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Original Article

BONE MARROW ASPIRATION AND BIOPSY FINDINGS IN PATIENT WITH HEMATOLOGICAL DISORDERS IN A TERTIARY CARE CENTER FROM EASTERN NEPAL: AN INSTITUTIONAL EXPERIENCE

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ABSTRACT

Background

Bone marrow study is an important study which is performed when the peripheral blood examination and other laboratory tests and clinical signs and symptoms are suggestive and sometimes inconclusive of both hematological neoplastic and non-neoplastic conditions.
The aim of this study was to study about the indications of bone marrow to assess the diagnostic value and comparison of microscopic findings with immunophenotyping and molecular studies.

Methods

A total of 102cases were analyzed retrospectively and prospectively from January 2022 to October 2023. All the bone marrow aspiration and trephine biopsy received at the laboratory during this period were included in the study and other cases were analyzed form medical record of the department.

Results

Among the 102 cases, mean age of the patient was 48 years and majority were male patients. The age range was between 17-80 years. The male: female ratio was 1.25:1. Weakness was most common presenting complain. Acute leukemia was the most frequent diagnosis (24.5%) followed by myeloproliferative neoplasm (7.8%), primary aplastic anemia (6.9%), myelodysplastic syndrome (5.8%), megaloblastic anemia (4.9%) and plasma cell dyscrasia (3.9%), CLPD (2.9%), ITP (1.9%). Reactive marrow constituted 3.9% and few of the rare diagnosis included hypereosinophilia with PDGFRA mutation,Leishmaniasis etc.

Conclusions

The study concludes the bone marrow aspirate and biopsy examination is still the gold standard technique for screening and definite diagnosis of hematological conditions. Immunophenotyping and molecular studies are important for treatment purpose and in case of cytomorphological dilemma.

Keywords: Bone marrow aspiration, Bone marrow pathology, Cytogenetics, Flow cytometry, Hematological diagnosis, Molecular studies, Trephine biopsy.

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INTRODUCTION

Bone marrow aspiration cytology and trephine biopsy is one of the important examination in diagnosis, categorizing of hematological disorders, infectious conditions, metabolic disease and metastatic carcinomas.[1] Bone marrow comprises of 3.5 to 6% of total body weight and is the major site of hematopoiesis. The bone marrow consists of the three hematopoietic lineage of cells, adipose tissue and stromal cells. The stroma is composed of connective tissue and vascular structures. The differentiation and maturation of granulocytes, monocytes, erythrocytes and megakaryocytes occur in bone marrow.[2]

Bone marrow examination is done mostly to find out causes of non-resolving anemia, bi-cytopenia or pancytopenia such as aplastic anemia, ineffective hematopoiesis, megaloblastic anemia, myelodysplastic syndrome, bone marrow replacement or invasion by leukemia, lymphoma, metastatic tumor, myelofibrosis, metabolic bone disease, storage disease, granulomatous conditions, and haemophago-lympho-histiocytosis and other infectious diseases[3].The procedure is also performed for culture of bone marrow, in the assessment of patients with pyrexia of unknown origin.[3,4] One of the major elements to be analysed in bone marrow examination is cellularity based upon the age. In the bone marrow aspirate,the variation in cellularity can occur due to hemodilution ;so the cellularity is assessed based upon the cellularity in the particles,however best assessed on bone marrow biopsy[4].The myeloid to erythroid ratio or the non erythroid to erythroid ratio is calculated based on the differential cells count[5].The count and abnormalities in the myeloid precursors cells, such as hypogranulation, hypergranulation , agranulation, hypolobation, pelguer-huet neutrophils is noted.The number of megakaryocytes including clusters, mature, immature forms, dysplasia, micromega-karyocytes, hypolobated or lobe segmented forms are noted. The percentage of erythroid cells and presence of features like-normoblastic or megaloblastic forms, binucleation, nuclear irregularity, karyorrehixis, karyolysis, internuclear bridging is documented. Viral inclusion like parvovirus,the percentage of precursors of erythroid series like pronormoblast, basophilic,orthochromaticnormoblast,polychro matophilic erythrocytes and Rbc morphology is also taken account[4].The major indication for the examination of bone marrow includes suspicion of leukemia in case of hyperleucocytosis or pancytopenia.In such cases the number of atypical cells including lymphoblast or myeloid blasts,monoblasts or abnormal promonocyte and presence or absence of Auer rods are noted.[5] The cytomorphologic assessment of the bone marrow study has nowadays been complemented by use of ancillary assays,such as flowcytometry, cytogenetic studies, molecular study and immunohistochemistry[5]. With introduction of NGS, Next generation sequencing like studies, the genetic diversity and clinical spectrum of leukemia and other hematologic neoplasms have become more clear and thus help in targeted therapeutic options. So, the bone marrow study has became more critical for categorizing, monitoring and planning the therapy in hematological malignancy[4,5].

