Original Article

The Usefulness of Morphology in Diagnosing various Malignancies on Bone Marrow Examination in Adults- A Single Centre Study

Nazia Khalid[1], Attika Khalid[2], Lubna Zafar[3], Nadia Arif[4], Mehmood ul Hasan[5]

[1] Senior Lecturer, Department of Pathology, Foundation University Medical College, Islamabad.
[2,4] Assistant Professor, Department of Pathology, Foundation University Medical College, Islamabad.
[3] Professor, Department of Pathology, Foundation University Medical College, Islamabad.
[5] Consultant, Department of Pathology, Tehsil Headquarters Hospital, Gujjar Khan.

Author`s Contribution
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[1,2,3,4] *Experimentation/Study conduction*
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Corresponding Author
Dr. Nazia Khalid
Senior Lecturer,
Department of Pathology,
Foundation University Medical College,
Islamabad
Email: drnaziakhalid@yahoo.com

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Abstract

Introduction: Bone marrow is the site of involvement of various neoplasms. The objective of this study was to determine the incidence of various malignancies (Haematological and non-Haematological) in adults diagnosed on morphological examination of bone marrow.

Materials and Methods: It was a single-centre, retrospective study conducted at the Department of Pathology, Fauji Foundation Hospital, Rawalpindi from January 2012 to December 2018. All patients above 15 years of age diagnosed as having Haematological or Non-Haematological malignancy involving bone marrow were included in the study. Data was analyzed using SPSS version 17.

Results: A total of 275 adult patients had malignancies involving bone marrow; 233 (84.7%) were females and 42 (15.3%) were males. Out of 275 patients, 50 (18.1%) patients had Acute Myeloid Leukaemia, 45 (16.3 %) had Chronic Myeloid Leukaemia (CML), 41 (14.9 %) having Non-Hodgkin lymphoma (NHL), 32 (11.6 %) having Acute Lymphoblastic Leukaemia (ALL), 31 (11.2 %) having Chronic Lymphocytic Leukaemia (CLL) and 27 (9.8 %) having Plasma cell Myeloma. Metastatic infiltrates were seen in 16 (5.8 %) patients. Myeloproliferative neoplasms (MPN) in 6 (2.1%), Essential Thrombocythaemia in 5 (1.8 %), Polycythaemia vera in 4 (1.4%), Primary myelofibrosis in 2 (0.7 %), Hodgkins Lymphoma in 2 (0.7 %), and Plasma Cell Leukaemia in 1 (0.3 %) patient were seen. Thirteen (4.7%) patients of Acute leukaemia and 6 (2.1%) patients of MPN required further testing by Immunophenotyping/Cytogenetics for a conclusive diagnosis.

Conclusion: Leukaemias were the most common malignancies involving bone marrow, followed by Non-Hodgkin Lymphomas, Plasma cell myeloma and Metastatic infiltrates. Morphology by light microscopy remains the single most useful tool for the diagnosis of malignancies, especially in under-resourced centres.

Keywords: Leukaemias, Lymphomas, Metastasis, Plasma cell myeloma.

Introduction

The incidence of malignancies is increasing worldwide. It affects people of both genders and all age groups.[1] Many of these involve the bone marrow. Leukaemias (acute and chronic) originate primarily within the bone marrow. These may be myeloid or lymphoid.[2] Others are lymphomas that arise due to clonal lymphoid proliferations. These are classified as Hodgkins Lymphoma (HL) and Non-Hodgkins Lymphomas (NHL). Lymphomas are primarily diagnosed on tissue biopsies. Bone marrow aspiration and trephine biopsy to detect bone marrow infiltration are carried out as part of the staging procedure.[3] A small percentage of Hodgkin's lymphoma patients have bone marrow involvement (Sudalaimuthu M[1], Basu D).[4] NHL may be low grade or high grade. Low-grade lymphomas are more likely to involve bone marrow of the patient (Brudno et al 2016).[5]

