DISTRIBUTION AND SPECTRUM OF HAEMATOLOGICAL DISORDERS ON BONE MARROW STUDY

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ABSTRACT

BACKGROUND

Haematological disorders include a wide range of diseases ranging from anaemias to haematological malignancies. Examination of the marrow is critically important in the study and management of wide variety of haematological disorders. Bone marrow examination is safe and useful test in reaching the final diagnosis.

MATERIALS AND METHODS

This descriptive study was carried out in the Postgraduate Department of Pathology, Government Medical College, Jammu, India over a period of five years (November 2011 to October 2016). 1600 cases were diagnosed by bone marrow aspiration. Complete blood count, peripheral smear and bone marrow study were performed in all cases. Those with inconclusive report due to inadequate sample were dropped.

RESULTS

Bone marrow aspiration from 1600 patients were analysed. The male-to-female ratio was 1.3: 1 with maximum number of cases in the age group of 11 - 20 years and 40% of the cases were in the paediatric age group. Nutritional anaemia contributed to the most common haematological disorders. Among them, the incidence of megaloblastic anaemia was highest (50%). The other haematological disorders were ITP (5%), Aplastic anaemia (2.50%), Haemolytic anaemia (0.62%), Haemoparasites (0.62%), Hypersplenism (0.37%), Hypereosinophilic syndrome (0.31%), Haemophagocytic syndrome (0.25%), Congenital dyserythropoietic anaemia (0.18%), Thalassemia (0.12%), Sickle cell disease (0.06%) and Niemann's pick disease (0.06%). In Malignant haematological disorders, the most common was found to be leukaemia (15.75%). Amongst these, acute lymphoblastic leukaemia (6.25%) was more common. Others were Multiple myeloma (1.62%), MDS (0.5%), Waldenstrom's macroglobulinaemia (0.25%), lymphomas (0.25%) and CMML (0.12%). One case of myeloproliferative variant of hypereosinophilic syndrome (0.06%) was diagnosed during the study period. Bone marrow mets (0.37%) were observed to be the most important cause of secondary bone marrow involvement by a non-haematological malignancy.

CONCLUSION

Bone marrow study plays a very important role not only in determining the cause of disease, but also helps in establishing a definitive diagnosis. It is one of the most common and safe procedures done routinely on outpatient basis.

KEY WORDS

Bone Marrow Aspiration, Bone Marrow Biopsy, Diagnostic Role, Haematological Disorders.

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BACKGROUND

Sir William Harvey described blood as "fountain of life and the primary seat of the soul. The marrow of our bones is the seedbed of our blood." Careful assessment of the blood elements is often the first step in assessment of haematological function and diagnosis. Bone marrow examination has been the corner stone of haematology practice, since its introduction into routine clinical use in the 1940s.[1] Bone marrow aspiration gives a more complete picture of the reaction of the haemopoietic tissue to anaemia than can be gained from peripheral blood smear alone.[2] The definitive diagnosis of primary and metastatic haematopoietic malignancies requires microscopic examination of marrow aspiration or trephine biopsy, because it provides direct evidence of the presence and the nature of disease. The bone marrow is involved in a variety of haematological and non-haematological disorders. The haematological diseases include leukaemias, lymphomas, nutritional deficiency diseases like iron deficiency anaemia, megaloblastic anaemia, anaemia of chronic disorders and hypoplastic anaemia. The bone marrow is also frequently involved in granulomatous disorders and metastatic disorders. Diagnosis and management of many haematologic diseases depends on examination of the bone marrow, which usually involves two separate specimens: a cytologic and a histologic preparation. While cytologic preparation of bone marrow obtained by aspiration allows excellent visualisation of cell morphology, the histological preparation of bone marrow allows optimal evaluation of cellularity, fibrosis or infiltrative disease.[3] The aspirate films are more sensitive for studying differential cell count and cytomorphology. When marrow aspiration leads to "dry tap," in such situations evaluation of bone marrow cellularity and abnormal architecture patterns and detection of structures other than the haematopoietic cells within the marrow are best achieved by bone marrow biopsy.[1] The present study is being

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conducted to study the distribution and spectrum of haematological disorders.