METHODS

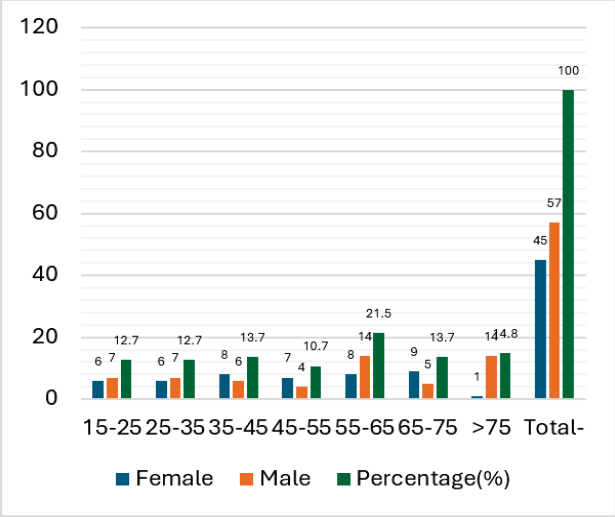
This was a observational, crossectional study conducted in the Department of Clinical Pathology, B & C Medical College, Teaching Hospital and research center from from January 2022 to October 2023. The procedure was performed by expert hematologist under aseptic conditions with consent from the patient. A total of 102 case were analyzed out of which 8cases were hemodiluted .For retrospective study, the reports and peripheral blood smear slides, bone marrow aspiration and biopsy slides were obtained from the records at the department. Peripheral blood smear and the bone marrow slides were examined. BMA slides were stained with May-Graunald Geimsa stain, Periodic Acid Schiff(PAS)etc. The slides were analyzed by pathologists. The results of the morphological examination were further confirmed using ancillary techniques like flow cytometry molecular studies like-RT-PCR,and cytogenetic studies including FISH, karyotyping by the samples for flow cytometry were collected in EDTA vials and cytogenetics were collected in heparin vials .The data from every patient including family and clinical data,physical examination, indication for BMA, and laboratory tests were collected from records.The data was entered in microsoft excel 2007and analyzed in SPSS version16.Inclusion criteria was set as all

the bone marrow aspiration and trephine biopsy received at the laboratory. Exclusion criteria was set as BMA with inadequate material or dry tap.The whole analysis was done according to declaration of Henlski.

RESULTS

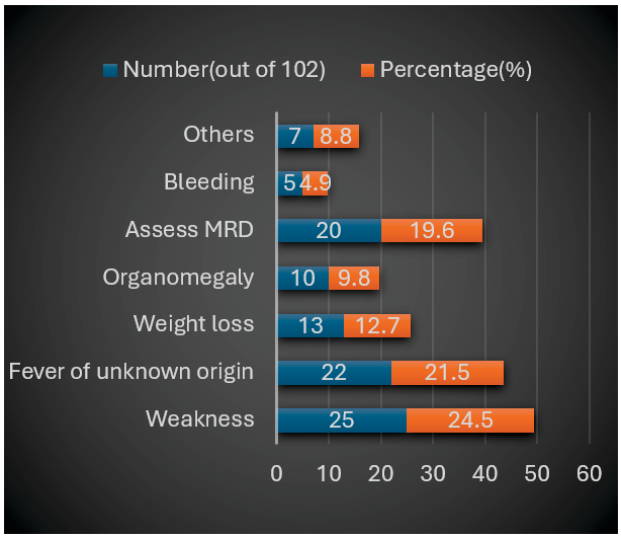
The mean age of the patients was 48 years and majority were male patients.The majority of the patient fall under 55-65 for males and 65-75 for females as shown in figure 1.

Figure :1 Age and Gender Distribution



Besides workup for minimal residual disease status,the majority of the cases presented with weakness(24.5%), followed by fever of unknown origin(21.5%),weight loss(12.7%), organomegaly (9.8), and bleeding (4.9%) as shown in Figure 2.

