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Original Article

Bone Marrow Examination: An audit from a tertiary care centre in Northern Sri Lanka

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Key words: bone marrow aspiration, trephine biopsy, haematological malignancies, non-malignant haematological disorders

Abstract

Introduction

Bone marrow examination is an invaluable haematological investigation for the assessment of many clinical conditions where it provides key diagnostic information.

Objectives: The study aimed to assess the indications and outcomes of bone marrow examination over three years.

Methods

A retrospective study design was used and data from January 2017 to December 2019 was retrieved from the archive maintained at the Haematology Unit, Teaching Hospital, Jaffna.

Results

A total of 857 bone marrow examinations were performed during the three year study period. The male to female ratio was 1:1.04. Age range was from 1 to 86 years with a mean of 52.96 years. The common indications for bone marrow examination were work up for unexplained cytopaenia, suspected haematological malignancies and plasma cell neoplasm. Of the total bone marrow examinations, 7.93% were performed to assess response to treatment of haematological malignancies, 21.82% were found to be normal active marrow and 70.24% were found to be having pathological conditions. Of those identified as pathological based on bone marrow findings 60.8% were malignant and 39.20% were nonmalignant. Acute leukaemia (10.5%) was the commonest haematological malignancy in the study group followed by plasma cell neoplasm (8.52%) and chronic myeloproliferative neoplasm (8.40%).The commonest acute leukaemia identified was acute myeloid leukaemia (7.47%).

Conclusion

Bone marrow examination plays a pivotal role in diagnosing malignant and non-malignant haematological conditions and some selected non haematological conditions. A precise pre-procedural assessment and subsequent clinical correlation would further improve the value of the investigation.

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Introduction

Bone marrow examination is an indispensable adjunct in the field of haematology and in some instances it may be the sole procedure by which a precise diagnosis can be made. It should be preceded by thorough clinical assessment, basic haematological investigations together with blood film examination and targeted biochemical, microbiological, and radiological investigations. Systematic assessment is essential, not only to select the patient for bone marrow examination but also to ensure that all relevant tests are performed on the material obtained [1].

Bone marrow aspiration and trephine biopsy are performed as two arms of the same procedure. Bone marrow aspiration specimens are particularly useful in ascertaining fine cytological details and can be utilized for supplementary investigations such as cytochemistry, immunophenotyping, cytogenetics, molecular genetics, and microbiology. Trephine biopsy allows complete assessment of marrow architecture and the pattern and distribution of abnormal infiltrate and at times that will be the only material to be examined in case of a 'dry tap'. Trephine biopsy material can be utilized for immunohistochemistry.

Teaching Hospital, Jaffna is a tertiary care centre in the Northern Province of Sri Lanka which serves a population of around two million. The Haematology Unit of the Teaching Hospital, Jaffna is well-equipped and has facilities to perform an array of haematological investigations except cytogenetic and molecular studies, which are outsourced as per requirement. Annually, around 6000 cases are referred to the Haematology Unit for consultation. Patients are short listed for bone marrow examination by the Haematologist based on clinical assessment followed by targeted laboratory and radiological investigations. Approximately 275-300 bone marrow examinations are carried out in this unit in a calendar year. Indications for bone marrow examination include evaluation of unexplained anaemia, neutropenia, thrombocytopenia, pancytopenia, leucoerythroblastic blood film or suspected bone marrow infiltration, suspected acute leukaemia, myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), chronic lymphocytic leukaemia (CLL), plasma cell myeloma (PCM), lymphoma, staging of lymphoma and fever of unknown origin (FUO).

This study was performed to determine the haematological and non haematological disorders which warranted bone marrow aspiration and biopsy, assess the diagnostic yield and describe the distribution of haematological disorders diagnosed on bone marrow examination at a tertiary care centre in Sri Lanka.

Methodology

This was a retrospective, descriptive study, designed as an audit, to evaluate the indications and diagnostic yield of bone marrow examination in a tertiary care hospital in the Northern Province, Sri Lanka, over a period of three years. The study was carried out at the Haematology Unit Teaching Hospital Jaffna, Sri Lanka. Ethics approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Jaffna (Ref. No: J/ERC/20/117/NDR/0233). All patients who underwent bone marrow examination over a period of three years (January 2017 to December 2019) were included. Patient's age, sex,

referring clinician and the indication for bone marrow were retrieved from the bone marrow biopsy request form. Final diagnosis of all patients was retrieved from the bone marrow data base maintained at the Haematology Unit. Referrals for bone marrow biopsy were made by consultants of all specialties and subspecialties of Teaching Hospital, Jaffna, base hospitals in the Jaffna District and some district hospitals of the Northern Province.

