Bone Marrow Abnormalities in HIV Disease

AK Tripathi*, R Misra+, Pramila Kalra**, Neetu Gupta***, R Ahmad***

Abstract
Bone marrow abnormalities are frequently observed in HIV infected individuals at all stages of the disease. The most common abnormal finding is dysplasia affecting one or more cell lines. Erythroid dysplasia is the most common type of dysplasia and is recognized in over 50% of HIV infected patients, abnormal granulocytic and megakaryocytic development is encountered in one-third of patients. Plasma cells are strikingly increased in bone marrow of HIV infected patients. It may represent a physiological response to antigenic stimulation by viruses, other infective agents or secondary to dysregulated B-cell proliferation due to HIV. Herein we present a review discussing the various bone marrow abnormalities associated with the HIV disease.

INTRODUCTION
Infection with human immunodeficiency virus type 1 (HIV-1) primarily involves a subgroup of T-lymphocytes (CD4+ve), but other cell types are also invaded by the virus, including cell lines within the haematopoietic system. Together with infectious, inflammatory and neoplastic processes, invasion of haematopoietic tissue by the HIV explains the haematological alterations, which are seen during the course of infection. An Indian study (Patwardhan MS et al) revealed anemia as most common hematological abnormality which was normocytic, normochromic type in 61% of patients. Thrombocytopenia was seen in 13% of patients.

Bone marrow examination in HIV infected patients is usually performed to evaluate peripheral cytopenias or when systemic infections or malignancies are suspected. It is clear, however, that in this population, abnormalities are frequently seen in all marrow cellular elements, as well as in the marrow matrix itself (Table 1).

Bone marrow changes include varying degree of dysplasia in one or more cell lines, most common being erythroid dysplasia seen in over 50% of infected patients, which in some patients may mimic a myelodysplastic syndrome. The human immune deficiency virus may be either directly or indirectly responsible for myelodysplastic alterations. The number of plasma cells is always increased. In many patients, the bone marrow stroma exhibits an increased amount of reticular fibres.

HIV-1 infection is associated with an increased risk of non-Hodgkin malignant lymphoma. Acute myelogenous leukaemia and myelomatosis have been described in patients with advanced disease.

The marrow morphologic characteristics are strongly

Table 1: Morphological and histological abnormalities of bone marrow in patients with AIDS

<table>
<thead>
<tr>
<th>Cytological features</th>
<th>M/E ratio 2:5:1</th>
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<tbody>
<tr>
<td>Hypercellular, normocellular or hypopcellular</td>
<td></td>
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<tr>
<td>Erythroid dysplasia</td>
<td></td>
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<tr>
<td>Erythroid hypoplasia (MAC infection, Zidovudine)</td>
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<tr>
<td>Myeloid dysplasia</td>
<td>Left-shifted, hyposegmented, maturation arrest at metamyelocyte stage</td>
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<tr>
<td>Megakaryocytes</td>
<td>Adequate to increased Dysplastic (hyposegmented, micromegakaryocytes, denuded nuclei)</td>
</tr>
<tr>
<td>Plasmacytosis</td>
<td></td>
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<tr>
<td>Lymphoid aggregates/infiltrates</td>
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<tr>
<td>Histiocytes</td>
<td></td>
</tr>
<tr>
<td>“Loose granulomas” (aggregates of plasma cells, lymphocytes, histiocytes)</td>
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</tr>
<tr>
<td>Erythropagocytosis</td>
<td></td>
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<tr>
<td>Increased eosinophils</td>
<td></td>
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<tr>
<td>Iron adequate to increased (reticulo-endothelial cell distribution)</td>
<td></td>
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<tr>
<td>Marrow matrix</td>
<td></td>
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<tr>
<td>Increased reticulin</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
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<tr>
<td>Serous atrophy</td>
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</tbody>
</table>

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associated with peripheral blood cytopenia of one or more lineage: anemia, granulocytopenia or thrombocytopenia are frequently described. The pathophysiology of these observed deficiencies are still unclear, although several mechanisms have been postulated as possible explanations for the hematological features in AIDS patients.