Figure 2: Presenting Symptoms

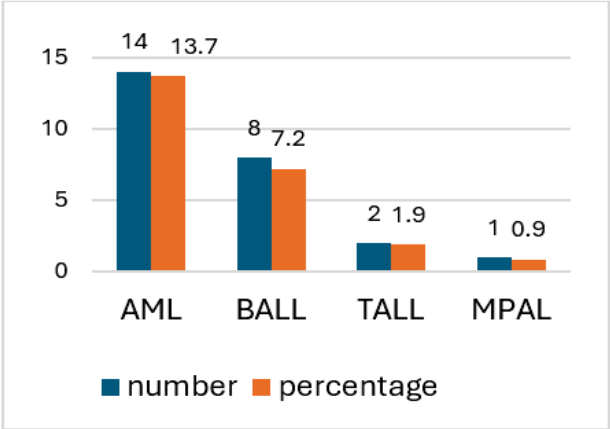


The peripheral blood smear of the pateints showed pancytopenia (15.6%); anemia (10%); bicytopenia (7.8%); Acute leukemia (myeloid-5% ,Lymphoid-6%); CML-4.5%; thrombocytopenia (26.4%); pancytopenia CLPD-3%; thrombocytosis-2%;neutrophilic leukocytosis-3%,normal findings-7%;dysplasia in neutrophils(2%), leucoerythroblastic picture;3% showed few blast cells in peripheral blood. The findings like pancytopenia, bicytopenia, thrombocytopenia, thrombocytosis etc, were not disease specific and were present in various conditions.

Bone marrow aspiration and biopsy findings:

Out of 102 total cases 24.5% constitute acute leukemia cases out of which 13.7% were AML with 1 cases of MO;2 cases of M2;4 cases of M3;2 cases of M1;2 cases with AML1 ETO;t(8,21)(q22;q22);7.2% constitute of B-Acute lymphoblastic leukemia; CALLA positive,1.9% TALL(1cases of EPTALL,1-TALL);1 case was Mixed Phenotype Acute leukemia which shows dual B and T cell markers on flow cytometry as summarized in Figure 3. below.

Figure: 3 Leukemia case distribution



The cases were further divided into malignant and non -malignant hematological conditions.Table1. explains the of malignant hematological conditions obtained in the study. Acute leukemia constitutes 24.5% ,plasma cell neoplasm 3.9% cases, myeloproliferative neoplasm constitute of the 7.8% cases, metastatic cases 0.9%, myelodydplastic disorder-5.8%, relapse cases 3.9% and MRD negative cases 15.6%.The sub distribution of this cases further and final diagnosis after flow cytometry and molecular studies are mentioned in the Table 1

Table 1: Malignant hematological conditions

Bone marrow diagnosis	Final diagnosis	Number	Flow cytometry /molecular studies
I.Acute leukemia	Total-	25(24.5%)	
1.AML	Acute myeloid leukemia	14(13.72%)	M0-1, AML1-ETO with t(8;21)(q22;q22):2 NPM1:1 PML-RARA:1; M5:1,M3:4,M2:2,M1:2
2.ALL	B-Acute lymphoid leukemia	8(7.2%)	CALLA positivity
3.ALL	T-Acute lymphoid leukemia	2(1.9%)	EPTALL-1,T-ALL:1
4.AL	Mixed Phenotype Acute leukemia	1(0.9%)	Bcell and Tcell markers-dual expression.
II.Plasma cell neoplasm	Total-	4(3.9%)	
1..Multiple myeloma	Multiple myeloma	1	18%clonal plasma cells ;IgG kappa M protein on IFE.t(11,14)onFiSH
3.Multiple myeloma	Light chain myeloma	1	IgA Kappa with Hb E heterozygous
4.Plasma cell dyscrasia	Polyclonal gammopathy	1	8% polyclonal plasma cell
5.Plasma cell leukemia	Plasma cell leukemia	1	40%plasma cells; M band in IgG lambda region;t(4,14);IGH:MAF
Plasma cell dyscrasia	MGUS	1	7% clonal plasma cells
III.Myeloproliferative neoplasm	Total	8(7.8%)	
1.CML	CML(AP+CP+BP)	1+3+1(3.9%)	t(9,22)(q34.1;q11.2) BCR-ABL1 fusion gene by RT-PCR ,p210
2.Essential thrombocytosis	Essential thrombocytosis	2(1.9%)	MPL;CALR, Mutant of Exon 9(Type 1) Deletion positive
3.Polycythemia vera	Polycythemia vera	2(1.9%)	JAK-2 V617 JAK2 exon-12 mutation
4.CLPD	CLL/SLL	3(2.9%)	13q14 del in FISH. CD5,CD23,CD200,CD20 positive,sIGL-lamda dim
5.Hypereosinophilia	Myeloid lymphoid neoplasm with eosinophilia and gene rearragement	1(0.9%)	PDGFRA gene rearrangement
IV.Malignant non-hematological condition-Signet ring adenocarcinoma		1(0.9%)	
V.MDS		6(5.8%)	FISH for MDS: Del7q, 20q, 15q deletion; Flow for blast percentage-EB1,EB2
VI.MDS to AML(EBII from MDS,EB2 from MDS)		2(1.9%)	Tp53 mutation
VII.Relapsed ALL+AML(>5%blast in BMA)		2+2(3.9%)	>0.01%blast by flow or Quantitative pcr positive
VIII.MRD cases on remission		16(15.6%)	<o.o1 %blast by flow or Quantitative pcr negative

