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Original Research Article

Hematological Changes in HIV Infection

Ruchee Khanna[1], Anjali Vijay S[2], Seemitr Verma[3], Vinay Khanna[4], Varun Kumar Singh[5], Chethan Manohar[6]

[1]Associate Professor, [3]Assistant Professor, [6]Professor, Department of Pathology, [4]Associate Professor, Department of Microbiology, Kasturba Medical College, MAHE University, Manipal, Karnataka 576104, India. [2,5]Assistant Professor, Department of Pathology, Melaka Manipal Medical College, MAHE University, Manipal, Karnataka- 576104, India.

Corresponding Author:

Anjali Vijay S, Assistant Professor, Department of Pathology, Melaka Manipal Medical College, MAHE University, Manipal, Karnataka- 576104, India.

E-mail: anjali.vijay@manipal.edu

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Abstract

Acquired immunodeficiency syndrome (AIDS), one of the most devastating infectious diseases to have emerged in recent history is characterised by impairment of cellular immunity with severe reduction in T-helper cells. Complications of AIDS include opportunistic infections, unusual neoplasms and unexplained lymphadenopathy. Hematological abnormalities "involving all the three lineages of blood cells" are among the most common complications of AIDS infection. Hundred cases of HIV patients were studied for various cytopenias and bone marrow changes. Cytopenias was seen commonly in HIV patients, most frequently anemia (97%), followed by thrombocytopenia (40%) and leucopenia (34%). Dyspoietic cells were seen in all lineages, in bone marrow study. Megakaryocyte dyspoiesis was seen in 91% cases on bone marrow biopsy (BMB), whereas bone marrow aspirate showed erythroid dyspoiesis in 75% cases and myeloid dyspoiesis in 45.8% cases. BMB showed atypical lymphoid aggregates in 11% cases and abnormal cells were seen in 9% cases. Granuloma was seen in 22 cases on BMB, out of which 8 cases showed AFB positivity and one case showed intracellular yeast form suggestive of histoplasma. The study showed disparity between peripheral cytopenias and marrow hyperplasia which suggests mechanisms of either ineffective hematopoiesis, abnormal release or increased peripheral destruction.

Keywords: HIV; AIDS; Hematological changes, Bone marrow changes; Cytopenia; Dyspoiesis.

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Introduction

Acquired Immune Deficiency Syndrome (AIDS) was first recognized as a new disease in 1981 when increasing numbers of young homosexual men were afflicted with unusual opportunistic infections and rare malignancies.[1] A retrovirus, now termed human immunodeficiency virus (HIV), was subsequently identified as the causative agent in 1983. Since then it has become one of the most devastating infectious diseases to have emerged in recent history.[2,3] The classical manifestation of AIDS is the impairment of cellular immunity with severe reduction in T-helper cells.[4,5] Complications

of AIDS include opportunistic infections, unusual neoplasms and unexplained lymphadenopathy. The hematologic complications of AIDS have not yet received much attention compared to its other features.[6]

Hematological abnormalities "involving all the three lineages of blood cells" are among the most common complications of HIV infection.[7] Cytopenias often cause symptoms like infections, anemia and bleeding and contribute to the complications suffered by patients with AIDS. There are multiple mechanisms for these changes and they are caused by both quantitative and qualitative defects in marrow. Immune cytopenias can occur directly due to HIV infection, whereas the effects of opportunistic infections, lymphomas, other malignancies and anti-retroviral therapy (ART) also play an important role.[8]

Most of the HIV patients show morphological abnormalities of bone marrow (BM) even in the absence of other pathological processes and the severity of abnormality increases as the disease worsens.[9] Despite the frequency of BM morphological abnormalities seen in HIV disease, there is no specific histological feature.[10,11] Around 70% of HIV infected patients show normocellular marrow.[12] Hypercellularity is found to be the most common abnormality in bone marrow.[10,13,14] Hypocellular marrows are seen in only 5% of cases.[9] Bone marrow hypoplasia and necrosis are rare even in advanced disease.[11] Dysplastic features are seen in approximately 70% of HIV patients.[14,15]

Materials and Methods

The study on hematological parameters and bone marrow changes in retroviral infection was carried out in Department of Pathology, Kasturba Medical College, Manipal University, Manipal.