Bone marrow may also be involved by several Non-Haemopoietic tumours, commonest being originating from the prostate, breast, lung, thyroid, kidney, and stomach. Bone marrow involvement by solid tumours has an impact on overall survival and treatment response of the patient. (Kucukzeybek BB et al 2014).[6]

In the case of leukaemias, bone marrow aspirate is usually sufficient to make the diagnosis. However, bone marrow trephine biopsy is required in cases where bone marrow aspirate alone is not sufficient to provide adequate information, for example in cases with fibrosis (Gandapur et al., 2015)[7] or a dry tap (trephine imprints may be helpful), a pattern of involvement in lymphomas and metastatic deposits (Mangoch A).[8]

With the introduction of new techniques for diagnosis eg immunophenotyping, immunohistochemistry, and cytogenetics, the diagnosis of malignancies has become more accurate. However, morphological examination remains the first-line tool for diagnosis of disorders of bone marrow examination. In our country, these techniques are not available in most of the laboratories.

The present study was undertaken to assess the role of morphological examination to detect the incidence of various haematological and non-haematological malignancies involving bone marrow in adults.

Material & Methods

It was a retrospective study and data was taken from 1st January 2012 to 31st December 2018 at the Department of Pathology, Fauji Foundation Hospital, Rawalpindi. Results of bone marrow examination of patients above 15 years of age were analyzed. Cases of relapse of malignancies and follow up cases of Haematological and Non-Haematological malignancies were excluded from the study, to avoid duplication. In all cases, a thorough history and clinical examination were performed. Complete blood counts were obtained using automated haematology analyzer Sysmex XT-2000i and Xn-1000. Bone marrow aspiration and trephine biopsy were taken from the posterior superior iliac spine. Peripheral blood smear and bone marrow aspirate were stained using Leishman stain. Cytochemistry i.e. Sudan Black B (SBB), Acid Phosphatase (ACP), Periodic Acid Schiff (PAS), Alpha naphthyl acetate esterase (ANAE), and Leukocyte alkaline phosphatase (LAP) were applied to bone marrow aspirate for typing of leukaemias. Trephine biopsy was processed using a standard protocol. A silver impregnation technique was done for reticulin staining to assess fibrosis. Immunophenotyping and Cytogenetics of the patients were sent in selected cases with an inconclusive diagnosis on morphology. Data was entered in and analyzed by using Statistical Package for the Social Sciences (SPSS) version 17. Mean and median were used to express quantitative variables, whereas qualitative variables were expressed using frequency and percentages.

Results

A total of 2242 bone marrows were performed. Out of these, 275 were the adults having bone marrow malignancies.

A total of 275 adult patients had malignancies involving bone marrow; 233 (84.7%) were females and 42 (15.3%) were males. Out of 275 patients, 50 (18.1%) had Acute Myeloid Leukaemia, 45 (16.3 %) had Chronic Myeloid Leukaemia (CML), 41 (14.9 %) having Non-Hodgkin lymphoma (NHL), 32 (11.6 %) having Acute Lymphoblastic Leukaemia (ALL), 31 (11.2 %) having Chronic Lymphocytic Leukaemia (CLL) and 27 (9.8 %) having Plasma cell Myeloma. Metastatic infiltrates were seen in 16 (5.8 %) patients. Myeloproliferative neoplasms (MPN) in 6 (2.1%), Essential Thrombocythaemia in 5 (1.8 %), Polycythaemia vera in 4 (1.4%), Primary myelofibrosis in 2 (0.7 %), Hodgkins Lymphoma in 2 (0.7 %), and Plasma Cell Leukaemia in 1 (0.3 %) patient were seen. Thirteen (4.7%) patients of Acute leukaemia and 6

(2.1%) patients of MPN were diagnosed by Immunophenotyping/Cytogenetics.

Prevalence and age-distribution of various malignancies and frequencies of males and females are shown in Table 1 and Figure 1 respectively.

