Original Article

Clinical Audit of Bone Marrow Examination - Suggesting the Impact of Procedural Checklist to Improve its Quality

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A b s t r a c t

Objective: The purpose of bone marrow biopsy includes diagnosis, staging, prognosis, and treatment response for various hematological and non-hematological disorders. The present study aimed to observe the frequent indications for the performance of bone marrow biopsy and the frequencies of various disorders diagnosed using the procedure.

Methodology: This descriptive retrospective audit was conducted in the Hematology section at Indus Hospital and Health Network and included bone marrow biopsies performed from January 2021 to October 2022 with patients >16 years and belonging to either gender. Bone marrow trephine biopsy was performed using Jamshidi needle from posterior superior iliac spine while aspiration was performed from same site using a spinal needle.

Results: A total of 111 bone marrow biopsy procedures were performed. The procedure was performed with ease in 68.4% of the cases by competent residents. In 27.9% cases procedure was performed with difficulty due to patient related causes which included immobility, displaying non-cooperation or irritability, or difficulty in the localization of the bone. Maximum diagnosis (63.1%) was made when the core depth was >1.0 cm. Hematological diseases were the most common diagnosis (69.4%); of which the majority were malignant (70.1%)in almost half of the cases. Concordance was present between the suspected diagnosis and the conclusive diagnosis made in the bone marrow biopsy report. Bone marrow was found to be normal in 13.5% (n=15) patients. Chronic myeloid leukemia (n=17; 22.1%) and aplastic anemia (n=9; 11.7%) were the most frequent malignant and benign disorders respectively. The overall diagnostic yield for the present study was 82.9% while based on indication, visceromegaly produced a yield of 87.1%.

Conclusion: Splenomegaly was observed to be the most common indication for procedure referrals in our center. Core size of >1.0 cm was found to have the highest diagnostic utility. Chronic Myeloid Leukemia and aplastic anemia were the most frequent hematological diagnoses in the present study.

Keywords: Bone marrow biopsy, indications, hematological disorders, non-hematological disorders.

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Introduction

Bone marrow examination plays an important role in the diagnosis, staging and management of various hematological disorders such as leukemia, and lymphomas.[1, 4] Moreover, this procedure also has a diagnostic role in numerous non-hematological disorders or systemic illnesses such as pyrexia of unknown origin (PUO), storage disorders (Gaucher's disease), infectious diseases (Leishmania), granulomatous lesions.[1-3] and metastatic solid tumors.[4, 5] Also patients with non-hematological or systemic disorders may present with signs and symptoms overlapping to that of hematological disorders such as pallor, bleeding, lymphadenopathy, or visceromegaly (liver, spleen). In such cases, the bone marrow examination helps either in the confirmation of the suspected disease or might help in reaching the diagnosis of non-hematological/systemic disease.[6, 7] Also patients referred with a certain provisional diagnosis may be found to have any other disease on bone marrow examination.

Bone marrow aspiration and trephine biopsies are often performed both in the inpatient and outpatient settings for the diagnosis of a multitude of hematologic disorders. Bone marrow aspiration, a reliable diagnostic modality for marrow assessment involves the removal of bone marrow fluid and provides information about cellular size, morphology, differential count, dysplasia, hemophagocytic activity, hemoparasite, storage cells and presence or absence of malignant hematolymphoid /non-hematolymphoid cells. Trephine biopsy on the other hand involves the removal of a core from the bone

including marrow and provides extensive information about marrow cellularity, cell morphology, cell population, disease characteristics of cells, reactive features, presence or absence of extramedullary cells/metastatic disease, architectural arrangements, drug related/post-chemotherapeutic changes and hematopoietic activity.[4] It also plays a key role in the cases where bone marrow aspiration is not useful as a result of dry tap due to fibrosis or infiltration.[8, 9] Both trephine and aspirate require good-quality specimen, along with detailed clinical information. Microscopic assessment of the bone marrow aspirate and trephine morphology is aided by the use of cell markers via immunohistochemistry where needed to reach the final diagnosis.

