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Our Issues, Our Drugs, Our Patients

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Managing adult treatment through case study discussion

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Infectious Diseases Unit
Referral summary

- 20-year-old male
- HIV infected, CD4 count = 17 cells/mm$^3$
- Seen at a district hospital
- Problems: loss of weight, loss of appetite and night sweats
- Investigated for mycobacteria tuberculosis
  - GeneXpert: MTB not detected on 2 sputum samples
  - Sputum microscopy (auramine): negative repeatedly
- TDF/FTC/EFV commenced
- He developed jaundice 2 weeks later.
STOP and THINK
What are the considerations?

• Drug induced liver injury secondary to efavirenz
• Immune reconstitution syndrome
  – Viral: Hepatitis B, Hepatitis C, CMV (cholangiopathy)
  – Mycobacterial (TB or NTM)
  – Fungal infections (Histoplasmosis)
• Biliary obstruction due to non-benign process
• Haemolysis
Case

• ART was discontinued
• Referred to tertiary hospital
• Clinical presentation
  – Thin, generalized muscle wasting, ill looking
  – Fever 38°C
  – Alert and cooperative
  – Pale, deep jaundice
  – No peripheral lymphadenopathy
  – Hepatomegaly, liver span 16cm
  – Splenomegaly
# Laboratory results

<table>
<thead>
<tr>
<th>Assay</th>
<th>Result</th>
<th>Assay</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>7.2</td>
<td>Bilirubin (umol/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjugated bil</td>
<td>312 205</td>
</tr>
<tr>
<td>Mean cell volume (fl)</td>
<td>91</td>
<td>ALT (IU/L)</td>
<td>58</td>
</tr>
<tr>
<td>Erythrocytes (cells/L)</td>
<td>1.4 x 10^{12}</td>
<td>AST (IU/L)</td>
<td>153</td>
</tr>
<tr>
<td>Leucocytes (cells/L)</td>
<td>5.7 x 10^{9}</td>
<td>ALP (IU/L)</td>
<td>2074</td>
</tr>
<tr>
<td>Platelets (cells/L)</td>
<td>103 x 10^{9}</td>
<td>GGT (IU/L)</td>
<td>1046</td>
</tr>
<tr>
<td>CD4 count (cells/mm^3)</td>
<td>9</td>
<td>HIV viral load (copies/L)</td>
<td>227 226</td>
</tr>
</tbody>
</table>
Case summary

• HIV infected patient
• Baseline CD4 count = 9 cells/mm³
  – Jaundice 2 weeks after commencing ART
  – Bicytopaenia, erythrocytes and platelets
  – Hepatosplenomegaly
STOP and THINK
Reasons for the bicytopenia

• Bone marrow infiltration
  – Infective: mycobacterial, fungal
  – Malignant: lymphoma, myeloproliferative disorder

• Sequestration
  – Hypersplenism

• Peripheral destruction
  – Thrombotic thrombocytopenic purpura
  – Platelets low, erythrocytes low
New considerations?

• Lymphoma
• Infective
  – TB or NTM
  – Fungal
• Portal hypertension
  – No features of chronic liver disease
• Drug induced liver injury less likely
Investigations
Investigations

• Ultrasound abdomen
  – Confirming hepatomegaly, increased echogenicity
  – Splenomegaly with splenic hypodensities
  – No dilated bile ducts
  – No lymphadenopathy
  – Small amount of ascites
• Hepatitis B surface Ag negative
• Hepatitis C antibody negative
• CMV IgM negative
• Plan to perform a liver biopsy
Investigations

- Peripheral smear
  - Anisocytosis, scanty polychromasia, mild target cells, scanty schistocytes
  - Leucopenia
  - Adequate platelets
- Reticulocyte count
  - Absolute reticulocyte count = $0.013 \times 10^{12}$ (0.05-0.1)
  - Reticulocyte production index = 0.1 (<1 inadequate bone marrow response)
# Investigations

<table>
<thead>
<tr>
<th>Assay</th>
<th>Results</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>7.9 umol/L</td>
<td>11.6 – 31.3 umol/L</td>
</tr>
<tr>
<td>Transferrin</td>
<td>1.17 g/L</td>
<td>2.15 – 3.65 g/L</td>
</tr>
<tr>
<td>Percentage saturation</td>
<td>27%</td>
<td>20 – 50%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>5249 ug/L</td>
<td>24 – 336 ug/L</td>
</tr>
</tbody>
</table>
STOP and THINK
Biopsy

- Liver
- Bone marrow
Liver biopsy

- ZN stain multiple AFB
- Poorly formed granuloma
- Culture: MTB antigen test negative
Bone marrow biopsy

- Intracellular clumps of linear bead-like structures are seen within the distorted areas
- Ill-defined area of loosely formed granulomas
Gastroscope and Duodenal biopsy

• ZN stain showed AFB
• Stained with PAS
• Suggestive of NTM
Common Acid Fast Pathogens Found in HIV Infected Hosts. Consider the following:

(i) all mycobacteria including *M. tuberculosis*, *M. leprae*, and *M. avium-intracellulare*,

(ii) *Actinomyces nocardia*,

(iii) *Cryptosporidium parvum*,

(iv) *Isospora belli*. 


Sterile specimen (bone marrow aspirate or biopsy, liver, lung, or lymph node biopsy)

Microscopy

AFB seen
- GeneXpert MTB/Rif
  - MTB detected
    - Treat as mycobacteria tuberculosis; if rifampicin resistant, treat as MDR-TB
  - MTB not detected
    - SD Bioline MPT64 TB Antigen Rapid
      - MTB antigen detected
        - Treat as mycobacteria tuberculosis
        - Await drug susceptibility testing
      - MTB antigen not detected
        - Consider NTM
        - Send specimen for PCR
        - Await TB culture

AFB not seen
- Consider another diagnosis and await TB culture
- If SD Bioline MPT64 TB Antigen Rapid not available await TB culture result

**Figure 3: Proposed diagnostic algorithm for NTM.**
Management?

• Rifampicin
• Isoniazid
• Pyrazinamide
• Ethambutol
• Rifafour®
• Clarithromycin
Our management

- Rifafour
- Clarithromycin
- Treated patient for 2 weeks
- Initiated ART, TDF/FTC/EFV
- Patient slowly recovered
- Until...
Case

• Complained of blurring of vision and decreased visual acuity
• CMV PCR positive
• CMV Viral load 1000 copies/mL
• CD4 count = 61 cells/µL (baseline 9 cells/µL)
• Treated for CMV retinitis
Proposed Criteria For Diagnosis of IRS*

• HIV positive
• Receiving HAART:
  – Decrease in HIV-RNA from baseline
  – Increase in CD4 count from baseline (may lag)
• Symptoms consistent with inflammatory process
• Clinical course not consistent with:
  – Expected course of previously diagnosed opportunistic infection
  – Expected course of newly diagnosed opportunistic infection
  – Drug toxicity

Conclusion

• High index of suspicion for an opportunistic infection in patients with low CD4 counts
• High index of suspicion for IRS in patients with low CD4 counts
• The drug isn’t always the culprit