and hypoxia
- Work up revealed
  1. HIV positivity CD4 = 200 cells/µL
  2. BAL: PCP pneumonitis
  3. Cotrimoxazole (septrin) 21 days and prednisone
  4. Improvement
- Non compliance - no follow up
Few months later, he complained:
- cough, dry sputum
- dizziness worsening headache,
- deviation of the walk on the left side
- No confusion, no fever

**Physical examination:**
- Looks very sick, cachexia
- Cervical lymph nodes
- Bilat firm pruritic nodules on the arms and legs

**Laboratory examination:**
- CD4: 26 cells/µL
- Sputum negative for AFB in ZN stain
Case Report (2)

- Cerebro Spinal Fluid: clear colorless
  - normal opening pressure, protein normal
  - glucose: 100 mg - no pleocytosis

- Differential Diagnosis:
  1. Infectious (*Cryptococcal toxoplasmosis, CMV, Nocardia, MTB*)
  1. Malignancy – Lymphoma

- Skin biopsy: **prurigo nodularis** (*epidermal proliferation*)

- LN biopsy: **caseiting granuloma**

*Anti TB treatment (INH, RF, ETB, PZA) and HAART (EFV regimen)*
Extra Pulmonary TB

- Very frequent in HIV infected people (50% /15%)
- Related to the degree of immunosuppression (>70% when CD4< 200)
- Children : high frequency of meningitis and progressive disease
Key points 1

- Tuberculosis is the major cause of morbidity and mortality in HIV infected
- HIV increased the rate of progression and reactivation of TB
- HIV modifies the presentation of TB and make diagnosis difficult with a high frequency of EPTB
- TB accelerates the progression of HIV (TNF)

All HIV infected should be evaluated for TB
All TB infected should be offered HIV test
Key points 2

- Treat TB before over initiating HAART
- Rifampicin has significant drug interaction with ARV drugs
- Understand paradoxical reaction
- Identify drug resistance
- High suspicion, early institution of anti TB drugs and close monitoring is the key to successful management

Thank you !!!!!
Child / Adult TB/HIV

- **Tuberculosis infection**
  - children: recent transmission
  - adult: reactivation

- **Incidence:**
  - Children vs adults: Low incidence in well controlled TB country
  - 20 fold increase TB incidence in HIV + / HIV –

- High rate of mortality and morbidity

- **Disease severity:** age (<3 years) life threatening manifestations
  - immune status

- **Diagnosis:** close contact+ TST+ Xray (IGRA)