In light of these factors, a retrospective audit was performed with the aims of identifying the prevalent indications for bone marrow procedures and evaluating the alignment between these indications and the final diagnoses, thereby assessing the procedure's utility. Additionally, we examined specific procedural parameters to serve as key performance indicators, enhance specimen yield, and pinpoint areas requiring further training and skill development.

Methodology

This retrospective descriptive audit was conducted at the Hematology department of the Indus Hospital and Health Network over 21 months extending from January 2021 to October 2022. The study was evaluated by the Institutional Ethics Committee of IHHN and an exemption was provided due to the retrospective nature of the study (IHHN_IRB_2022_12_019). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The bone marrow procedure test request was requested by clinical hematology or medicine team for both IPD and OPD patients. Informed written consent was taken from the patients/guardian before the performance of the procedure. All adult (≥16 years) male and female patients who underwent the bone marrow biopsy procedure, both in-patients with suspicion of bone marrow involvement by any hematological or non-hematological disorders were enrolled in the study. The bio-data, relevant medical history, examination findings, clinical indication, and information related to the procedure were recorded in a standardized bone marrow procedure proforma. Patients who are <16 years of age were not included in the audit, as due to institutionalist policy, such patients are seen in the pediatric ward and any procedure, if needed, is performed by the pediatricians.

Firstly, the bone marrow trephine specimens were obtained using Jamshidi needle from the posterior superior iliac crest as per the standard technique after injecting local anaesthesia at the puncture site. The samples collected were sent to the histopathology department, packaged in buffered 10% formalin solution, for histologic processing. The trephines were decalcified and paraffin-embedded blocks were stained with the usual Haematoxylin and Eosin (H&E) stain and examined. Appropriate marrow immunohistochemical, and reticulin stains were used where necessary. Bone marrow aspirations were also carried out during the same procedure by using a spinal needle. Multiple aspirate and touch imprint slides were made and visually inspected for the presence of particles. Bone marrow aspirate samples for cultures, flow cytometry and cytogenetics were obtained where requested. The samples were sent to the haematology laboratory for processing and reporting. Samples for bone marrow cultures, flow cytometry and cytogenetics were sent to respective departments. Bone marrow aspirates and touch imprints were stained by Wright-Giemsa stain. The cases were observed by hematology team including resident doctors and hematologists.

All the cases were observed in the light of clinical findings, suspected diagnosis and the final diagnosis was made based on the findings in bone marrow examination. The primary endpoint was to assess the diagnostic yield which was defined as the proportion of contributive bone marrow examinations amongst the total procedures performed for diagnostic purposes as per indications and patient characteristics.

The analysis was performed using SPSS software (version 24.0, SPSS, Chicago, Illinois, USA). Categorical variables such as indications, diagnoses, and procedural information (level of difficulty, difficulties observed, attempts made during aspirate/trephine, marrow quality, number/length of biopsy cores) were presented as frequencies with percentages while continuous variable

such as age was mentioned as median (Interquartile range-IQR) after the assessment of normality of the data. An association was also observed between the size of the core on trephine and its diagnostic utility using the Chi-Squared test/Fisher Exact test. A p-value of <0.05 was considered to be statistically significant.

Results

During the 21-month study period, a total of 111 bone marrow biopsies were performed in adult patients and thus reviewed. The present study reported a slight male preponderance with male to female ratio of 1.1:1. The median age of study participants was observed to be 45 years (31.6 – 60.0 years). The indications for the performance of bone marrow procedure are depicted in Figure 1 which showed splenomegaly (43.2%) as the most frequent sign followed by hepatomegaly (26.1%) and lymphadenopathy (18.0%).
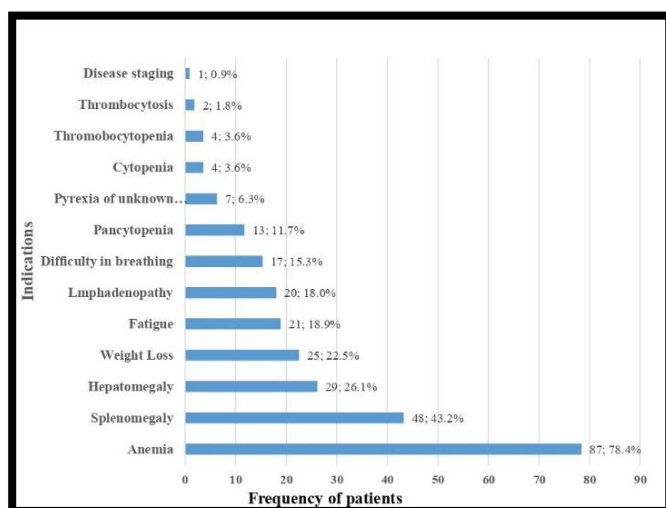