Study type: Retrospective Prospective study

Study sample: 100 cases of HIV positive patients at Kasturba Medical College, Manipal University, Manipal over a period of 2 years whose bone marrow was done. Seventy three cases of 2014 and 27 cases of 2013 were reviewed.

Peripheral smears were stained with Leishman stain and various cytopenias and RBC morphology was studied in peripheral smear.

All bone marrow examinations, comprising of aspiration smears, trephine biopsy and special stains (Zeihl Neelson stain, Mucicarmine stain) were reviewed. Four bone marrow aspirates were excluded from the study as 3 showed dry tap and 1 was very dilute.

All the bone marrow aspirate smear were stained with Leishman's stain as per standard procedure. Bone marrow aspirate iron study was done in all cases using Perl Prussian Blue stain and presence of acid fast bacilli was studied using Zeihl Neelson stain, if done.

All trephine biopsy sections were stained with Hematoxylin and Eosin stain as per standard procedure. Special stains like Zeihl Neelson stain was done in 77 aspirate specimens and 51 biopsy specimens. Mucicarmine stain was performed on 32 bone marrow biopsy cases.

Results

Cytopenias

Out of 100 patients studied, majority (97%) of patients presented with anemia. Rest of the 3 patients had normal hemoglobin. Leucopenia was seen in 34% cases and thrombocytopenia in 40% patients. Most of the patients had normal WBC count and platelet count. Pancytopenia was seen 25% cases.

CD4 COUNT (/μL)

CD4 counts were available for 92 cases. Majority, 73 cases (79.3%) had CD4 counts less than 200/μL. Only 2 cases (2.2%) had CD4 counts more than 500/μL.

RBC Picture on Peripheral Smear

Peripheral smear was available for evaluation in all 100 cases. Majority of patients showed normocytic normochromic RBC morphology (85%). Microcytic hypochromic RBC picture was seen in 5% cases whereas macrocytes were present in 10% cases.

On comparing bone marrow aspirate and bone marrow biopsy cellularity, BMB is considered more reliable in assessing cellularity of marrow since the architecture of the marrow is intact. This explains the discrepancy seen in assessment of cellularity between aspirate and biopsy in the present study. BMA is more reliable to study erythroid and granulocyte number because the M:E ratio would reflect the number of the respective cell lineage. In the present study, the assessment of number of erythroid and myeloid elements in the aspirate and

Table 1: Comparison Between BMA and BMB

	BMA (*n* = 96)	BMB (*n* = 100)
Cellularity for age, Cellular	39 (40.6%)	55 (55%)
Hypocellular	7 (7.3%)	16 (16%)
Hypercellular	50 (52.1%)	29 (29%)
Erythropoiesis: Normal	50 (52.1%)	62 (62%)
Decreased	28 (29.1%)	22 (22%)
Increased	18 (18.8%)	16 (16%)
Erythropoiesis dyspoiesis	72 (75%)	NA
Granulopoiesis : Normal	50 (52.1%)	53 (53%)
Decreased	18 (18.7%)	9 (9%)
Increased	28 (29.2%)	38 (38%)
Granulopoiesis dyspoiesis	44 (45.8%)	NA
Megakaryocyte: Normal	44 (45.8%)	34 (34%)
Decreased	42 (43.8%)	2 (2%)
Increased	10 (10.4%)	64 (64%)
Megakaryocyte dyspoiesis	68 (70.8%)	91 (91%)
Lymphoid cells, increased	6 (6.2%)	31 (31%)
Eosinophils, increased	14 (14.6%)	25 (25%)
Plasma cells, increased	46 (47.9%)	37 (37%)