MATERIALS AND METHODS

This descriptive study was done in the Postgraduate Department of Pathology, Government Medical College Jammu, India for a period of five years (November 2011 to October 2016). A total of 1600 cases were included in this study. Patients with history and clinical feature like pallor, fatigue, bleeding in the form of bruise or petechiae, persistent fever, bone or joint pains, organomegaly and lymphadenopathy were taken up for detailed haematological evaluation. Patients referred from district hospital and other health care centres of our state were also included in this study. Those with inconclusive report due to inadequate sample were dropped from the study. Complete blood count including haemoglobin, total and differential leucocyte count and platelet count were performed using automated haematology analyser. Peripheral smear examination was done after Leishman stain. Bone marrow aspirate smears obtained were stained with May-Grunwald-Giemsa and Perls' Prussian blue stain. Bone marrow trephine biopsy was done in selected patients where marrow aspiration yielded blood only (dry tap). Haematoxylin and eosin and reticulin stains were used when needed. Then data was analysed manually by frequency and percentage.

RESULTS

A total number of 1600 patients were included in this study. Among these 896 (56%) were males and 704 (44%) were females with sex ratio of 1.3: 1. The patient distribution into different age groups was studied. The maximum number of patients (29.5%) of haematological disorders who underwent bone marrow examination was in the age group of 11 - 20 years. Haematological disorders were found to affect adults (60%) more than paediatric age group (below or equal to 18 years of age) (40%). (Table 1) shows the age distribution. Patients presented with overlapping clinical features (Table 2). Generalised weakness (76%) and fever (40%) were the most common presenting symptom. Pallor (90%) was the most frequently observed sign.

Age Group (in yrs.)	No. of Patients	Percentage (%)
0-10	269	16.7
11-20	474	29.5
21-30	236	14.7
31-40	186	11.6
41-50	178	11
51-60	135	9
>60	122	7.6
Total	**1600**	**100**

Table 1. Age Wise Distribution of Haematological Disorders

Bone marrow examination findings are given in (Table 3). Out of 1600 cases detected during the said period, majority cases were nutritional deficiency anaemias. Among them, the incidence of megaloblastic anaemia was highest followed by dual deficiency anaemia and iron deficiency anaemia. In malignant haematological disorders, the most common was found to be leukaemia (Fig. 1) followed by multiple myeloma (Fig. 2). Other haematological disorders diagnosed were Hypereosinophilic syndrome, Haemophagocytic syndrome, congenital dyserythropoietic anaemia, thalassemia, sickle cell disease with haemolytic crisis (Fig. 3), Niemann's pick disease (Fig. 4). One case of myeloproliferative variant of hypereosinophilic syndrome was diagnosed during the study period (Fig. 5). Bone marrow mets were observed to be the most important cause of secondary bone marrow involvement by a non-haematological malignancy. Out of 6 cases of metastatic deposits, 3 cases were of adenocarcinoma lung (Fig. 6), 2 cases were of adenocarcinoma prostate and 1 case was of neuroblastoma. Distribution of subtypes of haematological and non-haematological malignancies are given in (Table 4).

Clinical Presentation	Total No.	Percentage (%)
Pallor	1440	90
Weakness	1216	76
Fever	640	40
Bone pains	170	10.6
Weight loss	288	18
Bleeding	315	20
Lymphadenopathy	160	10
Organomegaly	360	23