Figure 1: Indications for the performance of bone marrow examination

The parameters related to the performance of the bone marrow procedure are mentioned in Table I. The procedure was performed with ease in 68.4% of the cases by competent residents. There were 31 (27.9%) cases in which the procedure was performed with difficulty due to patient related causes which included immobility, displaying non-cooperation or irritability, or difficulty in the localization of the bone. This difficulty in the performance of the procedure led to multiple attempts i.e. 3-4 being made for the extraction of aspirate

Table I: Procedural parameters	
PARAMETER	n (%)
Procedures performed by	
R1	2 (1.8)
R2	24 (21.6)
R3	21 (18.9)
R4	44 (39.6)
R1+R2	2 (1.8)
R1+R3	6 (5.4)
R2+R3	7 (6.3)
R3+R4	1 (0.9)
R1+R2+R3	4 (3.6)
Level of Difficulty	
Easy	76 (68.4)
Difficult	22 (19.8)
Required Assistance	7 (6.3)
Difficult and Required Assistance	6 (5.4)
Procedural difficulties	
Bleeding	9 (8.1)
Difficulty in localization of bone	12 (10.8)
Obese patient	7 (6.3)
Irritable patient	3 (2.7)
No difficulty observed	87 (78.4)
Number of attempts for aspirates	
1	80 (72.1)
2	24 (21.6)
3	3 (2.7)
4	1 (0.9)
Not done	3 (2.7)
Number of attempts for trephines	
1	65 (58.6)
2	38 (34.2)
3	2 (1.8)
4	4 (3.6)
Not done	2 (1.8)
Quality of marrow material	
Particulate	41 (36.9)
Aparticulate	44 (39.6)
Haemodiluted	27 (24.3)
Number of Cores	
0	3 (2.7)
1	56 (50.4)
2	38 (34.2)
3	12 (10.8)
4	2 (1.8)
Length of Cores (cm)	
0.5-1.0	41 (36.9)
1.0-2.0	56 (50.4)
>2.0	14 (12.6)
R1: Year 1 Resident; R2: Year 2 Resident; R3: Year 3 Resident; R4: Year 4 Resident	

and trephine in 4 (3.6%) and 6 (5.4%) of the cases respectively. There were 11.7% of the cases that required senior assistance. Bone marrow aspirate material was found to be particulate in 36.9% while hemodiluted material was observed in 24.3% of cases. It

was further observed that the core size of >1.0 cm and a single core was adequate to reach a diagnosis in most of the patients.

Table II: Association between core size and its diagnostic utility.				
Core size		Diagnostic utility		p-value
		Contributive	Non-contributive	
0.5 – 1.0 cm	Yes (n=41)	32 (78.0)	9 (22.0)	0.434
	No (n=70)	60 (85.7)	10 (14.3)	
1.0-2.0 cm	Yes (n=56)	48 (85.7)	8 (14.3)	0.460
	No (n=55)	44 (80.0)	11 (20.0)	
>2.0 cm	Yes (n=14)	12 (85.7)	2 (14.3)	1.000
	No (n=97)	80 (82.5)	17 (17.5)	

