Haematological aspects of HIV

Willem van Schalkwyk
Haematology Pathologist
Haematology and HIV

• Haematological manifestations of HIV common.
• Occur at all stages of infection.
• Often first clinical manifestation of HIV.
• Commonest abnormalities:
  – Cytopenias esp anaemia of chronic disease and ITP.
  – Hematologic effects of drug therapy.
  – Opportunistic infections.
  – Coagulopathies
  – TTP
  – Lymphoid neoplasms.
Basic approach to cytopenias

• Production defect (ie in bone marrow)

OR

• Increased peripheral destruction/loss of blood cells
Stem cells in HIV infection

Potential targets for HIV:
• Express CD4 cell surface antigen and co-receptors CXCR4 and CCR5.
• Recent studies have identified detectable virus in CD34+ haemopoietic progenitor pool.

Other mechanisms of stem cell dysfunction:
• Interaction of virus with cell surface induce functional defects.
• Alteration of the cellular and cytokine mileu of the BM.
BM stromal elements in HIV infection

*Stromal cells susceptible to HIV infection:*
- Impaired ability to support haemopoiesis.

*Secretion of inhibitory cytokines:*
- Induce bone marrow dysfunction.
- Progenitor cell death with reduced stem cell pool.
Bone marrow morphological changes in HIV

Normal

HIV
Bone marrow morphological changes in HIV
Bone marrow opportunistic infections

• May cause cytopenias via BM infiltration.
• BM biopsy provides quick morphological evidence of infection.
• Peripheral blood or bone marrow aspirate TB culture to species and sensitivity.
• Gene-expert PCR not recommended for blood/bone arrow aspirate (can do on sputum, CSF, FNA, biopsy tissue).
Bone marrow opportunistic infections

Acid-fast bacilli identified by Ziehl-Neelsen stain.

Disseminated cryptococcal infection identified by Methenamine silver stain.
Patient presented with bicytopenia and fever (CD4 count $10 \times 10^6 /l$). Trephine biopsy shows non-caseating granulomata with multinucleate giant cells (black arrow). ZN stain: numerous AFBs packing the giant cells and histiocytes. Morphology characteristic for mycobacterium avium complex (confirmed on Mycolytic blood cultures).
Hodgkin Lymphoma of the bone marrow

Malignant infiltrations of the bone marrow often present with cytopenias
## Drugs in HIV: haematological complications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
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<tr>
<td>AZT/ZDV</td>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Anaemia, Neutropenia (dose dependent)</td>
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<tr>
<td>Lamivudine</td>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Pure red cell aplasia (rare)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>CMV infection</td>
<td>Anaemia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Bactrim</td>
<td>PCP prophylaxis</td>
<td>Megaloblastic anaemia, neutropenia, thrombocytopenia</td>
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<tr>
<td>Amphotericin B</td>
<td>Antifungal</td>
<td>Anaemia, leucopenia and thrombocytopenia</td>
</tr>
<tr>
<td>INH, Rifabutin (RIF)</td>
<td>Anti TB</td>
<td>Anaemia, neutropenia, thrombocytopenia. Aplastic anaemia RARE</td>
</tr>
</tbody>
</table>

Opie, J SAMJ June 2012 “Haematological Complications of HIV Infection”
Drugs in HIV: haematological complications

**Dapsone**
- Used in prophylaxis and treatment of PCP.
- Oxidative haemolysis (especially in G6PD deficiency).
- Damage to red cell membrane and globin chains of haem group.
Drugs in HIV: haematological complications

Isoniazid (INH)

- Reversible sideroblastic anaemia.
  - Pyridoxine depletion.
- Characterized by iron deposition in erythroblast mitochondria.
- Also associated with:
  - Dyserythropoiesis
  - Pure red cell aplasia
  - Neutropenia
  - Thrombocytopenia
  - Aplastic anaemia.
Approach to anaemia in HIV

- Anaemia is a common feature of HIV-related disease.
- Independent predictor of morbidity and mortality.
- Degree of anaemia correlates with disease progression.
- cART correct HIV-associated anaemia in a significant number of patients.
- Ongoing anaemia associated as a marker of treatment failure.
- Important variable in monitoring HIV disease progression and management, particularly in resource-limited settings.
### Approach to anaemia in HIV

#### Reduced Red Cell Production

1. Unrelated to HIV
   - a. Haematinic deficiencies
     (Iron, Vit B12/folate)
   - b. Pre-existing condition
     (thalassaemia/sickle cell disease)

2. Related to HIV
   - a. Anaemia of Chronic Disease
   - b. Infection
     (Parvo B19, TB, histoplasmosis, cryptococcus)
   - c. Malignancy
     (NHL, Hodgkin’s, Castleman’s)
   - d. Drugs
     (AZT, Bactrim, Ampho B, Ganciclovir, INH)

#### Increased Red Cell Loss

1. Unrelated to HIV
   - a. Blood loss
   - b. Haemolysis
     (malaria, membrane/enzyme disorder)
   - c. Hypersplenism eg portal hypertension

2. Related to HIV
   - a. Haemolysis eg TTP, AIHA
   - b. Blood loss eg GI infection/malignancy
Anaemia of Chronic Disorders

- Most frequent cause of anaemia.
- Cytokine suppression of haemopoiesis.
- Low erythropoietin levels with blunted response to low Hb.
- Reduced iron utilization.
- Levels of cytokines correlate with the viral load and the severity of the cytopenias.
- cART beneficial to BM function.
Parvovirus B19

- Small single stranded DNA virus
- Can cause severe chronic anaemia in AIDS patients
- Pure red cell aplasia with a block in erythroid maturation.