Treatment of the haematological abnormalities aims primarily at reducing replication of HIV-1, thereby diminishing suppression of haematopoiesis by the virus infection, and at controlling the opportunistic infections during the course of the disease. Specific antiviral therapy is most successful in correcting thrombocytopenia. The possibility of bone marrow suppression mediated by a toxic drug effect should always be considered in these patients.4

**PATHOGENESIS OF BONE MARROW ABNORMALITIES**

Infection of marrow mesenchymal stem cells (MSC’s) with HIV-1 may abrogate their growth properties and hematopoietic supportive functions. To delineate the cell type infected and factors responsible for deleterious effect, human bone marrow cells were exposed to HIV-1 *in vitro*. The results suggested that HIV-1 infection of stromal cells might produce inhibitory factors, which suppress clonogenic potential of MSCs.5

Several defects in bone marrow progenitor cells have been described. Reduced colony growth factor has been demonstrated for granulocyte - macrophage progenitor cells (CFU-GM), multipotential hematopoietic progenitor cells (CFU-GEMM), and megakaryocytic progenitor cells (CFU-Mk), as well as early erythroid progenitor cells (BFU-E) and megakaryocytic colonies (CFU-Mg) in most patients with AIDS.6 That defective progenitor cell growth might be secondary to suppressor T cells is suggested by the observation that T-lymphocyte depletion enhances colony formation by progenitor cells in AIDS patients but not in normal individuals. The inhibitory effect of added T-cells is inversely proportional to the T4 to T8 lymphocyte ratio. Using different culture techniques, other investigators have demonstrated an inhibitory effect of serum from patients with early infection or later AIDS on BFU-E and CFU-GM colony formation.7

No inhibitory effect of serum on normal marrow stem cells was observed. The inhibition appears to be mediated by a serum antibody directed to an HIV structural protein. In addition, there is now ample evidence that CD34 progenitor cells from normal bone marrow and fetal hepatic hematopoietic cells can be infected with HIV *in vitro* although the extent of infection may be limited in asymptomatic patients.8

HIV-1 infection of cells of the monocyte/macrophage lineage within the bone marrow and peripheral blood plays an important role in the pathologic events leading to the development of the acquired immunodeficiency syndrome (AIDS) as well as HIV-1 dementia. The TF-1 erythro-myeloid cell line is being utilized as a model cellular phenotype to examine HIV-1 infection of a hematopoietic progenitor cell population. Expression of TF-1 cell surface marker RNAs and protein was characterized by RT-PCR and FACS respectively, and compared to those of the well characterized U-937 monocyte cell line. Transcription factors in TF-1 and U-937 cells that have been shown to be important for sustaining the expression of HIV-1 LTR activity were also examined. These studies form the foundation for investigations into the relationship between HIV-1 infection of bone marrow and peripheral blood precursor cells of the monocyte/macrophage lineage and pathogenesis associated with HIV-1 infection of the immune and central nervous system (CNS).9

It is not yet known whether HIV infection of marrow stromal cells may play a role in altering hematopoiesis, however HIV infection of microvascular endothelial cells impaired their capacity to respond to IL-1-α-induced release of IL-6 and G-CSF. Exaggerated expression of tumour necrosis factor, Interleukin-1, and transforming growth factor-β1 by HIV infected moncytoid cells further impede hematopoiesis.10

**CELLULAR ABNORMALITIES**

**Dysplasia**

A remarkable degree of dysplasia has been noted in the myeloid, erythroid and platelet precursors. Although erythroid dysplasia is the most common finding, being recognized in over 50% of HIV-infected patients, abnormal granulocytic and megakaryocytic development is encountered in approximately one-third of patients.

**Myeloid maturation** is in general left-shifted.11 The myelodysplastic changes in the myeloid lineage include the presence of abnormal myeloblast with high nuclear/cytoplasmic ratio and abnormal folded or cleaved nuclei,12 as well as large myelocytes, metamyelocytes, and bands with megaloblastic appearing nuclei13,14 and Pelger cells reflecting dysfunctional nuclear maturation (Fig. 1).15 Few studies showed dysgranulopoiesis to be more frequent and more accentuated than other kinds of dys hematopoiesis.15 Intense vacuolization, especially in the granuloblastic series, is very frequent. Although several of the dysplastic changes noted in HIV infected patients resemble those seen in preleukemic syndromes, myeloid leukemia in AIDS, though reported, is very uncommon.16 As noted previously, direct infection of marrow precursors by HIV may contribute to these defects, although this issue remains controversial.17,18

**Dyserythropoiesis**, although initially reported less often than myelodysplasia, it is now increasingly recognized.14 Abnormalities include erythroblasts with lobulated, binucleated and fragmented nuclei, as well as basophilic stippling in more mature red blood
cells. Dyserythropoiesis may be manifested by florid megaloblastic change. This is found unrelated to serum cobalamin and folate levels, or to drug therapy with Zidovudine or folate antagonists, although these drugs might accentuate it.