biopsies is comparable. Morphology of erythroid and myeloid cells are best studied on bone marrow aspirate in which various dyspoietic forms can be studied. Bone marrow biopsy is more reliable for assessment of megakaryocyte number since BMA diluted with sinusoidal blood can give false impression of reduced megakaryocyte number. This explains the reduced megakaryocytes which were seen in 43.8% in BMA as against 2% in BMB, since 57 cases in the present study had a dilute BMA. Sixty four percent of BMB showed increased megakaryocytes, as compared to 10.4% in BMA, which makes BMB more reliable to assess megakaryocyte number. All the dyspoietic forms of megakaryocyte are better picked up on BMB, which explains the increased number of hypolobated forms, polylobated forms and multinucleated forms seen in BMB in the present study. However micromegakaryocytes and immature forms are appreciated more reliably in BMA. In the present study, micromegakaryocytes were seen in 71% BMB, as against 30.2% in BMA. This descripancy is perhaps due to the section passing through one pole of megakaryocyte which may appear as micromegakaryocyte in the biopsy. Anucleate megakaryocyte fragments seen in 3 cases in BMB were also perhaps due to the above reason. Immature megakaryocyte were seen in 41.7% of BMA as against 23% in BMB since the cytoplasmic basophilia which can be appreciated in the BMA which helps in recognising them as immature forms.

Lymphoid and plasma cell number is more reliably picked up on BMA. Eosinophil number is better appreciated on BMB as dilution may affect number of eosinophils in BMA, as seen in the present study in which increased eosinophils were appreciated in 25% in BMB as compared to 14.6% cases in BMA.

BMA Cellularity (Corrected for Age) and Peripheral Cytopenia

Peripheral cytopenias were not directly predictive of cellularity on marrow. Cytopenic patients most frequently showed hypercellular marrow. Forty eight (51.61%) anemic patients, 17 (54.83%) leucopenic and 22 (61.11%) thrombocytopenic patients showed hypercellular marrow on bone marrow examination. Hypocellular marrow aspirate was associated with least incidence of cytopenias.

Relation Between BMB Cellularity and Peripheral Cytopenia

Majority of patients with anemia, 52 cases (53.60%), 15 cases (44.11%) of leucopenic patients, and 17 cases with thrombocytopenia (42.5%) had cellular marrow spaces. Bone marrow suppression was the cause of cytopenia in 16% of cases. Twenty nine percent cases had hypercellular marrow suggesting intramedullary or peripheral destruction as the cause of cytopenia.

BMA- Erythroid Dyspoiesis

Bi/multi nucleate forms seen in 51 cases (53.1%) and megaloblastoid forms found in 27 cases (28.1%) were the most common dyspoiesis seen in erythroid lineage, followed by presence of nuclear budding in 18 cases (18.8%), karyorrhexis in 9 patients (9.4%), intranuclear chromatin bridges and cytoplasmic vacuolations in one case each (1%).

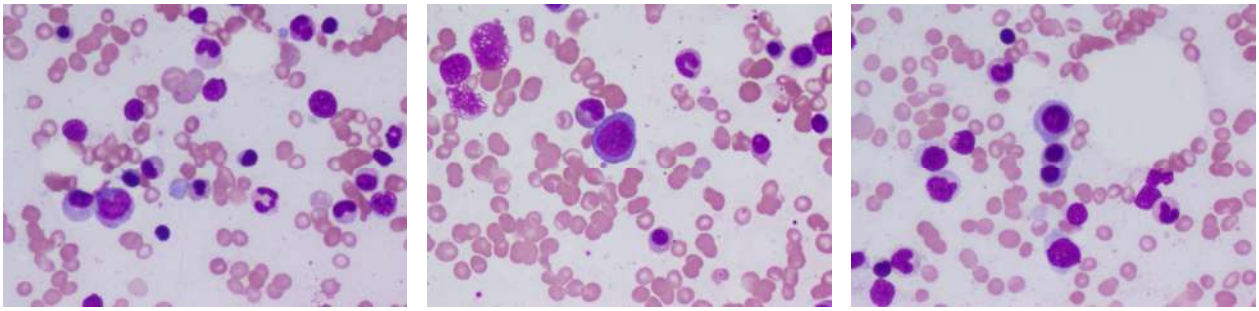


Fig. 1: Erythroid Dyspoietic Forms-Nuclear Budding, Megaloblastoid Form, Binucleate Forms.