Table 2: shows that out of the total cases 34.3% of cases showed non-malignant findings. Reactive marrow constitute of 3.9% cases. immunethrombocytic purpura 1.9%, nutritional anemia 1.9%,megaloblastic anemia 4.9%,mixed iron and vitamin B-12 deficiency was observed in 1.9%, autoimmune hemolytic anemia in 0.9%,persistent neutrophilic leukocytosis in 1.9%;methotrexate induced aplastic anemia in 0.9%,dengue induced aplastic anemia in 0.9%.Leishmaniasis was noted in 1 case(0.9%).The further ancillary studies performed are explained below.

Table 2 : Non malignant Hematological conditions-35

Bone marrow/Final diagnosis	Number	Percentage	Ancillary /other studies
Reactive marrow	4	3.9%	None
ITP	2	1.9%	None
Nutritional anemia IDA	2	1.9%	Iron profile
Megaloblastic anemia	5	4.9%	Vit-B12,folicacid,intrinsic factor study
Mixed deficiency anemia	2	1.9%	Both above.
Reactive myelofibrosis	1	0.9%	Reticulin stain and Molecular studies to rule out PMF
Drug induced myelofibrosis	1	0.9%	Reticulin stain and Molecular studies for PMF
Aplastic anemia	7	6.8%	Cytogenetics,chromosomal breakage studies were adviced.
PNH	2	1.9%	PNH clones in neutrophils and monocytes: Negative.CD45, CD15, CD64, GPI linked antibodies CD14, CD24 and FLAER.
Hypocellular marrow	2	1.9%	none
Autoimmune hemolytic anemia	1	0.9%	Coombs test,Serum LDH etc
Persistent Neutrophilic leukocytosis (BCR1-ABL negative)	2	1.9%	BCR-ABL-1 negative
Drug induced aplastic anemia	2	1.9%	Cytogenetics,chromosomal breakage studies were adviced.
Infection induced/Virus induced aplastic anemia	1	0.9%	Cytogenetics,chromosomal breakage studies were adviced.
Leishmaniasis	1	0.9%	Confirmed with rk-39 test

DISCUSSION

Bone marrow aspiration and biopsy is an important examination for diagnosis of several hematological neoplastic, non-neoplastic conditions as well as nonhematological conditions and treatment monitoring.[6,7]

In our study,out of total cases 24.5% constitute acute leukemia cases.13.7%were diagnosed AML (1 case of MO; 2 cases of M1,2 cases of M2;4 cases of M3; 2 cases with AML1, ETO;t(8,21)(q22;q22)).

ALL cases were 7.2%; constituted of B-Acute lymphoblastic leukemia; CALLA positive,1.9% TALL (1cases of EPTALL,1-TALL);1 case was Mixed Phenotype Acute leukemia which shows dual B and T cell markers on flow cytometry. Our findings support that not only morphology, immunophenotyping complemented by molecular studies, like RT-PCR, Next generation sequencing etc. are needed for proper categorization of Acute leukemias.[8,9]

Plasma cell disorder constitute of 3.9% of disorders consisting of multiple myeloma(1),Plasma cell leukemia(1);Polyclonal gammopathy(1);light chain myeloma(1);MGUS(1). Bone marrow studies showed increased plasma cells and flowcytometry; serum protein electrophoresis and Immunofixation was done to see the clonality of plasma cells and for light chain restriction study.The count of plasma cell along with count in touch imprint and confirmation with excess of plasma cells on biopsy helped in more accurate diagnosis of the plasma cell dyscrasia.[10]

Chronic myeloid leukemia constitute 3.9% of the cases, every cases showed hyperleukocytosis with increase in myeloid precursor cells.The translocation study;t(9,22)(q34.1;q11.2)BCR-ABL1 fusion gene was by RT-PCR ,p210 transcript was detected. Other similar study also showed 4%CML cases.[11] Other myeloproliferative neoplasm ET (1.9%), PCV (1.9%) were diagnosed by bone marrow studies; later molecular studies was conducted for therapeutic purposes.