**Erythroid hypoplasia** (Fig. 2) that may be severe is reported in some patients with AIDS or ARC, in patients receiving zidovudine and in the setting of systemic MAC (Mycobacterium avium complex) infection. Pure red cell aplasia or severe hypoplasia secondary to persistent parvovirus B19 infection has also been described in immunocompromised patients with and without HIV infection.

**Megakaryocytic dysplasia** is increasingly recognized in patients with fully developed AIDS with or without isolated thrombocytopenia. Dysplastic changes that have been described consists of micromegakaryocytes with denuded nuclei and megakaryocytes with hyposegmented or fragmented nuclei. Ultrastructural analysis of megakaryocytes from AIDS patients with thrombocytopenia has demonstrated marked ballooning or blebbing of peripheral zone. In addition, abnormal clustering of megakaryocytes on bone marrow biopsy sections, similar to that seen in myeloproliferative syndromes, has also been described. As noted previously, dysplastic changes observed in megakaryocytes, the detection of HIV RNA in megakaryocytes from infected patients and the clinical response in 50-68% of patients with HIV related thrombocytopenia to zidovudine are all consistent with the view that the megakaryocyte itself is a target for HIV infection in vivo.

**Cellularity**

Bone marrow from HIV-infected patients is sometimes difficult to aspirate. The true marrow cellularity is better appreciated on trephine biopsy, which is typically normocellular to hypercellular, even in the setting of peripheral cytopenias in a majority of patients. Hypercellularity of the marrow in the face of peripheral cytopenias is a very common finding in HIV disease and is likely to reflect myeloid dysplasia and ineffective haemopoiesis. The myeloid to erythroid ratio usually ranges from 2-7:1, reflecting the combined effects of myeloid hyperplasia seen even in patients with peripheral cytopenias and erythroid hypoplasia. A higher degree of erythroid hypoplasia is likely to reflect the increased use of zidovudine, which can suppress erythropoiesis.

**Plasma Cells Abnormalities**

Plasma cells are often strikingly increased in the marrow of HIV-infected patients seen in 31-85% of patients. These may represent a physiological response to antigenic stimulation by viruses or other infective agents, or may be secondary to dysregulated B-cell proliferation due to HIV. The marrow plasmacytosis is not confined to only those patients with advanced HIV disease in whom opportunistic infections could be implied, but also seen in patients at an early stage who had no concurrent infections. The plasma cells are often morphologically abnormal with moderate dysplasia and large bi or trinucleated cells which may appear in clusters. Russel bodies with multiple globules have also been described. Although myeloma has clearly been reported in AIDS, patients may present with monoclonal spikes on serum protein electrophoresis and marrow plasmacytosis with plasma cell aggregates and atypical forms, but without a clonal proliferation of plasma cells.

**Paraproteinemia** occurs in about 9% of homosexual HIV-antibody positive men without AIDS. This is much higher than the incidence of paraproteins in healthy people of comparable age and may result either from changes in T-cell regulation or from the activation of B lymphocytes directly infected by HIV. Some of the
paraproteins have activity against HIV gag and pol gene products and may represent a vigorous immune response to HIV infection.\textsuperscript{30}

**Lymphoid Aggregates**

Lymphoid aggregates are common and have been reported in 10-50% of patients with AIDS and ARC.\textsuperscript{11,12,19-21} They may be small, well circumscribed and composed of small round lymphocytes or large, poorly defined and mixed with histiocytes. Infiltrating lymphocytes have also been described that are atypical or cleaved and located in paratrabecular areas.\textsuperscript{19,21} However, when paratrabecular localization of lymphocytes is seen, it is important to rule out the possibility of non-Hodgkin’s lymphoma, since lymphomas in AIDS patients involve bone marrow in up to 50% of cases.