Bone marrow examination was carried out after taking informed written consent by trained and competent medical officers under aseptic conditions according to the standard operative procedure from the posterior iliac crest using local anaesthesia. General anaesthesia was used in children. No immediate or long-term complications were reported. Films of aspirated marrow, crushed particles and imprints of trephine biopsies were made at the bedside and fixed once they were thoroughly dry. Romanowsky and Perls stains were used routinely. In relevant cases, bone marrow aspirate samples were taken for immunophenotyping, cytogenetics and microbiological tests using a second syringe. Trephine biopsy specimens were placed immediately into a fixative, decalcified, and embedded in paraffin wax. Thin sections were cut and stained with hematoxylin and eosin and reticulin stain. Immunohistochemistry was performed in essential cases. Both bone marrow aspiration and trephine biopsy were examined and reported by a single consultant haematologist who has been working in the same station since 2010. The haematologist utilized clinical features, radiological findings and laboratory investigations, including flow cytometry and cytogenetics when indicated, to arrive at a definitive diagnosis. A report was issued in a timely manner.

Results

During the three-year study period, a total of 857 bone marrow biopsies were performed out of 19,398 referrals received for diagnostic workup. There were 418 males and 439 females with a male: female ratio of 1:1.04. The patients' ages ranged from 1 to 86 years with a mean age of 52.96 years. Children under the age of 12 years were 36 (4.2%). Referrals were received through physicians (600; 70%), oncologists (145; 16.9%), surgeons (39; 4.6%), paediatricians (33; 3.9%), peripheral hospitals (33; 3.9%) and obstetricians (7; 0.8%). Table 01 summarizes the indications for bone marrow examination. The more common indications included investigation of unexplained cytopaenia, suspected haematological malignancies and suspected plasma cell neoplasms.

Table 01: Indications for bone marrow examination

No	Indication for bone marrow examination	Frequency(%)
01	Work up for unexplained cytopaenia	283(33.0)
02	Suspected haematological malignancies	239(27.9)
03	Suspected plasma cell neoplasm	148(17.3)
04	Assessment of remission status after treatment of haematological malignancies	68(07.9)
05	Staging bone marrow for lymphoma	63(07.4)
06	Infective screen for pyrexia of unknown origin	35(04.1)
07	Leucoerythroblastic blood film and suspected bone marrow infiltration	20(02.3)
08	Suspected storage disease	1(00.1)
	Total	857(100.0)

Bone marrow examination findings

Of 857 bone marrow examinations performed, 187 (21.82%) were reported as normal active marrows. Sixty-eight (7.93%) marrows were performed for assessment of remission status after treatment of haematological malignancies. Six hundred and two bone marrows (70.24%) were reported as pathological. Spectrum and frequencies of various pathological conditions are summarized in Table 2.

Table 02: Spectrum and frequencies of various pathological conditions

Categories	Classification	Subtypes	N (%)
Malignant haematological disorders			**358(41.77)**
	Acute Leukaemia		**90(10.50)**
		Acute Myeloid Leukaemia (AML)	64
		B-Lymphoblastic Leukaemia (B-ALL)	21
		T-Lymphoblastic Leukaemia (T -ALL)	04
		Mixed phenotype Acute Leukaemia	01
	Plasma cell Neoplasm		**73(08.52)**
		Symptomatic plasma cell myeloma	51
		Monoclonal Gammopathy of Undetermined significance (MGUS)	15
		Asymptomatic plasma cell myeloma	03
		Plasma cell leukaemia	02
		Light chain myeloma	01
		AL Amyloidosis	01
	CMPN		**72(08.40)**
		Chronic Myeloid Leukaemia (CML)	28
		Essential Thrombocythaemia	18
		Polycythaemia Vera (PV)	14
		Primary Myelofibrosis	12
	Myelo Dysplastic Syndrome (MDS)		**68(07.93)**
	Myelo dysplastic/ Myelo proliferative neoplasm		**12(01.40)**
		Chronic Myelo Monocytic Leukaemia (CMML)	12
	Chronic Lympho Proliferative Disorder (CLPD)		**42(04.90)**
		Mature B cell neoplasm	12