Table 2. Clinical Presentation of Haematological Disorders

Haematological Diagnosis	No.	Percentage (%)
Megaloblastic anaemia	800	50
Dual deficiency anaemia	300	18.75
Acute lymphoblastic leukaemia (ALL)	100	6.25
Acute myeloid leukaemia (AML)	90	5.62
Idiopathic thrombocytopenic purpura	80	5.0
Aplastic/ hypoplastic anaemia	40	2.50
Chronic myelogenous leukaemia (CML)	40	2.5
Iron deficiency anaemia	36	2.25
Multiple myeloma (MM)	26	1.62
Chronic lymphocytic leukaemia (CLL)	20	1.25
Haemolytic anaemia	10	0.625
Haemoparasites	10	0.62
Myelodysplastic syndrome (MDS)	08	0.5
Bone marrow mets	06	0.37
Hypersplenism	06	0.37
Hypereosinophilic syndrome	05	0.31
Lymphoma	04	0.25
Waldenstrom's macroglobulinaemia	04	0.25
Haemophagocytic syndrome	04	0.25
Congenital dyserythropoietic anaemia	03	0.18
Chronic myelomonocytic leukaemia (CMML)	02	0.12
Thalassemia	02	0.12
Infective pathology	02	0.12
Sickle cell disease with haemolytic crisis	01	0.06
Niemann's pick disease	01	0.06
Myeloproliferative variant of hypereosinophilic syndrome	01	0.06
Total	**1600**	**100**

Table 3. Distribution and Spectrum of Haematological Disorders diagnosed by BMA

Type	Subtype	Total No.	Percentage (%)
ALL (100)	ALL-L1	70	4.37
	ALL-L2	30	1.87
AML (90)	AML-M0	02	0.12
	AML-M1	22	1.37
	AML-M2	28	1.75
	AML-M3	13	0.81
	AML-M4	24	1.5
	AML-M5	10	0.62
	AML-M6	01	0.06
CLL (20)	CLL	20	1.25
CML (40)	CML-cp	30	1.8
	CML-ac	03	0.18
	CML-bp	07	0.43
Lymphoma(4)	NHL	03	0.18
	HL	01	0.06
Metastatic Deposits (6)	Adenocarcinoma lung	03	0.18
	Adenocarcinoma prostate	02	0.12
	Neuroblastoma	01	0.06

Table 4. Distribution of Subtypes of Haematological and Non-Haematological Malignancies

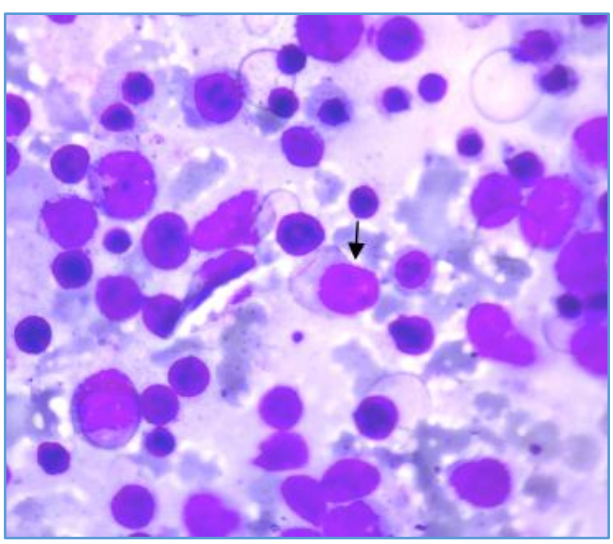

Figure 1. BMA showing Erythroid Precursors with some Myeloblasts and one Myeloblast with Auer Rod (↑) in AML-M6 (MGG 100X)

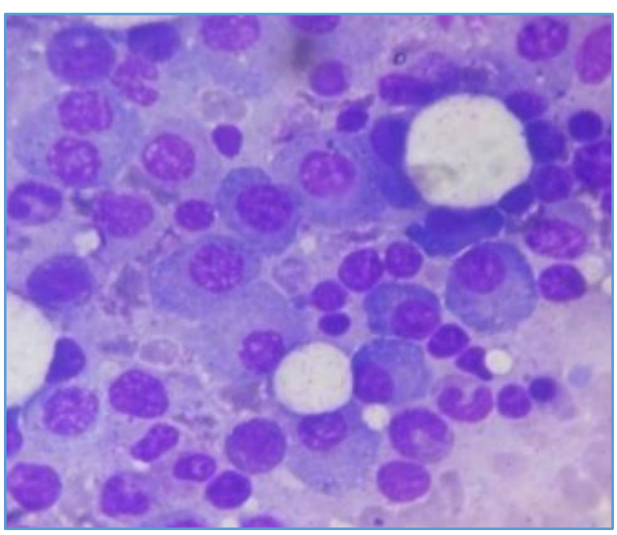

Figure 2. BMA showing Plasma Cells in MM (MGG 100X)