CLL (2.9%) constituted of the CLPD cases and all the cases diagnosed on peripheral blood and aspirate and showed increased atypical lymphocytes with soccer ball like chromatin and showed13q 14 del in-FISH study which is one of the most common cytogenetic finding in CLL cases.[12]

One percent case showed hypereosinophilia and PDGFRA gene mutation on cytogenetics analysis for hypereosinophilia.[13]

Myelodysplastic syndrome (3.9%) were mainly found in cases with non- resolving anemia and bone marrow showed dysplasia in myeloid, megakaryocytic or erythroid series.Myeloid series showed dysplasia in form of hypo-granulation ,hyper- granulation, hypolobation. Megakaryocyte showed hypolobated and hyperlobated forms. Erythroid series showed dysplasia in form of karyorrehxis, karyolysis etc.Blasts more than 1%-5% were classified as EB-1.MDS confirmation was done by blast count aided with flowcytometry and FISH study in cases with blasts percentage 6-19%.[14]Two cases

converted from MDS to AML in follow up. Both were found to have Tp53 mutations.[15]

Out of total 4 cases (3.9%), two known cases of ALL and two known cases of AML showed relapse on minimal residual disease evaluation; rest 16 cases showed less than 5% blasts on bone marrow aspirate and were later confirmed on flow cytometry by blasts percentage less than 0.01%.[16]

Out of total cases 34.3% of cases showed non-malignant findings. Reactive marrow constitutes of 3.9% cases. Immunethrombocytic purpura 1.9%,nutritional anemia 1.9%, megaloblastic anemia 4.9%,mixed iron and vitamin B-12 deficiency was observed in 1.9%, autoimmune hemolytic anemia in 0.9%, persistent neutrophilic leukocytosis in 1.9%, methotrexate induced aplastic anemia in 0.9%, dengue induced aplastic anemia in 0.9%. Leishmaniasis was noted in 1 case(0.9%). This findings were similar to findings in the done in institute based on central Nepal.[17]Reactive myelofibrosis was noted in 0.9%,Ayurvedic drug induced myelofibrosis was noted in 0.9% and aplastic anemia was noted in 6.8%;hypocellular marrow due to unknown etiology was noted in 1.9%. Other similar studies showed total incidence of hypoplastic marrow to be 5.3%,19%,29%,14% respectively.[17-20]

Reactive marrow was the diagnosis of exclusion and iron deficiency, hemolytic anemia and megaloblastic anemia were also the diagnosis of exclusion aided with biochemical studies. Infectious etiology-leishmaniasis was detected on bone marrow aspiration study. PNH and neutrophilic leukocytosis were diagnosis of exclusion and were diagnosed by flow cytometry and BCR-ABL negative status.

PNH cases showed cellular bone marrow, myeloid and megakaryocytes lineage cells were decreased in bone marrow aspiration studies however showed increased erythroid precursors, less cytopenia and showed feature of hemolysis in peripheral smear. Mixed phenotype and M0 cases required flow cytometry for confirmatory diagnosis[21].However 23/25 leukemia cases were suspected on peripheral blood smear.MGUS and polyclonal gammopathy were diagnosed by SPEP and IFE studies[22],multiple myeloma and plasma cell leukemia were diagnosed in bone marrow studies. CLPD, Chronic lymphoid leukemia,small lymphocytic leukemia were diagnosed primarily on bone marrow and flow cytometry was done for MRD status. Metastatic adenocarcinoma with signet ring cells was confirmed on bone marrow trephine biopsy[23].Immunethrombocytic purpura, essential thrombocytosis, aplastic anemia, hypocellular marrow were diagnosed on bone marrow biopsy. So, bone marrow aspiration and biopsy along with combination of various ancillary techniques are gold standard in diagnosing various hematological conditions. Sensitivity ranges from 75-100% according to category of cases,the sensitivity increases when bone marrow aspiration is combined with bone marrow biopsy.[24]

CONCLUSION

This study concludes that bone marrow aspiration and biopsy is an important tool to diagnose hematological neoplastic and non neoplastic conditions through cytological smear study and biopsy assessment and it also provides material for immunophenotyping, cytogenetics, molecular genetics studies and other investigations which helps in further categorization, treatment and prognostication of these conditions.[25]

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