BMA- Myeloid Dyspoiesis

Myeloid dyspoiesis was seen in 44 cases, out of which giant forms, 27 cases (28.1%) and abnormal nuclear lobation, 23 cases (24%) were most commonly seen, followed by detached nuclear lobes, 8 cases (8.3%), hyposegmented forms, 2 cases (2.1%), hypersegmented forms (1%), hypogranular forms (1%) and ring form (1%).

Megakaryocyte Dyspoiesis

Megakaryocyte dyspoiesis was seen in 68 cases (70.8%) on BMA. The most commonly recognized forms were multinucleate forms in 33 patients (34.4%) and micromegakaryocytes in 29 cases (30.2%) whereas BMB showed megakaryocyte dyspoiesis in 91% cases with micro megakaryocyte and hypolobated forms commonly seen.

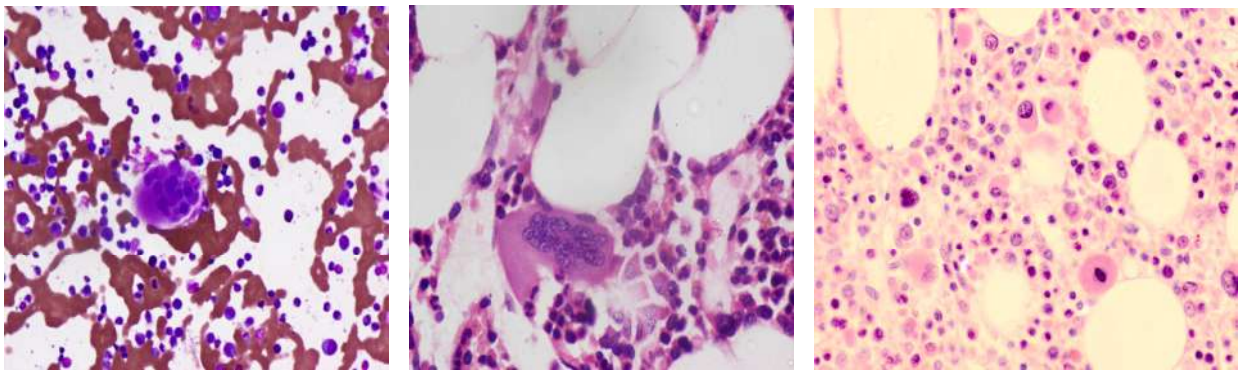


Fig. 2: Megakaryocyte Dyspoiesis- Multinucleated Megakaryocyte, Polylobated Form, Hypolobated Form.

BMB- Aggregate of Lymphoid Cells and Abnormal Cells

Out of 100 cases studied, 18% cases showed benign lymphoid nodule. Aggregate of atypical lymphoid cells were seen in 11%, and 9% showed infiltration by abnormal cells. Five out of nine cases of abnormal cells were not associated with lymphadenopathy or any evidence of systemic lymphoma. Rest of the 4 cases showed systemic lymphoma involvement, out of which, one case presented with rectal proliferative growth, which on biopsy showed HIV associated Non-Hodgkin's Immunoblastic Lymphoma with plasmacytic differentiation. Second case had gastric growth, which on biopsy showed NHL-DLBCL. The third patient presented with mass with disc prolapse involving T5-T6 level, which was diagnosed as NHL-Mantle cell lymphoma on biopsy. Fourth case had cervical lymphadenopathy, which was biopsied and diagnosed as Anaplastic Large cell Lymphoma, null cell type.

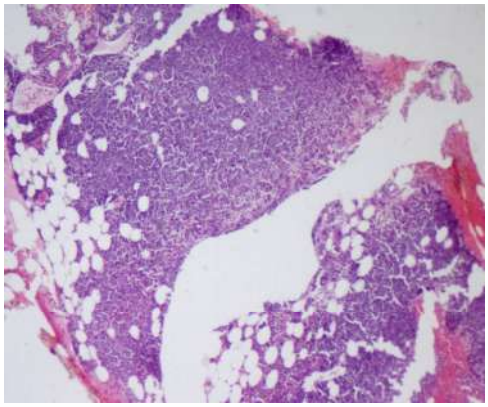


Fig. 3: Aggregate of Atypical Lymphoid Cells.