Despite an insignificant association, it was observed that the maximum number of diagnoses were made when the depth of the core was >1.0 cm (Table II). The distribution of the diagnosis made based on the bone marrow examination is shown in Table III. Out of 111 study participants, 69.4% had a hematological disease while none were found to have any non-haematological/systemic illness. Majority of the patients i.e. 70.1% diagnosed with a haematological disease, had hematological malignancy while the remaining were benign conditions. Chronic myeloid leukaemia (31.5%) was found to be the most common malignant haematological disorder within the malignant category followed by multiple myeloma (12.9%). In the benign category, Aplastic Anemia (39.1%) was the most frequent disease followed by Idiopathic Thrombocytopenic Purpura (30.4%). In a smaller subset of patients (17.1%) no conclusive diagnosis was made despite the performance of the bone marrow examination. The indications for the performance of bone marrow procedure in these patients included suspected cases of bone marrow failure syndrome (n=8), leukemia (n=6), lymphoma (n=1), thrombocytosis (n=1), paraoxysmal nocturnal hemoglobinuria (n=1), pyrexia of unknown origin (n=1), and monoclonal gammopathy of undetermined significance (n=1). We further observed that in almost half of the cases, concordance was present between the suspected diagnosis and the conclusive diagnosis made in the bone marrow biopsy report. Bone marrow was found to be normal in 13.5% (n=15) patients.

Table III: Diagnoses as per bone marrow examination.	
DISORDERS	N (%)
Haematological (n=77/111; 69.4%)	
Malignant	54/77 (70.1)
Leukaemia: Acute Myelogenous Leukaemia (AML) Acute Lymphoblastic Leukaemia (ALL) Chronic Lymphoblastic Leukaemia (CLL)	4 (5.2) 2 (2.6) 2 (2.6)
Myeloproliferative Neoplasms (MPN): Chronic Myeloid Leukemia (CML) Myelodysplastic Syndrome (MDS) Myeloproliferative Neoplasms –Not otherwise specified (MPN-NOS) Primary Myelofibrosis (PMF) Essential Thrombocythaemia (ET) Polycythaemia Vera (PV)	17 (22.1) 5 (6.5) 3 (3.9) 2 (2.6) 2 (2.6) 2 (2.6)
Lymphomas: Non-Hodgkin's Lymphoma (NHL) Hodgkin's Lymphoma (HL)	5 (6.5) 3 (3.9)
Plasma Cell Dyscrasia: Multiple Myeloma (MM)	7 (9.1)
Benign	23/77 (29.9)
Bone Marrow Failure: Aplastic Anemia (AA)	9 (11.7)
Idiopathic Thrombocytopenic Purpura (ITP)	7 (9.1)
Red Cell Disorders: Anemia of Chronic Disease (ACD) Congenital Dyserythropoietic Anemia (CDA) Haemolytic Anemia (HA) Megaloblastic Anemia (MA) Refractory Anemia (RA)	1 (1.3) 1 (1.3) 1 (1.3) 1 (1.3) 1 (1.3)
HaemophagocyticLymphohistiocytosis (HLH)	1 (1.3)
Hypereosinophilic Syndrome (HES)	1 (1.3)
Non-Haematological	0
Normal bone marrow	15/111 (13.5)
Diagnosis not made	19/111 (17.1)

Table IV: Diagnostic yield for various indications.	
Indications	Diagnostic yield (%)
Visceromegaly	87.1
Pancytopenia	86.6
Pyrexia of unknown origin	85.7
Lymphadenopathy	85.0

In case of a provisional diagnosis of pancytopenia, the procedure resulted in the final diagnosis of malignant disorders [AML (n=2), CML (n=1), HCL (n=1), MDS (n=1)], benign disorders [AA (n=2), ITP (n=1), hemolytic anemia (n=1)], and a presence of normal marrow in 5 cases. Similarly, in cases with a clinical indication of PUO, the final diagnosis observed were malignant disorders [CHL (n=2)], benign disorders [ITP (n=1)], and

normal marrow (n=3). The overall diagnostic yield in the present study was 82.9% while based on indications, visceromegaly had the highest yield (87.1%) followed by pancytopenia (86.6%) (Table IV).

Discussion

Bone marrow examination is considered an important modality for the diagnosis of suspected disease, in the evaluation of disease staging, or treatment response in case of hematological disorder as well as in the evaluation of patients with non-hematological/systemic illnesses.[1, 7, 9, 10] The present study determined the major indications and the frequencies of numerous disorders observed.

