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MYELODYSPLASIA IN UGANDAN PATIENTS WITH HIV / AIDS: AN AUTOPSY STUDY
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MYELODYSPLASIA IN UGANDAN PATIENTS WITH HIV/AIDS: AN AUTOPSY STUDY

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ABSTRACT

***Background*: Myelodysplasia has been reported to occur quite frequently in the spectrum of HIV/AIDS disease and is thought to be partly responsible for bone marrow failure in these patients. However, the frequency and type of myelodysplasia appear to differ at different stages of the disease in different populations with mechanisms of its development not well understood.**
***Objective*: To document the pattern of myelodysplasia in Ugandan patients with terminal HIV/AIDS disease.**
***Design*: Prospective descriptive study.**
***Setting*: Department of Pathology, Faculty of Medicine, Makerere University College of Health Sciences**
***Subjects*: Bone marrow necropsies from patients who died with AIDS disease at Mulago teaching hospital in Kampala, Uganda during a one-year period.**
***Results*: Eighty-four (84%) of the 50 cases studied had myelodysplasia with 39 cases having megakaryocytic myelodysplasia. Myelodysplasia involving erythroid cell series occurred in 23 and in 20 of these cases was in combination with megakaryocytic dysplasia. Granulocyte myelodysplastic features were observed in only two cases and these two cases did not have other cell lines involved.**
***Conclusion*: Myelodysplastic features are common in HIV patients with megakaryocytic and eythroid cell lines being the most affected. This could be due to the direct HIV effect, or the combined effect of opportunistic infections, neoplasms, drugs and HIV itself affecting the haemopoietic stem cell and or its microenvironment.**

INTRODUCTION

Myelodysplasia is reported frequently in HIV / AIDS patients throughout the spectrum of the disease and is thought to be partly responsible for anaemia, neutropenia and thrombocytopenia (1, 2, 3). However the frequency and type of cell line with myelodysplastic features appear to differ with stage of HIV / AIDS disease and population settings (8). This difference in pattern is difficult to explain but appears to be multifactorial with factors like level of viral load, CD 4 bearing cells, nutritional deficiencies, drugs used in the treatment of opportunistic infections and anti-retroviral drugs plus possibly opportunistic infections (4). Hence, this study was aimed at documenting the myelodysplastic features of bone marrow at the terminal stage of HIV / AIDS in a Ugandan African population.

MATERIALS AND METHODS

The study was carried out in the Department of Pathology, Faculty of Medicine, Makerere University between 2005 and 2006. Fifty consecutive patients who died of natural causes in this study period and were HIV seropositive had their bone marrows studied. Bone including bone marrow blocks three um thick were obtained from sternum, vertebrae and iliac crest, fixed in 10% buffered formal saline for a maximum of 24 hours and then decalcified in formic acid for 6-12 hours. These tissues were paraffin embedded and sectioned at 4 μ. These sections were stained with haematoxylin and eosin (H&E), Ziehl Neelsen (ZN) and periodic acid schifft (PAS) to diagnose infections. Myelodysplasia was characterised by abnormal maturation as well as architectural arrangement of the different cell lines.

RESULTS

The 50 cases studied included 26 males and 24 females with age ranging from 17 to 57 and mean age of 32 (SD 8.3) years. All the 50 cases were severely wasted with 18 out 24 females weighing 50kg and below while in males, 20 out of 26 weighed below 50 kg. Forty-four (88%) had myelodysplasia and of these 21 were males while 23 were females. Eighteen out of the 44 cases had *mycobacteria* in their bone marrow while 15 had *cryptococcus neoformans* infection in the bone marrow. There was one case of *histoplasmosis capsulatum* infection and two cases with un identifiable fungal elements.

Table 1 shows age and sex distribution of the three cell lineages of dysplasia and there was no statistical difference in sex of the various cell lines ($x^2 = 0.03$, p value = 0.87). There was also no significant difference between the mean age of the three cell line. (p-value = 0.86).