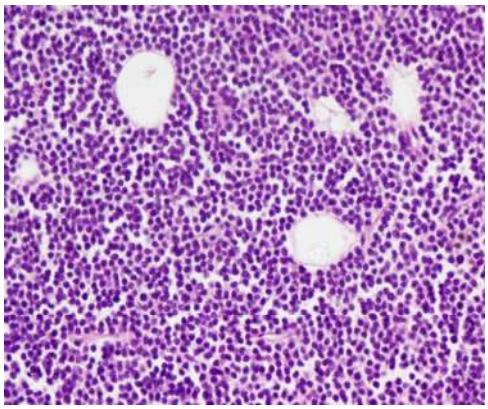


Fig. 4: NHL-Low Grade (Mantle Cell Lymphoma)

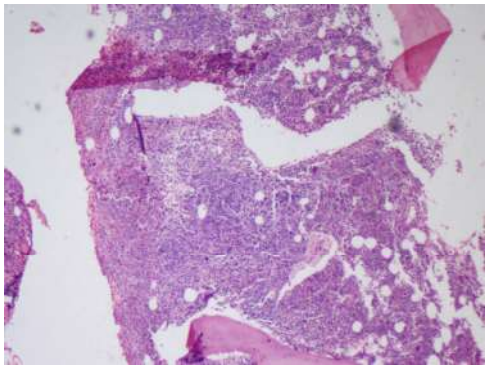
Relation Between CD4 Count and Granuloma

BMB AFB and BMA AFB was positive in 8 and 1 case respectively, in 22 cases of granuloma, with CD4 counts <200/µL. Six cases of well -defined granuloma and 2 cases of ill- defined granuloma had BMB AFB positive. Apart from AFB positivity in 8 cases, intracellular yeast form suggestive of Histoplasma was seen in one case.

*Total 28% cases showed granuloma, but 3 cases were not included in the table as CD4 count was not available for them.

Association Between CD4 Count and Lymphoma

Eight cases (11%) with atypical lymphoid aggregates and 5 cases (6.8%) with abnormal lymphoid cells had CD4 counts of <200/ µL. *Cases with aggregate of atypical lymphoid cells/ abnormal cells without CD4 count, is not depicted in the table.



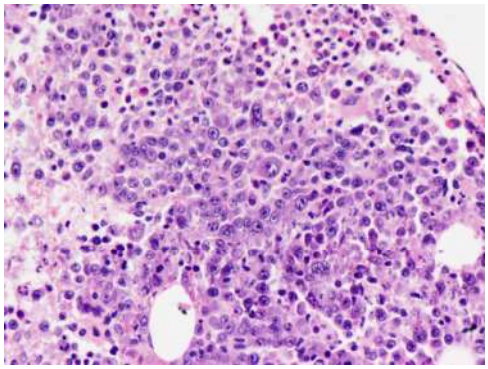
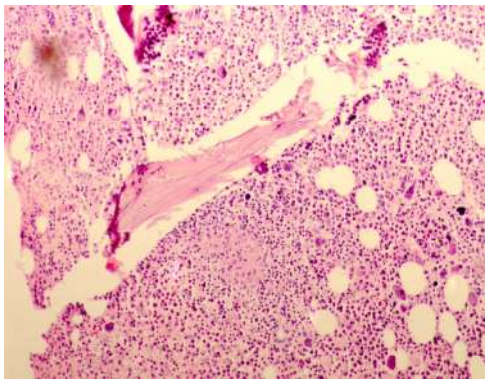


Fig. 5: NHL-High Grade (HIV Associated NHL With Plasmacytic Differentiation).