		Mature T cell neoplasm	04
		Chronic Lymphocytic Leukaemia	19
		Bone marrow Involvement by CLPD	07
	Myeloid/Lymphoid neoplasm with Eosinophilia and gene rearrangement		**01(00.12)**
Malignant Non-Haematological conditions			**08(00.93)**
		BM metastasis by carcinoma	04
		BM metastasis by Ewings sarcoma	02
		BM metastasis by sarcoma	01
		BM metastasis by neuroblastoma	01
Nonmalignant haematological conditions			**236(27.54)**
		Immune thrombocytopenic purpura (ITP)	92(10.74)
		Reactive marrow	87(10.15)
		Nutritional anaemia	15(01.75)
		Acquired Aplastic Anaemia	13(01.52)
		Polycythaemia other than PV	10(01.17)
		Fanconi Anaemia	05
		May Hegglin	04
		Reactive myelofibrosis	03
		Drug Induced Aplastic Anaemia	02
		Hypocellular marrow with the background of Lymphoma	01
		Cyclical Neutropenia	01
		Evans syndrome	01
		PNH	01
		Pure red cell aplasia	01
Total			**602(70.24)**

Of the 68 bone marrows done for assessment of remission status after treatment, 42 (61.76%) were in morphological remission. Six marrows were reported as hypocellular and 20 marrows showed either relapse or residual disease. One hundred and forty-eight bone marrows were performed on suspicion of plasma cell neoplasm and 73 (49.32 %) were found to be positive. Sixty-three bone marrows were done for staging in patients diagnosed with lymphoma of which 7 (11.11 %) were found to be positive for involvement.

Discussion

Bone marrow aspiration and trephine biopsy, when performed on selected patients after a complete haematological assessment, are very useful in the diagnosis of malignant and

nonmalignant haematological conditions, certain systemic illnesses, non haematological malignant conditions when metastasized to bone marrow, staging of lymphoma and assessment of response after treatment for haematological malignancies.

In our cohort of patients (857), age ranges are comparable to other studies [2-6]. Slight female preponderance was noticed in contrast to other studies [2,4,5,6]. Children under 15 years constituted 5.95% which is less than another study [2] where children under 15 years constituted 19.1%. This could be partly attributable to the fact that whenever the circulating blasts are identified in the peripheral blood film in suspected paediatric acute leukaemia cases flow cytometry is done on peripheral blood for confirmation of diagnosis and classification. Confirmed cases are transferred to national paediatric oncology unit for treatment where a baseline bone marrow is done. However, adult patients are only transferred to the Oncology Unit of the same hospital after full diagnostic work-up.

Work up for unexplained cytopaenia and suspected haematological malignancies were common indications for bone marrow biopsy in our study. Suspected haematological malignancy was the common indication in some studies [2,4] while in some other studies, anaemia, splenomegaly and infectious disease screening were common indications [3,5,6] Among the malignant haematological conditions diagnosed on bone marrow examination, acute leukaemia was the commonest which is comparable to others in the literature [2,5,6] while in other studies, lymphoma [3] and plasma cell myeloma [4] were the commonest haematological malignant conditions reported.

Among acute leukaemias, acute myeloid leukaemia (AML) was the most common (71.11%). Age at presentation of patients with AML ranged from 2 to 85 years with a median age of 59 years. Worldwide peak age of AML is in the 7^{th} decade [7]. The lower age range in our cohort of patients may reflect the true distribution of AML or referral bias. Only one child under 12 years with trisomy 21 had AML and the remaining patients were over 12 years with a male: female ratio of 1: 1.2.

B-ALL was the second most common acute leukaemia. Age ranged from 1 to 76 years with a median age of 23 years and a male: female ratio of 1:0.75. Only two cases under 12 years of age were diagnosed on bone marrow examination. However, during the study period of 3 years, 10 paediatric B-ALL cases were diagnosed in the peripheral blood by flow cytometry. The age of these patients ranged from 3 months to 11 years with the median age of 3 years and a male: female ratio of 1:1.5. These cases were not included in the study as a bone marrow biopsy was not undertaken in these patients.