**Bone Marrow Involvement In Lymphoma**

Extralymphatic presentation of non-Hodgkin’s lymphomas occurs in up to 90% of patients with HIV infection and lymphoma has been reported to involve the bone marrow in 50% of cases.\textsuperscript{3} Thus, bone marrow involvement may be the presenting site of lymphoma. The lymphomas are typically high grade Burkitt’s or non-Burkitt’s lymphomas, although well differentiated types have also been described. Hodgkin’s disease is, in comparison to patients without HIV infection, more likely to involve extralymphatic sites, including the bone marrow that is usually recognized at staging after Hodgkin’s lymphoma diagnosis on a lymph node or other tissue biopsies but occasionally the marrow involvement is the only apparent manifestation of the disease.\textsuperscript{32}

**Other Abnormalities**

Additional cellular abnormalities of bone marrow include increased numbers of histiocytes, few showing haemophagocytosis, noncaeseating granulomas and the presence of “loose granulomas” consisting of aggregated histiocytes, lymphocytes and plasma cells.\textsuperscript{19,28} In many of the patients with HIV infection which showed increased numbers of marrow histiocytes, there is no obvious infective cause and it is likely that HIV itself triggered histiocytic proliferation and phagocytosis, probably by initiation of cytokine production resulting in macrophage stimulation. Histiocytic phagocytosis of erythroid cells and occasionally granulocytes and platelet has been described,\textsuperscript{33} but this is a nonspecific finding that may also occur in a variety of viral, fungal and bacterial infections. As a result of HIV infection, the marrow produces a histiocytic reaction, which varies from increased number of histiocytes to a full blown hemophagocytic syndrome with severe pancytopenia.\textsuperscript{34}

**Pseudogaucher cells** have also been described from a patient with MAC infection in which large foamy histiocytes on Wright Geimsa stain were shown to contain numerous mycobacterial organisms.\textsuperscript{35}

Although peripheral blood eosinoplilia is rarely seen, marrow eosinoplilia is common and has been reported in 9-61% of patients with AIDS.\textsuperscript{19,28}

**Bone marrow iron stores** are adequate to increase in reticuloendothelial cells indicating a defect in iron utilization similar to that seen in other chronic disease states.\textsuperscript{36} Sideroblasts with or without the presence of ringed forms have also been described but are uncommon.\textsuperscript{3,13}

**Granulomas** are an infrequent finding in bone marrow biopsies and may be associated with a broad spectrum of infectious and non-infectious disorders.\textsuperscript{37}

**Abnormalities In Bone Marrow Matrix**

Abnormalities in the bone marrow matrix are frequently seen and include increased reticulin or fibrosis\textsuperscript{11,12} and serous atrophy or “gelatinous transformation”.\textsuperscript{19,20} The increase in marrow reticulin may be focal or diffuse and may be increased in the areas of granuloma formation and lymphoid aggregates. In majority of patients, bone marrow aspiration is difficult or not uncommonly dry, probably as a result of one or more of these abnormalities.

**Opportunistic Infections Involving Bone Marrow**

Bone marrow histology or culture may be particularly useful in documenting opportunistic infection and should be performed in HIV infected patients with undiagnosed fever or constitutional symptoms, especially those with low CD4 cell numbers.\textsuperscript{38} Although it has been argued that blood cultures have sensitivity comparable to the bone marrow cultures in diagnosing disseminated mycobacterial infection, bone marrow examination with special histological staining can certainly provide a more rapid method of diagnosis for both opportunistic mycobacterial and fungal infections.\textsuperscript{39} Infectious agents reported to involve the bone marrow in patients with AIDS are listed in Table 2.

**Table 2 : Infections involving the bone marrow in patients with AIDS**

<table>
<thead>
<tr>
<th>Infection</th>
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<tbody>
<tr>
<td>Mycobacterium avium complex</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
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<tr>
<td>Mycobacterium xenopi and kansasi</td>
</tr>
<tr>
<td>Histoplasma</td>
</tr>
<tr>
<td>Cryptococcus</td>
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<tr>
<td>Toxoplasma</td>
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<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Leishmania</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td>Disseminated cat scratch</td>
</tr>
<tr>
<td>Parvovirus B 19</td>
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HAART AND BONE MARROW CHANGES

In patients treated with HAART an immune reconstitution associated with increased whole blood cell count has been described. The effect of HAART on the number of CFC's and long term culture initiating cells (LTC-IC) using long term bone marrow culture cells in a group of subjects with HIV-1 infection has been investigated. Controlling HIV-1 replication by HAART could determine restoration of stem cell activity, probably because of suppression of factors, which inhibit normal hematopoiesis.

REFERENCES


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**Announcement**

**5th International Symposium on Diabetes**

Venue: Mumbai  
Date: 21st & 22nd January 2006  
Theme: Master Class for Clinicians and Educators for Emerging Treatments in Diabetes and Complications

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**Core faculty:**  
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