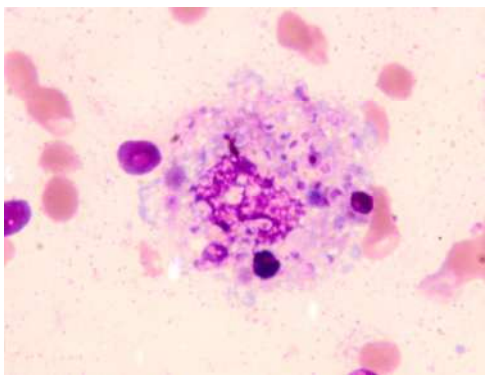


Fig. 6: Histoplasma in Macrophage in BMA.

Discussion

A variety of hematological abnormalities are associated with infection by HIV. Peripheral cytopenias involving one or more hematopoietic cell lineage is the most common abnormality seen. Bone marrow aspiration and biopsy frequently revealed hypercellularity, dysplasia involving one or more hematopoietic cell line, increased plasma cells and histiocytes, lymphoid aggregates, granulomas and infiltration by lymphomas.

Table 2: Cytopenia

	Anemia	Leucopenia	Thrombocytopenia	Pancytopenia
Spivak et al.[16] (*n* = 12)	10 (83.33%)	8 (66.66%)	3 (25%)	2 (16.66%)
Castella et al.[12] (*n* = 49)	42 (85.71%)	28 (57.14%)	15 (30.61%)	NA
Kotwal et al.[17] (*n* = 55)	45 (81.81%)	7 (12.72%)	11 (20%)	10 (18.18%)
Parinitha et al.[18] (*n* = 250)	210 (84%)	163 (65.2%)	45 (18%)	17 (6.8%)
Venkataraman et al.[19] (*n* = 19)	18 (94.73%)	8 (42.10%)	13 (68.42%)	NA
Present study (*n* = 100)	97 (97%)	34 (34%)	40 (40%)	25 (25%)

In the present study 97% patients had anemia and 34% had leucopenia, in concordance with the study done by Venkataraman et al.[19] (94.73% and 42.10% respectively). Thrombocytopenia was seen in 40% cases, in concordance with study done by castella et al.[12] (30.61%). Pancytopenia was seen in 25% cases, in concordance with the study done by Kotwal et al.[17] (18.18%).

Table 4: Bone Marrow Changes in HIV Patients

	Karcher et al.[21] (*n* = 212)	Kotwal et al.[17] (*n* = 55)	Mittal et al.[22] (*n* = 75)	Spivak et al.[16] (*n* = 12)	Castella et al.[12] (*n* = 49)	Present study
Cellular marrow	72/212 (33.96%)	37 (67.3%)	47 (62.6%)	4 (33.3%)	35/55 (63.63%)	55/100 (55%)
Hypercellular marrow	112/212 (52.83%)	10 (18.2%)	12 (16%)	5 (41.66%)	8/55 (14.54%)	29/100** (29%)
Hypocellular marrow	28/212 (13.20%)	8 (14.5%)	16 (21.33%)	3 (25%)	9/55 (16.36%)	16/100** (16%)
Normal M:E	NA	NA	NA	NA	25/55 (45.45%)	50/96 (52.1%)*
Increased M:E	NA	NA	NA	NA	7/55 (12.72%)	28/96 (29.2%)*
Decreased M:E	NA	NA	NA	NA	17 (34.69%)	22/96 (22.91%)*
Erythroid dysplasia	85/152 (55.92%)	2 (3.6%)	51 (68%)	NA	NA	72/96 (75%)*
Granulocytic dysplasia	28/152 (18.42%)	5(9.1%)	18 (24%)	NA	NA	44/96 (45.83%)*
Megakaryocytic dysplasia	47/152 (30.92%)	1(1.8%)	27 (36%)	NA	NA	91/100** (91%)
Granuloma	28/212 (13.20%)	7 (12.7%)	1 (1.33%)	NA	8/55 (14.54%)	28/100** (28%)
AFB +ve	12/212 (5.66%)	3 (5.4%)	0 (0%)	NA	6/55 (10.90%)	8/100** (8%)

*M:E ratio, erythroid and granulocytic dysplasia was studied in 96 cases, in whom bone marrow aspirate was available

**Cellularity, megakaryocyte dysplasia, granuloma and AFB positivity was studied in 100 cases

Majority of the patients showed NCNC anemia (85%) followed by MCHC anemia (5%), in concordance with the study done by Castella et al.[12] (73% and 6% respectively). Macrocytic RBC picture was seen in 10% cases, in concordance with the study done by Kotwal et al.[17] (11.11%).

