Haematological manifestations in HIV

Maresce Bizaare

AWACC 2013
Cytopaenias in HIV

- Most common complication of HIV
- Anaemia is most common cytopaenia
- ITP occurs in 30%, may be first manifestation of HIV
Laboratory approach to cytopaenia

- FBC, diff, smear
- Retic count → haemolysis/peripheral loss or production problem
- UE/LFT/LDH/CMP
- Nutritional deficiencies: B12/Folate/Iron studies
- Hepatitis B/EBV/Parvo
- BMAT low threshold
Some causes of Anaemia

<table>
<thead>
<tr>
<th>Decreased RBC production</th>
<th>Increased Red cell loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV itself</td>
<td>Haemolysis</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td>Blood loss</td>
</tr>
<tr>
<td>Drugs</td>
<td>Hypersplenism</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
</tbody>
</table>
**Drugs causing cytopaenias**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cytopaenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>Anaemia, Neutropenia</td>
</tr>
<tr>
<td>D4T</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Bactrim</td>
<td>Anaemia, Neutropenia, Thrombocytopenia</td>
</tr>
<tr>
<td>INH/Rifampicin</td>
<td>Anaemia, Neutropenia, Thrombocytopenia</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Anaemia, Leucopenia, Thrombocytopenia</td>
</tr>
</tbody>
</table>
Case 1...Ms PN

- Consulted for patient with Bicytopaenia
- 35/40 pregnant

- From History:
  - On HAART, CD4 235, started in pregnancy, uncertain VL
  - Diagnosed 11 weeks previously with B12 deficiency, had received B12 injections
  - Hb was 6.4 at time, now 11.3
  - Persistently low plts -- last count 54
  - Normal WCC
  - No renal impairment
Investigations

- Normal MCV/MCH
- Coombs negative
- B12 started to improve (low normal) / Folate normal
- Iron studies normal
- Hep B negative
- Rest of viral screen was negative
- US abdomen nad

- Impression: Multifactorial causes
- B12 deficiency, corrected with injections-> accounts for improving Hb
- Low platelets (?ITP/ pregnancy related thrombocytopaenia)
Management plan

- Review history: No transfusions, only had 2x B12 injections
- Assessment: B12 deficiency (Inadequately replaced) and ? ITP

- Plan:
  - Replace B12 appropriately
  - Start prednisone
  - Patient delivered few days later
  - Reviewed in clinic 2/52 later
  - FBC completely normal with plts of 233
Learning point

- Good history
- Replace B12 appropriately
- 1000mcg x 5/7 \( \rightarrow \) weekly x 4/52 \( \rightarrow \) monthly
Thrombocytopenia

- Thrombotic Thrombocytopenic Purpura (TTP)
- ITP
- Drugs
- Opportunistic infections
- Hypersplenism (due to chronic liver disease)
- Malignancy
Isolated Thrombocytopenia

- Low threshold to do a BMAT
- Might pick up Bone marrow infiltrations or opportunistic infections
- Prednisone 1mg/kg/day
- Polygam to optimise for surgery
- Splenectomy
- Prophylaxis
  - Vaccines: Pneumococcal and Meningococcal prior to splenectomy
  - Pen VK 250mg bd (2 years)
Case 2

- Ms SB → 16 years old
- Pregnant → 24/40
- CD4 356, HAART naïve
- Initial complaint: Lower abdominal pain and haematuria

- Examination: Apyrexial, pallor, no lymphadenopathy
- Petechiae +
- No chronic liver disease, no hepatosplenomegaly
- No neurological impairment
Initial investigations

- FBC: HB 7.3  Plts 24  WCC 10
- UE/LFT normal,
- LDH elevated -882 (N:100-190)
- Iron studies normal
- B12/Folate normal
- INR normal
- ANF neg
- Coombs neg
Initial management

- Smear not followed up
- ITP suspected
- Started on steroids
- Haematology consulted after 10/7 when no platelet increment noted
Considerations in patient

- HIV associated TTP

Unlikely:
- HIV associated ITP
- Gestational thrombocytopenia
TTP Pentad

- Thrombocytopenia
- Microangiopathic Haemolytic Anaemia (MAHA)
- Fluctuating neurological signs
- Renal impairment
- Fever
Differences

- No classical Pentad

- Pathogenesis is different

- Treatment is different: Responds to plasma infusion, rate of relapse low, HAART essential
HIV: A changing landscape

- Incidence 15-40x that of non-infected individuals
- >80% of TTP cases in SA found to be HIV+
- Missed diagnosis
HIV associated TTP

- TTP may be the initial presenting feature of HIV disease
- Remission is dependent upon improving the immune status of the patient.
Figure 1: Proposed Mechanism for the Initial Onset of HIV-associated Thrombotic Thrombocytopenic Purpura

1. HIV Infection
   - Increased cytokine release
   - Micronutrient, e.g., zink deficiency
   - Production of autoantibodies to ADAMTS13

2. Increased VWF synthesis and release by endothelium
   - Decreased ADAMTS13 synthesis and release by endothelium

3. Microvascular thrombosis

4. Haemolytic anaemia and thrombocytopenia

5. HIV-associated TTP
Evidence for Plasma infusion

- Prospective study by Novitsky et al Groote Schuur Hospital
- Compared HIV associated TTP with HIV negative TTP
- All HIV+ patients responded to FFP infusions and their platelet count and serum LDH levels normalized significantly faster than the HIV negative group
Treatment of HIV-TTP

- Plasma infusion
  - FDP (Freeze dried plasma) 30ml/kg/day (can add loop diuretic)