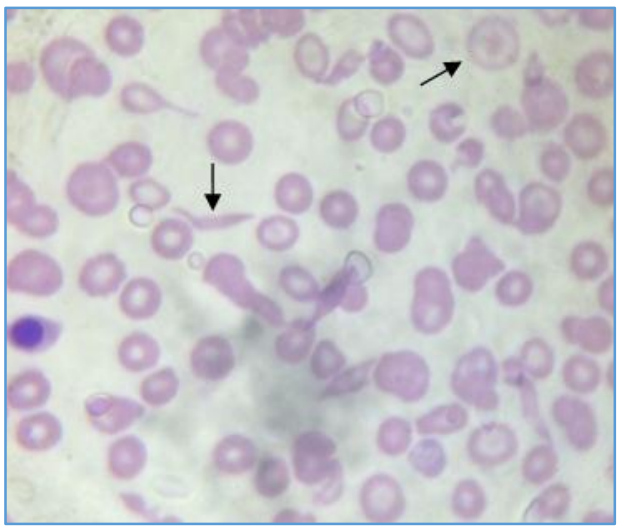

Figure 3a. PBF showing Nucleated Red Cell, Target Cells (↑) and Sickle Cells (↑) in Sickle Cell Disease with Haemolytic Crisis (Leishman's Stain 100x)

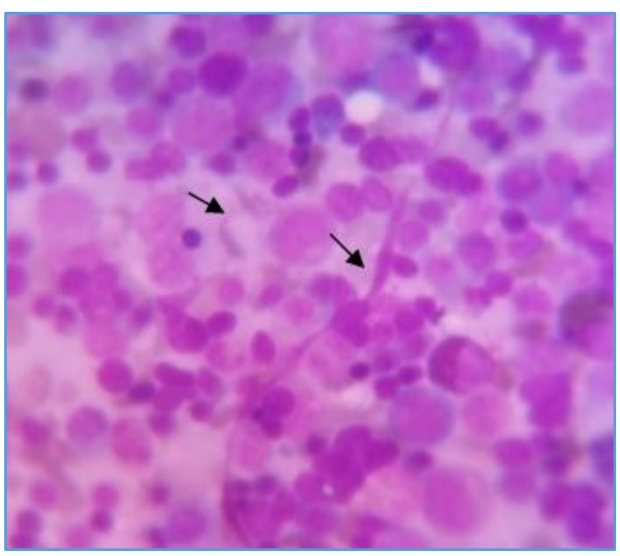

Figure 3b. BMA showing Abnormal Elongated Sickle Cells (↑) in Sickle Cell Disease (MGG 100X)

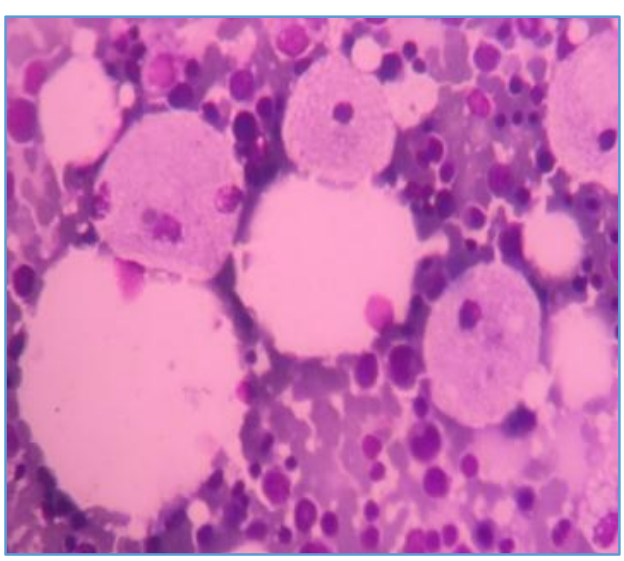

Figure 4. BMA showing Niemann-Pick Cells in Niemann's Pick Disease (MGG40X)