Table 1: Basic Clinical Features

Disorder	n	Percentage (%)	Median age (years)
AML	50	18.1	51
CML	45	16.3	48
NHL	41	14.9	57
ALL	32	11.6	48
CLL	31	11.2	67
PCM	27	9.8	62
Metastasis	16	5.8	50.5
Acute Leukemia	13	4.7	50
MPN	6	2.1	62
ET	5	1.8	38
PV	4	1.4	47.5
PMF	2	0.7	61.5
HL	2	0.7	64.5
PCL	1	0.3	38
Total	275		

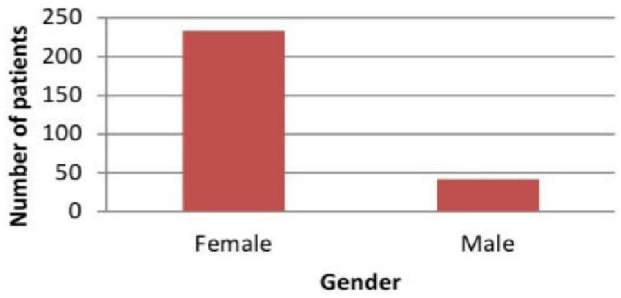

Figure 1: Frequencies of Males and Females

Discussion

Bone marrow examination is crucial for the diagnosis of various hametological malignancies as well as for the staging of Lymphomas and Non Haematological tumours.

The diagnosis involves a multi-step procedure. In the case of leukaemias, the FAB classification based on the morphological examination of peripheral blood smear and bone marrow aspirate along with cytochemistry is sufficient for diagnosis. Newer techniques including immunophenotyping help classify the subtypes of AML and ALL as well as establishing the diagnosis in cases with ambiguous morphology, whereas cytogenetics and molecular analysis are predictors of prognosis and minimal residual disease, respectively. Regarding lymphomas, these tests are also helpful in confirmation of the diagnosis in case of bone marrow aspirate/biopsy showing involvement by lymphoid infiltrate. Immunohistochemistry on bone marrow trephine biopsy specimen is used to diagnose cases showing metastasis in bone marrow with an unknown primary site. However, these techniques are not available in a large majority of setups in our country. A prompt diagnosis is required to start the management which is readily provided by morphological examination of peripheral blood smear and bone marrow of the patient.

In our study, Leukaemias was the most common disorder followed by Lymphoma, Plasma cell myeloma and Metastasis. Among leukaemias, acute leukemias were more common compared to chronic leukaemias. A study conducted by Gandapur et al,[7] Khan M I[9,] and Kusum et al[10] found a similar distribution of malignancies in the bone marrow.

Among Acute leukaemias in our study, Acute myeloid leukaemia was more prevalent than Acute Lymphoblastic Leukaemia. The former studies (by Gandapur et al and Khan MI) have shown more cases of ALL compared to AML. This is most likely because of the reason that peadiatric patients were also included in that study along with adult patients and ALL is more common in children. A study by Kusum et al have shown comparable results to our study. The majority of the patients in that study are adults (n=103) compared to children (n=26). A study by Hossain et al[11] have also shown more cases of AML compared to ALL; among those diagnosed as ALL in those studies, the majority were children.

The bone marrow of 43 (15.6%) patients was involved by Lymphomas. There were 41 (14.9%) cases of *Non-Hodgkins lymphomas* (NHLs) and only 2 (0.7%) cases of Hodgkins Lymphoma. This is because of the lower incidence of involvement of bone marrow by HL as compared to NHLs (Sudalaimuthu M, Basu D., 2016).[12] There were patients of all age groups with a median age of 57 years and 64.5 years for NHL and HL respectively. A study by Sultan S et al showed a slightly lower age distribution of 50 years for NHL.[13] In England the median age was much higher i.e 69.1 years (Smith et al., 2015).[14] The difference in age is based on the ethnic distribution with people in Europe developing the disease at older ages, most likely due to a longer life expectancy in West (Sultan S et al 2018).[13] A much lower median age i.e 30 years was reported for Hodgkin's lymphoma in a study

previously conducted in Pakistan (Sultan et al 2016).[15]That study was exclusively performed on patients of Hodgkin's lymphoma and with large sample size. Data from West, however, suggests first peak incidence in younger individuals as well as the second one in more than 60 years of age (W Townsend 2012).[16]