Megakaryocytic dysplasia was the most common followed by erythroid dysplasia and myelodysplasia. Twenty cases had both erythroid myelodysplasia and megakaryocytic dysplasia, while only one cell linage dysplasia occurred in 24 cases. Of these 24 cases with one cell linage dysplasia, 19 had pure megakaryocytic dysplasia, three pure erythroid dysplasia and two myelodysplasia.

Hypercellularity was a major finding with very few cases being hypocellular(12%) and normocellular (14%).

Figure I

Clustering of hypolobulated micromegakarocyte x200

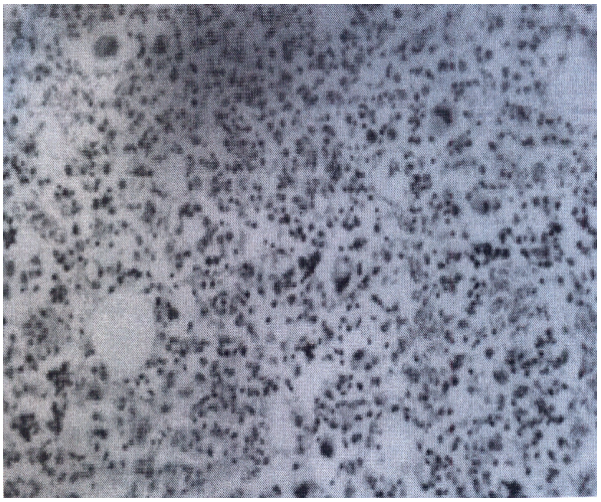

Figure II

Bone marrow shows hypercellular marrow. Some of the normoblasts are binucleated x 400

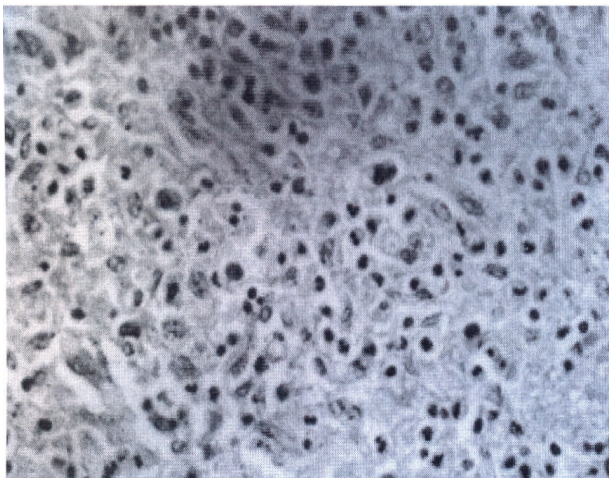

Table 1

Age and sex distribution of cases with myelodysplasia

Cell type	Megakaryocyte	Combined megakaryocytes and erythroids	Erythroid	Granulocyte
No of cases	19	20	3	2
M:F	9:10	10:10	2:1	0:2
Mean age	32 (SD 8.45)	31.7 (SD 9.96)	28.5(SD 5.65)	26.5 (SD 4.95)

Figure i shows megakaryocytic clustering, nuclear hypolobulation of micromegakaryocytes and abnormal localisation of megakaryocytes as the only dysplastic changes found in the megakaryocytic myelodysplasia. In the erythroid series binucleated normoblasts (fig ii) were found in 22cases and only one case had erythroid megaloblasts. Cytoplasmic vacuolation was the only dysplastic change found in the two granulocytic myelodysplastic cell series.

DISCUSSION

The severe weight loss coupled with tuberculosis and fungal infections found in our cases qualified them to be in terminal stages of HIV / AIDS disease and this could probably explain the high prevalence of myelodysplasia (5). Similar findings have been reported by Diebold *et al* (6) who found 91% of patients with terminal stage of HIV / AIDS disease

with myelodysplasia. In another study by Marche *et al* (7), myelodysplasia was found in 74.4% of the 125 patients studied at different stages of HIV infection and frequency was related to the severity of the infection. However Tripathi *et al* (8) did not show any correlation between HIV RNA load and the occurrence of myelodysplasia and this was thought to be due to the small numbers of cases studied.