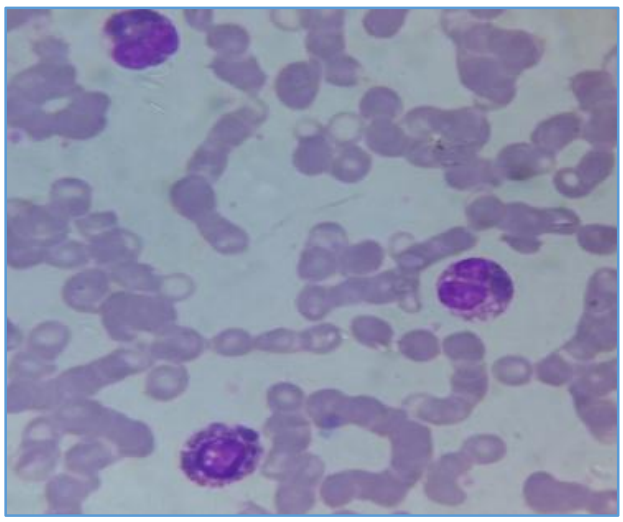

Figure 5a. PBF Showing Eosinophilia with Eosinophilic Myelocyte in Myeloproliferative Variant of Hypereosinophilic Syndrome (PDGFRA and FIP 1 L 1+ve) Leishman's Stain 100X

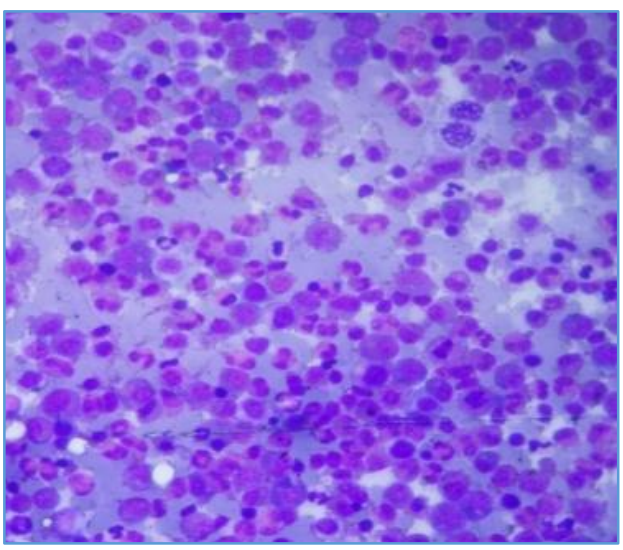

Figure 5b. BMA showing Increase in Eosinophils and Eosinophilic Precursors in the Same Patient (MGG 40X)

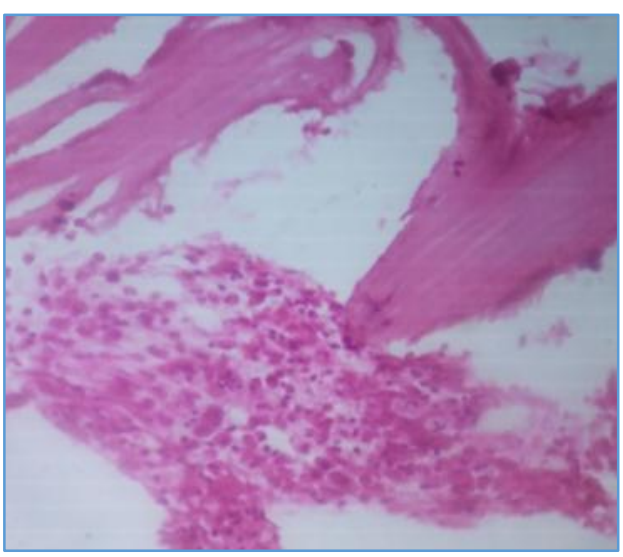

Figure 5c. BM Trephine Biopsy showing Infiltration of Eosinophils and their Precursors in the Same Patient (H and E 10X)