Plasma cell myeloma (PCM) constituted 27 cases (9.4%) of all malignancies. This is following a study previously conducted by Khan H [17] which showed 10.2% of patients involved by multiple myeloma. It also corresponds to the global data according to which the prevalence of PCM is approximately 10% of all Haematological malignancies (Hameed A et al).[18] Median age of the patients was 62 years. A slightly lower median age of 57 years has been reported for PCM patients in a study conducted by Sultan S et al 2016.[19] This study was carried out with larger sample size. Also, the difference in the stage of presentation of patients to health care facility might be a contributory factor. A higher median age of 70 years has been reported in West (Hameed A et al).[19] A longer life expectancy and better health care facilities of people in the West compared to those in our country is probably the reason for the difference reported.

There was one case of Plasma cell leukaemia (PCL) which corresponds with its rare occurrence worldwide (Ravi et al 2018).[20]

Among *Chronic leukemias*, the incidence of Chronic Myeloid Leukemia (CML) was higher as compared to Chronic Lymphocytic leukemia (CLL), 45 patients (16.3 %) vs 31 patients (11.3 %). This is following studies previously done in Pakistan which showed that 12.4% of patients had CML and 9.8% had CLL. (Gandapur et al).[7] In Europe, however patients with CLL constitute a higher percentage compared to those with CML. (Sant M et al., 2010).[21] This is due to the geographical differences in the distribution of CLL which is more common in Western than Asian countries (Schwartz GG, Klug MG.).[22]

Certain disorders were infrequently reported in our study including *Myeloproliferative neoplasms* comprising of 5 (1.8 %) Essential Thrombocythaemia (ET), 4 (1.4 %) Polycythaemia Vera (PV) and 2 (0.7 %) Primary myelofibrosis (PMF). The data reported by Yap et al [23] have reported the same prevalence whereas a study previously conducted in Pakistan showed PV as the most prevalent MPN (Sheikh et al 2016).[24] However, the data from our study is scarce and may not be a representative of the prevalence of these disorders.

The involvement of bone marrow in a patient by non-Haematologic tumour is indicative of the advanced stage of that tumour and a poor prognosis. There were 16 (5.6 %) cases of *Metastatic infiltrates* involving bone marrow. A lower number of patients had metastatic deposits on bone marrow examination in a study previously conducted in Pakistan[25] i.e 10/443 patients (2.2%) while another study conducted by Mangoch A [8] showed a very low frequency 6/1600 patients (0.3%). The difference in prevalence is likely due to the timely presentation and ease of access to a health care facility. The above data indicate that the prevalence of various malignant disorders fairly correlates with that provided in other setups. Only a small proportion of our patients 6.8% required further testing to achieve a diagnosis. This shows that morphology alone can provide sufficient evidence for the diagnosis of malignancies.

Limitations

A female predominance was observed in our study in all types of malignancies. This is because our hospital mainly caters for female and children. Therefore our data is not representative of gender distribution in various types of malignancies. A study with a larger sample size including males is needed in this regard.

Conclusion

Acute and chronic leukaemias form the most common malignancies diagnosed with bone marrow examination in our study. A significant proportion of patients had bone marrow involvement by lymphomas whereas metastasis by solid tumours was relatively low. Only a small percentage of patients required further testing to reach a conclusive diagnosis. Therefore morphology by light microscopy remains the single most useful tool for diagnosis of malignancies, especially in under-resourced centres.

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