One of the important findings in the present study was that majority of the cases were diagnosed with hematological malignancies in comparison to benign ones. This is similar to the findings reported by an author from Saudi Arabia.[8] Furthermore, within the hematological malignancies, chronic myeloid leukemia was observed to be the most common disorder which was to be in contrast to a study by Qahtani et al. who reported acute leukemia to be the most frequent malignancy.[8] Following leukaemias, myeloproliferative neoplasms were the second most frequent malignant haematological disorder in the present study similar to the trend observed in the study by Qahtani et al.[8]

The benign hematological disorders were observed in 28.6% of the cases which was considerably lower than frequencies reported by other local studies i.e. 60-80%[10, 11] but higher than the one reported by a Saudi study (13.5%).[8] One of the reasons for lower frequency could be that benign disorders such as aplastic anemia, red cell disorders are more commonly diagnosed in early life hence detected in the paediatric population while the present study recruited patients above the age of 16 years old. Also, the referrals to our center for cases involving anemia and other benign cases is low. Aplastic anemia was the most common benign hematological disorder in the present study while another study reported ITP as the most common benign hematological disorder.[8]

In the present study, there was a small population in whom the marrow was found to be normal despite several patients having the clinical diagnosis of hematological disease and the procedure was done due to suspicion of a hematological disease or to evaluate the treatment response to therapy. This finding was also reported by Bashwari et al.[12]

An ideal specimen includes an abundance of spicules in the aspirate and an adequate bone marrow core (usually ≥1 cm in length), both key elements to establishing a diagnosis. Bishop et al. hypothesized that a direct relation was present between the length of the trephine core and the diagnosis of the tumor to be malignant.[13] The author further established a core size of 1.6cm for reliable detection of the marrow for tumors. According to WHO, whatever the indication may be, the recommended minimum adequate length for trephine biopsies is > 1.5cm. In the current study, we also observed that the maximum diagnosis of malignant disorders was found when the core size was >1.0cm.

In the present study, the diagnostic yield was 82.9% which was comparably considerably higher in comparison to another similar study which reported the yield to be 32.7%.[14] The current study reported highest diagnostic yields were observed for fatigue, PUO, lymphadenopathy, and pancytopenia. In contrast, Martellosio et al. reported the highest diagnostic yield observed for cytopenia, blood cythaemias and monoclonal gammopathy.[14]

The Institute of Medicine's report "Crossing the Quality Chasm" defined quality as the degree to which health services are constant with current professional information and upsurge the possibility of anticipated health outcomes.[15] With respect to bone marrow assessment, these goals may be operationalized as the degree to which these procedures result in specimens of high enough quality for pathologic review.

Checklists and audits have been used as tools to improve the quality of health care in both medical and surgical settings.[15-20] For example, use of the World Health Organization general surgical safety checklist in a multinational study resulted in an almost 50% decrease in mortality.[17] Such to do checklists focus on critical steps and logistics of procedures (e.g. ensuring the size of bone core length or no. of aspirate slides made) along with other parameters related to operator's technique. Similarly, use of a checklist for proper bone marrow specimen preparation may have the potential to improve specimen quality.

The observations of the study might be used to set key performance indicators (KPIs) for bone marrow biopsy procedures that may be helpful for audit and may provide information that collectively can improve the diagnostic utility and efficiency of the procedure and provide basis for training and improvement where needed. The list of parameters that can be used as key performance indicators (KPIs) and as an assessment tool for bone marrow biopsy competency and audit (Supplementary file A1). Improving the efficiency and quality of procedure will ultimately increase the ratio of accurate and timely diagnosis when bone marrow is indicated as a first hand tool so that it would benefit the patient.

Conclusion

Bone marrow examination plays an essential role in diagnosis and monitoring of various malignant and non-malignant hematological conditions and certain non-hematological conditions. A clear-cut pre-procedural assessment and subsequent clinical correlation would further improve the value of the investigation.

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