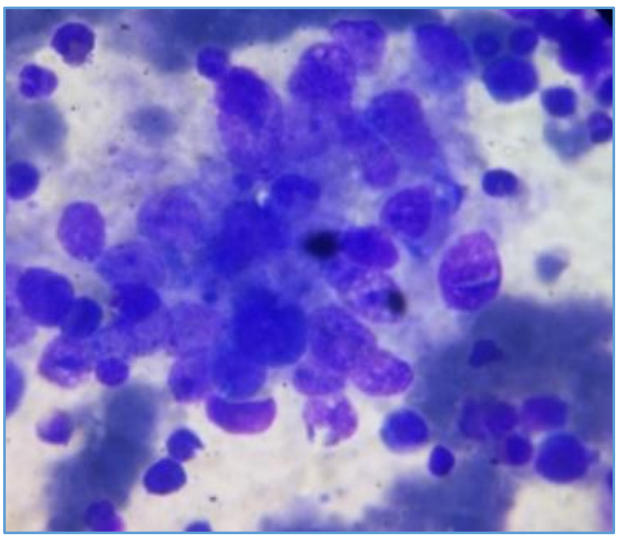

Figure 6. BMA showing Metastatic Deposits of Adenocarcinoma (MGG 100X)

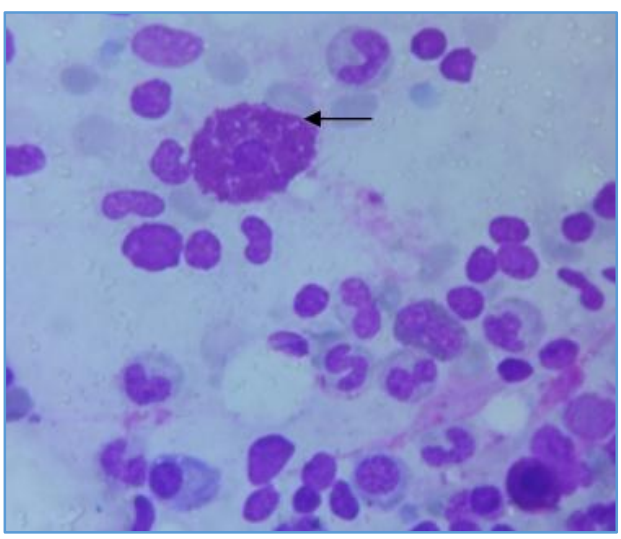

Figure 7. BMA showing Mast (↑) Cells, Lymphocytes and Plasma Cells in Waldenstrom's Macroglobulinaemia (MGG100X)

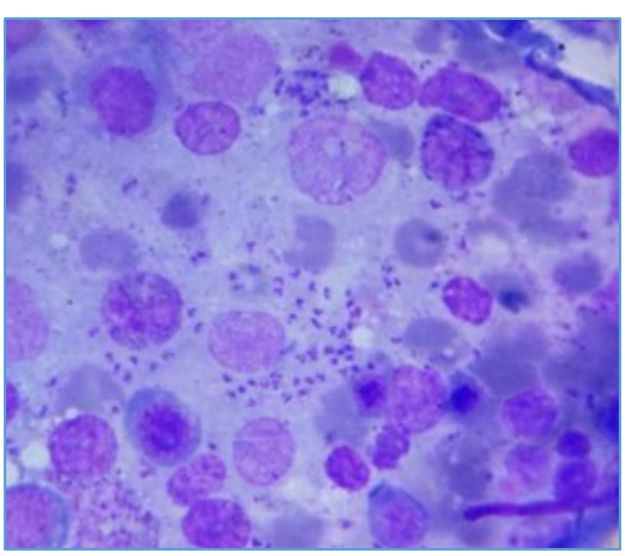

Figure 8. BMA showing LD Bodies in Visceral Leishmaniasis (MGG 100X)