Hypercellularity of bone marrow was a frequent finding. Previous reports indicate that most cases with HIV have hypercellular bone marrow (9). This was also observed in the study of Spivak *et al* (3) in which it was found five out twelve patients with severe HIV disease had hypercellular marrow. The hypercellularity observed in this study was mainly associated with increasing number of abnormal megakaryocyte and to large extent erthryoid cell lines. Khalil *et al (*10) also reported similar findings when they studied 18 patients with HIV infection and found 72% had hypercellularity mainly due to megakaryocytic hyperplasia. Similarly Delacrelaz *et al* (11) reported dysmegakaryocytopoiesis and dyserthropoiesis in 88% and 83% of the 18 patients studied. Bello *et al (*12) found abnormal maturation more prominent in megakaryocyte but unlike in the present study, abnormal granulocyte maturation was also prominent. On the other hand in the study of Tripath *et al* (8) the most commonly affected cell line was granulocytic followed by erthyroid. Schneider and Picker (1) also found granulocytic myelodysplasia more frequent although the degree of dysplasia was more severe in the megakaryocytic series.

In addition to the quantitative changes observed in this study, morphological cellular changes were also noted. The megakaryocytic series had the most striking changes including clustering of the megakaryocytes, a tendency often associated with myeloproliferative disorders. Other qualitative changes observed in the megakaryocyte series were micromegakaryocyte, hypolobulation of nuclei and abnormal localisation of megakaryocytes, features similar to those reported in pre-leukemic syndrome. In the erthryoid series the binucleated erythroblasts observed mainly in this study also were suggestive of hypoerthryopoiesis and would rule out the possibility of nutrition and drugs as causative factors. This was exemplified by the study of Karcher and Frost (13) who did not find any association between myelodysplasia and anti-retroviral drugs. Cytoplasmic vacuolation found in the only two granulocytic cell series has been reported by Tripathi *et al* (8) as the most important dysplastic change and accounted for 60% of the dysplastic changes in the granulocytes in their study. The pattern of involvement of different cell lines with megakaryocyte and erythrocyte being more frequently involved as observed in the present study would suggest a hypothesis similar to that brought forward by Linman and Bagby (14) concerning the evolution of pre-leukemic syndrome in which myelodysplastic changes affected erythrocytes initially, followed by platelets and lastly granulocytic series. This same argument had earlier been reported by Koeffler and Golde (15) who also found that there was erythroid hyperplasia and megablastoid features which were accompanied by micromegakarocytes in pre-leukemic syndrome. However Katsarou *et al* (16) were able to differentiate between myelodysplastic syndrome and HIV related myelodysplasia by finding abnormal karyotype in the latter. It has also been observed that CD34 + human haematopoietic progenitor are substantially not susceptible to HIV infection in either *vitro* or *vivo* and therefore their defects seem rather related to the alteration of bone marrow and peripheral blood microenvironments probably due to the presence of soluble HIV specific products rather than direct effect of the virus on the stem cell (17). More studies have demonstrated reduced colony growth factors for the haematopoietic progenitor cells in most patients with AIDS and the cause of the reduction of these factors need to be investigated (18) (Leiderman *et al* 1987). In support of the above theories in our study population, acute leukemia was not observed and there is no evidence that HIV / AIDS patients in this African population are at a high risk of developing acute leukemia (19).

In conclusion, myelodysplastic features are common in HIV patients with megakaryocytic and erythroid cell lines being the most affected .This could be due to the direct HIV effect, or the combined effect of opportunistic infections, neoplasms ,drugs and HIV itself affecting the haemopoietic stem cell and or its microenvironment, but this needs to be elucidated in further studies.