Table 3: Morphological Classification of Anemia Seen In HIV Infected Patients

Anemia	Kotwal et al.[17] (*n* = 55)	Parinitha et al.[18] (*n* = 250)	Marin et al.[20] (*n* = 63)	Castella et al.[12] (*n* = 49)	Present study (*n* = 100)
NCNC	30 (66.66%)	101 (40.4%)	11 (17%)	36 (73%)	85%
MCHC	10 (22.22%)	18 (7.2%)	2 (3%)	3 (6%)	5%
Macrocytic	5 (11.11%)	15 (6%)	NA	3 (6%)	10%

Most of the patients in the study had cellular marrow (55%), followed by hypercellular (29%) and hypocellular marrow (16%), which is in concordance with the study done by Kotwal et al.[17] (67.3%, 18.2%, 14.5% respectively). M:E ratio was found to be normal in most of the cases (52.1%), in concordance with study done by Castella et al.[12] (45.45%). The present study shows predominantly megakaryocyte dyspoiesis (91%), followed by erythroid dyspoiesis (75%) and myeloid dyspoiesis (45.83%), not in concordance with other studies mentioned in the table. In the present study, 28% cases showed granuloma, out of which 8 cases were AFB positive, which was in concordance with the study done by Karcher et al.[21] (granuloma-13.20% and AFB +ve–5.66%).

Table 5: Opportunistic Infections and Malignancy in HIV

Studies	Opportunistic infections	Malignancy
Karcher et al.[21] (*n* = 178)	21/212 (9.90%)	19/216 (8.79%)
Kotwal et al.[17] (*n* = 55)	4(7.27%)	2 (3.63%)
Treacy et al.[15] (*n* = 20)	3(15%)	1(5%)
Delacretaz et al.[23] (*n* = 18)	2(11.11%)	4 (22.22%)
Venkataraman et al.[19] (*n* = 19)	NA	2 (10.52%)
Castella et al.[12] (*n* = 49)	11/55(20%)	3/55 (5.45%)
Present study (*n* = 100)	9 (9%)	4 (4%)

Opportunistic pathogens were seen in 9% cases in the present study, which is in concordance with the study done by Karcher et al.[21] (9.9%). Eight cases showed AFB positivity along with granuloma in bone marrow biopsy in the present study, along with one case showing evidence ofHistoplasma in bone marrow specimen. According to the study done by Karcher et al.,[21] 12 cases (6%) showed evidence of acid fast bacilli, 5 cases (2%) showed encapsulated Cryptococcus forms and 4 cases (2%) showed intracellular yeast forms consistent with Histoplasma. Out of the 9 cases that showed abnormal cell infiltration in bone marrow biopsy, only 4 cases showed systemic lymphoma involvement. Rest of the 5 cases probably showed aggregate of atypical lymphoid aggregates which were perhaps mistaken for lymphoma. However follow-up data for these patients is not available. Study by Karcher et al.[21] showed Burkitt like lymphoma in 10 cases (5%), Hodgkin's Lymphoma in 7 cases (3%), Large cell immunoblastic lymphoma and Kaposi Sarcoma in one case (1%) each. Kotwal et al.[17] studied 55 patients and found 2 patients with NHL- DLBCL. Thus most studies have reported high grade lymphoma which is in concordance with the present study.

Notes:

- Funding information:
- This study has not received any funding from any agency.

- Compliance with ethical standards:

The study was reviewed and approved by institutional ethics committee at kasturba medical college, manipal. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the helsinki declaration of 1975, as revised in 2008. The study is retrospective and as per institutional policy, consent was taken from all patients, during admission, that

their data will be used for educational and research purposes.

Conflict of interest statement:

The authors declare that they have no conflict of interest.

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