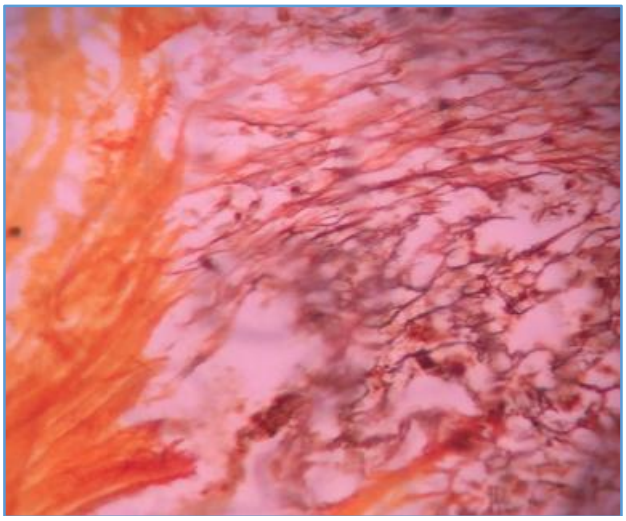

Figure 9. BMB showing Increased Reticulin Fibre Density and Thickness in Myelofibrosis (Reticulin Stain 40X)

DISCUSSION

Bone marrow aspiration is an important and useful clinical and laboratory investigation for the study of various haematological disorders. It is one of the most common and safe procedure and can be done routinely on an outpatient basis. The sex distribution of haematological disorders were recorded and overall more male cases were found 896 (56%) as compared to females 704 (44%). Male: Female ratio was found to be 1.3: 1. This observation was comparable to that in the study done by Thiyagarrajan P et al.[4]

In our study, the maximum number of cases were recorded among 11 - 20 years of age group 474 (29.6%), whereas less number of cases were seen in older age group i.e. > 60 years of age 122 (7.6%). Similar findings were seen in study conducted by Kibria SG et al.[5] However, Shastry SM et al[6] and Anjum MU et al[7] reported the maximum number of cases among 21 - 30 years of age group. The occurrence of pallor, fever, LAP, organomegaly, bone pains and bleeding manifestation in a particular haematological disorder as diagnosed by BMA were similar to study done by Dapus DO and James D.[8] These findings contributed to the request for bone marrow study as they are known to be related to haematologic diseases, particularly when found in combination in a patient. In our study, nutritional deficiency anaemias were the most common haematological disorders. Among these, megaloblastic anaemia contributed to the maximum number of cases. These findings correlate with study done by Jha et al[9] and Patel S et al.[10] The second most common was dual deficiency anaemia followed by iron deficiency anaemia. But in a study done by Gayathri et al[11] and Pudasaini S et al,[12] they found that dual deficiency anaemia is least frequent than iron deficiency anaemia. This could be due to the fact that mostly iron deficiency anaemia is treated on an outpatient basis in our centre and bone marrow examination is not routinely done to confirm its diagnosis. One case of sickle cell disease with haemolytic crisis and two cases of thalassemia were diagnosed during the study period similar to study done by Shastry SM et al.[6] Presence of sickle cells in the PBF pointed towards sickle cell disease and BMA showed hyperplastic marrow, erythroid hyperplasia with features of dyserythropoiesis and sickle cells. Blood smear is useful in the diagnosis of sickle cell disease, particularly if there is an urgent need for diagnosis and if the results of haemoglobin electrophoresis or high-performance liquid chromatography are not instantly available.[13]