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REFERENCES

1. Schneider, J. R. and Picker, L. J. Myelodysplasia in the Acquired Immune Deficiency Syndrome. *Am. J. Clin. Pathol.* 1985; **84**: 144-152.
2. Lake, J. P., Lee, S. and Spira, S. Bone marrow findings in AIDS patients. *Am. J. Clin. Pathol.* 1984; **81**: 799-800.
3. Spivak, J. L., Bander, B. S. and Quinn, T. C. Hematologic abnormalities in the acquired imunne deficiency syndrome. *Am. J. med.* 1984; **77**: 224-228.
4. Richman, D. D. Toxicity of Azidothymidine (AZT) in the treatment of patients with AIDS and AIDS related complex. *N. Engl. J. med.* 1987; **317**: 192-197.
5. Ledru, E., Diagbouga, S., Meda, N., Sanou, P. T., Dahourou., *et al*. A proposal for basic management of HIV disease in West Africa: use of clinical staging

and haemogram data. *Int. J. STD. AIDS.* 1998; **9**: 463-470.
6. Diebold, W., Tabbara, C. and Marche, J. Modifications de la moelle osseuse a divers stades de l'infection par VIH etudiees par biopsie medullaire chez quatre-vingt-cinq patients. *Arch. Anat. Cytol. Path.* 1991; **39**: 137-146.
7. Marche, C., Tabbara, W. and Mathiessen, L. The bone marrow in human HIV infection. A bioptic study of 125 cases. *Ann. med. Interne.* (Paris) 1992; **143**: 191-197.
8. Tripathi, A. K., Kalra, P., Misra, R., *et al*. Study of bone marrow abnormalities in patients with HIV disease. *JAPI* 2005; **53**: 105-109.
9. Paradela, A., Rivas, C., Fernandeza-Guerrero, M. and Roman, A. Histopathology of bone marrow biopsy in patients with human imunnodeficiency virus infection. *Rev Clin Esp* 1996; **196**: 9-15.
10. Khalil, S. H., Nounou, R. M., Frayha, H., Halim, M. A., Ellis, M., *et al*. Morphologic findings in patients with human immunodefiency virus (HIV) infection. *Ann. Saudi. Med.* 1996; **16**: 16-19.
11. Delacrelaz, F., Perey, L., Schmidt, P. M., *et al*. Histopathology of bone marrow in human immunodeficiency virus infection. *Vrchows Arch.* 1987; **411**: 543-551.
12. Bello, J. L., Burgaleta, C., Magalkon, M., *et al*. Hematological abnormalities in hemophilic patients with human immunodeficiency virus infection. *Am. J. Hematol.* 1990; **33**: 230-233.
13. Karcher, D. S. and Frost, A. R. The bone marrow in human immunodefiency virus (HIV)-related disease. Morphology and clinical correlation. *Am. J. Clin. Pathol.* 1991; **95**: 63-71.
14. Linman, J. W. and Bagby, G. C. The pre-leukemic syndrome (hemopoietic dysplasia). *Cancer* 1978; **42**: 854-864.
15. Koeffler, H. P. andGolde, D. W. Human pre-leukemia. *Ann Intern med* 1980;347-351
16. Katsarou, O., Terpos, E., Patsouris, E., *et al*. Myelodysplastic features in patients with long-term HIV infection and haemophilia. *Haemophilia* 2001; **7**: 47-52.
17. Re, M. C., Furlini, G., Zauli, G. and La Placa, M. Human immunodeficiency virus type-1 (HIV-1) and human haematopoietic progenitor cells. *Arch. Virol.* 1994; **137**: 1-23.
18. Leiderman, I. A. A glycoprotein inhibitor of *in vitro* granulopoiesis associated with *AIDS. Blood* 1987; **70**: 1267-1272.
19. Mbulateiye, S. M., Katabira, E. T., Wabinga, H., Parkin, D. M., Virgo, P., *et al*. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int. J. Cancer.* 2006; **118**: 985-990.