Among the 4 patients with T-ALL, three were adolescent males and one was an adult male. Ages of patients with plasma cell myeloma ranged from 43 – 86 years with the median age of 67 years. Male: female ratio was 1:0.68. These findings are similar to worldwide median age, which was reported as 65-70 years with a slight male predominance [7].

Among the 28 patients with CML, age ranged from 27 – 68 years with the median of 49 years. Male: female ratio was 1:0.65. This is similar to the worldwide median age which was reported as 5th and 6th decades of life with a slight male predominance [7].

Ages of patients with essential thrombocythaemia ranged from 25 – 86 years with the median age of 67 years. Three females were under 45 years. Male: female ratio was 1: 2. The global median age was reported as 50-55 years with a small peak in women of reproductive age [7].

Among the 19 patients with CLL, age ranged from 50-83 years with a median age of 68 years. Male: female ratio was 1:0.9. This is similar to the median age of 70 years with a slight male predominance reported in another study [7].

Ages of patients with MDS ranged from 21 to 85 years with the median age of 65 years. Male: female ratio was 1:1.34. International figures indicate over 60% of patients are over 70 years with slight male predominance [7]. In our cohort of patients there is female predominance and only 28% of patients were over 70 years.

In our study, 64 lymphoma patients had staging marrow and only 7 were positive (10.94%) while there was a 34% positivity rate reported in another study (1). Standardizing the length of trephine biopsy specimens and routine use of immunohistochemistry for staging marrows may be useful in increasing the detection rate. Bilateral trephine biopsies have also been shown to increase the detection rate further but at the expense of significant patient discomfort [8].

Among the nonmalignant haematological conditions, 92 cases (10.74% were diagnosed with immune thrombocytopenic purpura (ITP). Of these, the indication was unexplained cytopaenia in the majority (90 cases) and suspected haematological malignancy in the remaining 2 cases. The age of the patients varied from 1- 80 years with the median age of 54 years. Male: female was 1:1.56.

Of the total 857 bone marrows performed, 87 (10.15%) were reported as reactive marrows. These marrows were performed for a variety of indications including infectious diseases 30 (3,5%), suspected haematological malignancy 20 (2.33%), suspected plasma cell myeloma 13 (1.51%), unexplained cytopaenia 13 (1.15%), staging of lymphoma 9 (1.05%) and investigation of leucoerythroblastic blood film 2 (0.23%).

A further 187 of 857 marrows (21.82%) were reported as normal active marrows. The indications for those marrows were suspected plasma cell myeloma 62 (7.23%), unexplained cytopaenia 50 (5.83%), staging marrow for lymphoma 48 (5.60%), suspected haematological malignancy 18 (2.10%), infective screen 5 (0.58%), leucoerythroblastic blood film 03 (0,35%) and suspected storage disease 1 (0.16%).

Only 15 (1.75%) cases were reported as nutritional deficiency anaemia. Ages ranged from 17 – 73 years with a median age of 53 years. Male: female was 2:1.This low number

indicates that the majority of the nutritional anaemia are diagnosed with peripheral blood count, blood picture and laboratory assays for iron, folic acid and B12.

Acquired aplastic anaemia was diagnosed in 13 (1.52%) bone marrows. Ages ranged from 26-80 years with a median age of 58 years. Male: female: 1:2.25. Among the 5 cases of Fanconi anaemia, 4 were females. Age ranged from 3-9 years with a median age of 7 years. Two cases of drug induced hypocellular marrow were reported. One hypo cellular marrow was attributed to concurrent lymphoma.

Polycythaemia other than polycythaemia vera, reactive myelofibrosis, May Hegglin anomaly, cyclical neutropenia, Evans syndrome, pure red cell aplasia and paroxysmal nocturnal haemoglobinuria were the rare, nonmalignant haematological conditions reported in this cohort of patients (21/857; 2.45%)

Conclusion

Bone marrow biopsy, in conjunction with preprocedural clinical assessment and other relevant selected investigations, plays a pivotal role in the field of haematology. Regular audits will not only provide necessary information but also improve the utility of the procedure in a limited resource setting.

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