Leukaemia was the most common malignant haematological disorder present in 252 cases followed by Multiple myeloma 26 cases, Waldenstrom's macroglobulinaemia 4 cases (Fig. 7), metastatic deposits 6 cases, lymphomas 4 cases and CMML 2 cases. Similar results have been reported in a study done by Khan A et al[14] and Patel J and Popat VC[15] who also reported leukaemia as the most common malignant haematological disorder. Acute leukaemias were found to be more common than chronic leukaemia similar to studies conducted by Al-Ghazaly J et al[16] and Kulshrestha R et al.[17] ALL was found to be more common than AML, similar to a study done by Dapus DO and James D[8] and Anjum MU et al.[7] Among chronic leukaemia, CML cases were more frequent than CLL cases. This observation was comparable to that of Patel J and Popat VC.[15] Biopsy in two patients of CML showed increase in granulocytic series as well as megakaryocytes along with the presence of marrow fibrosis, thus giving the morphologic subtype (granulocytic and megakaryocytic subtype). Out of four cases of lymphoma, NHL cases were more frequent than HD similar to the study done by Troussard X et al.[18] Among non-haematological disorders, myelophthisic anaemia, especially bone marrow mets were most common. Three cases were of adenocarcinoma lung, two cases were of adenocarcinoma prostate and one case was of neuroblastoma. One case of metastatic deposits of poorly differentiated adenocarcinoma lung was diagnosed on biopsy. Ozkalemkas et al in their study observed the most common non-haematological malignancy involving the bone marrow to be adenocarcinoma with the primary focus in stomach in 5 cases, prostrate in 3 cases and lung in 1 case.[3] In our study, haemoparasite, i.e. Leishmania donovani (Fig. 8) causing kala-azar was reported in 10 cases. Majority of these patients were from the hilly areas. Haemoparasites can be a cause of haematological disorders and they should be specifically looked for while examining the bone marrow aspirate. There was one case of Niemann's pick disease. We found that bone marrow aspiration is helpful in making primary diagnosis of storage disease.

One rare case of myeloproliferative variant of hypereosinophilic syndrome (PDGFRA +ve and FIP1 L1 +ve) was diagnosed during the study period. Patient was being treated for heart ailments and was having eosinophilia (Rheumatic heart disease) and was sent to us for evaluation of sustained eosinophilia. In correlation with peripheral smear, bone marrow findings and after exclusion of secondary causes we diagnosed the case as myeloproliferative variant of hypereosinophilic syndrome as PDGFRA and FIP1 L1 fusion gene was positive. Bone marrow trephine biopsy was done in patients where marrow aspiration yielded blood only (dry tap). Marrow histological sections were examined for architecture, presence of foreign cells, marrow fibrosis, dyserythropoiesis and dysmegakaryopoiesis. Patients in whom bone marrow aspiration yielded scant material were diagnosed as aplastic anaemia on trephine biopsy. In patients where bone marrow aspiration yielded dry tap, marrow trephine biopsy revealed moderate-to-marked fibrosis with increased microvessel density, sinusoidal dilatation and increased atypical megakaryocytes. These cases were diagnosed as myelofibrosis (Fig. 9). Frisch et al[19] have also observed that in

the majority of cases myeloproliferative disorders, especially myelofibrosis may be recognised and classified by the initial bone marrow histology. Hence, the finding of a dry tap should never be dismissed as being due to faulty technique and always needs a bone marrow biopsy.

CONCLUSION

Bone marrow study plays a very important role not only in determining the cause of disease, but also helps in establishing a definitive diagnosis. Nutritional deficiency anaemias (particularly the megaloblastic anaemia) were the most common haematological disorders, thus it reflects the poor socio-economic and nutritional status of the society. The diagnosis of haematological disorders is achieved mainly by the examination of peripheral blood and bone marrow aspirate smears with trephine biopsies acting as a useful adjunct. However, a careful and detailed peripheral blood examination along with clinical information is still the cornerstone for suspecting a particular haematological disorder in most cases.

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