- Adjunctive corticosteroids
  - Prednisone 1mg/kg/day

- Folate
- Aspirin once plts > 100

- If no response in 72 hours → plasma exchange
## Outcome of patient

<table>
<thead>
<tr>
<th></th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOA</td>
<td>24</td>
</tr>
<tr>
<td>Consult:</td>
<td>13</td>
</tr>
<tr>
<td>2/7 of FFP</td>
<td>53</td>
</tr>
<tr>
<td>4/7 of FFP</td>
<td>132</td>
</tr>
<tr>
<td>8/7 of FFP</td>
<td>229</td>
</tr>
</tbody>
</table>
## Differences between ITP and TTP

<table>
<thead>
<tr>
<th></th>
<th>ITP</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Bleeding</td>
<td>“Clotting”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multi-organ involvement</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>No fragments</td>
<td>Fragments</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>HAART steroids</td>
<td>HAART Steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma exchange</td>
</tr>
</tbody>
</table>
Case 3...Ms ZN

- 35 years old referred from EDH
- HAART for 3 years
- CD4 395, undetectable Viral load
- Constitutional symptoms
- TB x3 in past, last 1 sensitive AFB + TB
- Examination revealed pallor and lymphadenopathy
investigations

- FBC: Hb 9.8 NNA, Wcc 3.53 (ANC 1.28) Plts 282
- Smear: no fragments
- Calcium and LDH were elevated
- US abdomen showed numerous lymph nodes
- Lymph node biopsy was done
Burkitt's lymphoma

- Very aggressive B cell NHL
- 1st lymphoma associated with HIV
- Incidence increasing in HAART era
- > 200x fold increase in HIV population
- HAART not decreased incidence
- 40% associated with EBV
- Rapidly dividing, doubling time of 24-48 hours
Burkitt Lymphoma

- More common when CD4 > 200
- Chronic antigenic stimulation of B cells by chronic HIV infection may be the pathogenetic mechanism
- Responds to chemotherapy
- HAART has allowed the use of high dose chemotherapy regimens
Alarm bells ring.....

Clinically:
- Lymphadenopathy, Hemosplenomegaly
- Jaundice, pyrexia

Laboratory:
- Cytopaenias
- Elevated WCC (circulating blasts: Burkitts leukaemia)
- LDH/ Ca elevated
- K+ elevated
- Renal impairment
Tumor Lysis Syndrome

- High proliferation rate
- Suspect if bulky disease
- Present with:
  - Hyperkalaemia
  - Hyperuricaemia
  - Hyperphosphataemia
  - Renal failure

- Management:
  - Fluids
  - Urinary alkalinisation
  - Allopurinol
Case 4

- 30 year old Ms GS
- HAART since June 2013
- Nadir CD4 73 → 290, (3/12 later), VL uncertain
- TB 2/52 prior to HAART (CXR changes, constitutional symptoms)
- Persisting symptoms, sternal mass started to slowly form
- Anaemia, thrombocytopenia
- Extensively investigated for MDR-TB
Examination

- Pallor, no lymphadenopathy
- Sternal mass
- Temporal mass
- Hepatosplenomegaly
Continuation.....

- Investigations:
  - Microcytic Hypochromic anaemia Hb 9.7, plts 112
  - Normal Ca
  - Elevated LDH >1000
  - CT: TB spondylitis, features of bronchiectasis, Erosive lesion in relation to manubrium sternum, multiple abdominal lymphadenopathy
  - Hepatomegally with multiple lesions
  - Homogenously enlarged spleen
  - Biopsy of sternal mass: DLBCL
Discussion on Diffuse Large B Cell Lymphoma (DLBCL)

- Most common histological subtype of NHL
- Incidence in SA is increasing exponentially primarily due to HIV pandemic
- Most patients symptomatic at presentation
- Constitutional symptoms, lymphadenopathy, hepatosplenomegaly, bone marrow involvement and cytopaenias more common in advanced stage
- Comorbidities such as TB increase the frequency and severity of clinical manifestations


Discussion

• Multiple pathologies for cytopaenias
• In this case: DLBCL and concomitant TB
• High index of suspicion in patient not improving on TB treatment
• Biopsy, Biopsy, Biopsy
Summary: What to consider in patients with Cytopaenias

- HIV induced
- Nutritional deficiency
- Opportunistic infections (eg TB)
- If Thrombocytopenia: ITP / TTP
- Malignancy
Indications for BMAT in HIV+

- Unexplained anaemia, abnormal red cell indices, cytopenias
- Isolated thrombocytopenias
- Unexplained organomegaly or presence of mass lesions inaccessible for biopsy
- Microbiological culture for investigation of PUO
Case 5

- Mr TZ, 34 years old
- Pulmonary embolus, Right DVT
- HAART naïve, CD4 89
- Examination and rest of baseline laboratory workup was essentially normal
Acquired Thrombophilia in HIV population

- Common
- Unusual sites common
- Risk highest with advanced disease (low CD4 and high VL) and co-existing infection and malignancies

**Contributors to Hypercoaguable state:**
- Increased VWF
- High incidence of lupus anticoagulant and antiphospholipid antibodies
- Acquired Protein C and S deficiency
Management

- HAART
- Prophylaxis in hospitalised immobile patients
- Thrombophilia testing expensive
- NB: False + low titres of Antiphospholipid antibodies common
Thank you for your time and attention 😊
References and acknowledgements

- ASH 2012: Guidelines on the diagnosis and management of TTP and other thrombotic microangiopathies
- ASH 2012: How to approach thrombocytopenia
- BJH 2005: Thrombotic thrombocytopenic purpura in patients with retroviral infection is highly responsive to plasma infusion therapy
- European Oncology and Haematology 2012: HIV-associated Thrombotic Thrombocytopenic Purpura
- Postgraduate Haematology 2011
- Dr JP Singh, Dr N Sewpersad (IALCH department of Haematolgy)
- Various patients