**Dx**
- HIV patients unable to generate IgM and IgG antibodies.
- PCR
- Giant promoblasts in BM.

**Rx**
- IV immunoglobulin therapy.
- Institution of cART results in spontaneous clearance of Parvovirus infection.
Parvovirus B19

Bone marrow aspirate

Glycophorin stain on trephine
Vit B12 deficiency

• Incidence 10 – 35%.
• HIV produces various degrees of absorptive dysfunction.
• Intestinal mucosa of the terminal ileum, the site of B12 absorption, is frequently the site of initial HIV infection.

• Serum VitB12 levels recommended in cases of:
  - Macrocytic anaemia
  - Weight loss and diarrhoea
  - Peripheral neuropathy
Auto-immune hemolytic anaemia

- Positive direct coombs in 18-43% of HIV patients.
- Symptomatic AIHA cases: cold and warm antibodies.

**Dx**
- Reticulocyte count unreliable.
- More reliable parameters of haemolysis: low haptoglobin, increased LDH and indirect hyperbilirubinemia.

**Rx**
- Corticosteroids
- IV immunoglobulin
- Withdrawal of offending drugs.
- Splenectomy
Evaluation of a HIV patient with anaemia

- Peripheral smear.
  - Morphological features of haemolysis.
  - Morphological features of haematytic deficiencies.
- Reticulocyte count.
- Haemolytic screen.
- Iron studies, Vit B12 and red cell folate levels.
- Exclude opportunistic process.
  - Disseminated TB
  - Parvovirus B19
- Evaluate drug therapy (e.g. AZT, Bactrim).
- Bone marrow biopsy in unexplained or refractory cases.
Thrombocytopenia in HIV

- ITP most common cause early in disease course.
- Can be the first manifestation of HIV.
- Bleeding rare.
- Commonly associated with ↑ levels of platelet associated IgG, IgM and circulating immune complexes.
- Unique mechanism
  - Antibody induced by HIV Gp120.
  - Cross-reacts with platelet GPIIb/IIa.

Baker et Al; The Complications of HIV infection  ASH 2003
Thrombocytopenia in HIV

• In advanced HIV due to BM failure, rather than increased peripheral destruction.
• Direct infection of megakaryocytes demonstrated.
  – Presence of HIV p24 antigen shown by immunohistochemistry
  – Expression of HIV RNA found using in situ hybridization
Leucopenia

- **CD4 lymphopenia** is hallmark of HIV infection with inverted CD4/CD8 ratio.

- **Neutropenia:**
  - Severe \(<0,5 \times 10^9\) associated with ↑ risk serious bacterial infection.
  - Effect of HIV on myeloid progenitor cells.
  - Dysregulation of BM micro-environment.
  - Reduced levels of G-CSF in HIV patients.
  - Anti-neutrophil antibodies frequent, but do not correlate with degree of neutropenia.
  - Good response to exogenous GCSF.

- **Monocytopenia:** Mono/macrophages infected via CD4 receptors. Cellular dysfunction. Abnormal forms seen.
Pancytopenia in HIV

PRODUCTION DEFECT

- B12/Folate deficiency
- Advanced HIV/AIDS
- Other viral infection
  - Parvovirus
  - Hep B, EBV, CMV
- Infiltration
  - Lymphoma
  - Opportunistic infection
  - Non-haemopoietic
- Drug toxicity
- Severe sepsis

↑ PERIPHERAL DESTRUCTION

- Hypersplenism
- Immune
The diagnostic utility of bone marrow biopsies performed for the investigation of fever and/or cytopenias in HIV-infected adults at Groote Schuur Hospital, Western Cape, South Africa

W. A. VAN SCHALKWYK, J. OPIE, N. NOVITZKY

- 147 consecutive bone marrow biopsies included for analysis
- 47% diagnostic yield:
  - 33% unique diagnosis by bone marrow biopsy.
  - 14% the diagnosis could be made with alternative diagnostic methods
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total diagnoses</th>
<th>Unique diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated mycobacterial infections</td>
<td>38 (26%)</td>
<td>20 (14%)</td>
</tr>
<tr>
<td>Diagnosis based on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trephine biopsy</td>
<td>20 (13%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Aspirate culture</td>
<td>9 (6%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Trephine biopsy and aspirate culture</td>
<td>9 (6%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Disseminated cryptococcal infections</td>
<td>2 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Malignant diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>4 (2.7%)</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Metastatic malignant melanoma</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune Thrombocytopenic Purpura</td>
<td>21 (14%)</td>
<td>21 (14%)</td>
</tr>
<tr>
<td>Parvovirus-induced pure red cell aplasia</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Drug-induced pure red cell aplasia</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Severe aplastic anaemia</td>
<td>1 (0.6%)</td>
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W. A. VAN SCHALKWYK, J. OPIE, N. NOVITZKY

- Predictors of a diagnostic BM examination:
  - Neutrophil count <0.5 x 10⁹/L \( (P = 0.003) \)
  - Hb < 6 g/dL \( (P = 0.018) \)
  - Previous TB diagnosis \( (P = 0.006) \)
- Predictors of a non-diagnostic BM examination:
  - No additional significant predictors
Summary

• SA highest global incidence of HIV
• Cytopenias:
  – Frequent and often first manifestation of HIV
  – Diverse causes requiring logical and thorough approach
  – May herald opportunistic infection or malignancy
  – BUT often cytopenias are due to HIV itself and thus respond to cART
• Increasing incidence of HIV associated lymphomas
• A quality bone marrow biopsy has a high diagnostic yield in the appropriate setting