HAEMATOLOGICAL CHANGES IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION. PART II

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SUMMARY

This second part of the review looks at change seen in the bone marrow haemostasis and malignancies found in HIV infection. Examination of bone marrow is requested in the presence of cytopaenias, splenomegaly, lymphomas and myelodysplasia. The findings include marrow hypocellularity, myelodysplasia and poor marrow recovery. Dysmegakaryocytopenia is found in 88% while dyserythropoiesis in 83% of cases. Mechanisms leading to these perturbations include direct HIV effect on marrow progenitor cells, effect of drugs and other infective diseases. Altered levels and functions of growth modify IL6 and G-CSF are also to contribute. Haemostatic disorder frequently noted is bleeding due to thrombocytopenia. Non-Hodgkin's lymphomas with aggressive characteristics and Kaposi's sarcoma are the commonly associated malignancies. Currently IL6 is being linked with the causation of KS and NHL. While standard approaches to the management of these malignancies tend to be the practices, adjustments are usually necessary in most patients.

Specific changes: The indications for bone marrow examination in HIV infection are peripheral blood cytopaenias, splenomegaly, lymphoma, leukaemia, and myelodysplasia(1). The changes seen in the bone marrow are consequences of: direct HIV infection, altered immunological mechanisms, effects of other infections, drugs, and chronic diseases. Indeed most of the peripheral blood changes observed are a reflection of the bone marrow changes(2,3).

These changes are associated with malfunctioning of haemopoiesis, impaired marrow recovery, and myelosuppression leading to myelopathy(4,5). In normal situations marrow recovery is mediated by stromal cell derived growth factors produced by microvascular endothelial cells (MVECs) which is directly infected by the HIV in 5% to 20% of cases(6). The release of IL6 and G-CSF are significantly reduced and is probably a result of direct HIV infection on the cells that produce these factors(7,8). The other factors, the transforming growth factor (TGF) that induces the release of IL6 and G-CSF are also significantly reduced(9). Further direct cytopathic effect of the HIV on haemopoietic progenitor cells is a consequence of HIV's tropism for lymphocytes and macrophages which are a major source of haemopoietic growth factors(9,10). The immune system is a recognised player in the marrow haemopoietic activity, this is reduced or curtailed by the HIV lympholytic effect(11,12).

The hypocellularity found in 20% of HIV infected cases demonstrates this inhibitory and suppressive action of the virus on haemopoietic progenitor cells(13). Dyserythropoiesis, dysgranulopoiesis and abnormal platelet production observed are due to myelopathic effects of the HIV infection(14). Red cell series are particularly affected, with associated megaloblastoid changes (15).

Red cell hypoplasia is frequently seen especially in association with disseminated mycobacterium avium intracellulare (MAI) and other opportunistic infective agents commonly found in association with these settings (15,16). Other changes noted in the bone marrow include increased number of histiocytes, which is often prominent and accompanied by haemophagocytosis. Increased lymphoid cells, and plasma cells are also not uncommonly found, and the presence of granulomas is not a rare finding. The cause of these changes are infections by MAI, cryptococcus spp. and histoplasm(a(15-17). Heyman et al showed marrow involvement by leishmania species(17).

We have not demonstrated this despite having a significant number of patients with leishmaniasis in our population (author's unpublished data). Reticuloendothelial iron blockade exhibited as increased stainable iron and sideroblastic changes are seen and are likely due to chronic disease and the myelopathy rendering utilisation of haematinics, iron included, defective. Trephine bone marrow cellularity may be normal, increased, or decreased(17).

The hypocellularity is usually associated with a poor yield at marrow aspiration but actual dry taps are rare and the trephine biopsies do not reveal myelofibrosis(16).

Myelodysplasia: This is well recorded by several observers as a sequela of HIV infection (author's unpublished data). It is probably due to a combination of factors that include the HIV, drugs and other infections(19).

These agents are thought to cause effects by impairing the progenitor cells in the bone marrow(19,20). The resulting features include, dysmegakaryocytopenia, and dyserythropoiesis seen in some series in 88% and 83% of the cases (21).

Other features include circulating asymmetric binucleated red blood cells, pseudo Pelger-Huet cells and
combination of cytopenias(22). Myelodysplasia is noted to be rare in the paediatric age group and the HIV associated is equally rarely found in paediatrics(23,24). Like the non HIV myelodysplasia, the HIV associated have been seen to transform to acute leukaemia particularly acute myeloid leukaemia(25).

Haemostatic disorders: Bleeding commonly seen in HIV infection is usually due to thrombocytopenia(author’s unpublished data). However patients suffering from congenital clotting disorders have an increased risk of bleeding if they have HIV infection(26,27). Severe haematemesis, melena, or haemoptysis following gastrointestinal opportunistic infection are not uncommon. Adequate replacement therapy in the affected patients is generally required to forestall the bleeding(27).

Thrombotic effects are not widely reported in HIV infected persons. This could be due to these events being rare or presenting with uncharasteristic symptoms and signs not primarily attributable to HIV infection. The author has however recorded two adults whose primary problems were skin avascular necrosis attributable to thrombosis in HIV infection. One of the patients had pulmonary tuberculosis and died after the onset of thrombotic lesions. The second patient received heparin infusions and later subcutaneous injections. No warfarin was ever given to this particular patient. He was later started on antiviral drug zidovudine (AZT). He remains clinically asymptomatic but his seropositive status remains. He has low lymphocyte count as well. It is four years since the thrombotic episode. Heparin has been noted to have anti-HIV activity (28).

Neoplasms: The spectrum of malignancies associated with HIV infection is increasing as the infected individuals live longer. Kaposi’s sarcoma was the first neoplasia to be associated with HIV infection and AIDS(29). Although not a haematological malignancy, bone marrow examination is usually an investigation in the patients who have Kaposi’s Sarcoma, particularly the lymphadenopathic type. However no report of bone marrow involvement by Kaposi’s sarcoma has been made. The lymphadenopathic type particularly has to be differentiated from other lymphoproliferative disorders and haematological malignancies. Our observation is that the HIV associated Kaposi’s sarcoma that primarily presents with lymph node enlargement in persons less than 45 years of age. Further, the initial treatment response to chemotherapy is superior to the cutaneous presenting type. The commonly noticed terminal event in lymphadenopathic presentation is the emergence of cutaneous component of Kaposi’s sarcoma (author’s unpublished data).

At present the haematological malignancies that are well described in HIV infection are lymphomas; mainly the Non-Hodgkin’s lymphomas(NHL) and Hodgkin’s disease(31). These lymphomas show clinical and pathological characteristics of aggressive patterns. Histologically, they commonly present a diffuse growth pattern, a high growth fraction, and a common B-cell origin with only occasional ones showing T-cell phenotype(32). Clinically, these are wide spread and tend to have extranodal involvement with the primary NHL of the central nervous system, gastrointestinal tract, bone marrow, and liver being frequent(31,32). IL-6 is currently associated with the pathogenesis of both the Kaposi’s Sarcoma and the NHL(33). However the mechanisms of this causal association is still lacking.

CONCLUSION

Periperal pancytopenia, raised ESR, rouleaux formation and myelodysplasia are found in many AIDS HIV infected persons. The pathogenesis of these changes are multifactorial and include the retroviral direct effect on the bone marrow precursor cells, cytolytic effect and indirect mechanisms such as immunological and alterations of the the haematopoietic growth factors. The linkage of IL-6 in the causation of Kaposi’s Sarcoma and high grade malignant lymphomas is certainly one of the most exciting new dimensions in this HIV infection.

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REFERENCES


