

Role of the Bone Marrow Examination among Undifferentiated Fever in Tropics

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Abstract

Background: Bone marrow aspiration and biopsy is one of the most important diagnostic tools for evaluation of undifferentiated fever. The positivity yield of these samples is highly specific that provides additional evidence for clinical decision making among the undifferentiated febrile cases. With this background we evaluated the bone marrow results of undifferentiated febrile cases for the last five years at B.P. Koirala Institute of Health Sciences, Dharan, Nepal. The objective of the study was to measure the sensitivity of the bone marrow investigations among undifferentiated febrile cohort.

Methods: A retrospective study was performed from January 2010 till December 2014 evaluating bone marrow reports. Completed request forms and the histopathological reports of the bone marrow specimens were reviewed. Statistical data was analyzed using SPSS 17 and p-value of <0.05 was considered significant.

Results: Over the half decade 319 specimens were collected for bone marrow biopsy out of that 27% were requested for undifferentiated fever. The mean and median age of the biopsy performed patients was 35 and 31 years respectively. Among all biopsy samples 59% was adequate for evaluation however among the undifferentiated febrile cases biopsy samples only 45% was adequate for evaluation. The sensitivity of bone marrow biopsy was 34%. There were 714 bone marrow aspiration samples of that 84% was adequate for evaluation. The most common etiological diagnosis for the undifferentiated fever from the marrow evaluation was visceral leishmaniasis (53%). The sensitivity of the bone marrow aspiration and aspiration or biopsy for visceral leishmaniasis was 95% and 98% respectively. (p value 0.03)

Conclusion: Bone marrow aspiration is highly sensitive and specific for the diagnosis of visceral leishmaniasis among the undifferentiated fever at tropics in Nepal.

Keywords: Bone marrow aspiration, Bone marrow biopsy, Sensitivity.

Introduction

Bone marrow examination is one of the important diagnostic tools for evaluation of undifferentiated fever. It provides diagnostic and prognostic outcome of the clinical diagnosis. The procedure is high yield investigation in an experienced hand associated with very rare severe complication [1]. Bone marrow evaluation compromised of marrow aspiration and biopsy. It has been found that trephine biopsy is superior to aspiration. It has a major role in assessing the cellularity, pattern of infiltration and is helpful in dry tap on aspiration due to fibrosis and infiltration where examination of an aspirate has been unsuccessful. Bone marrow aspiration and biopsy have no absolute contraindications, but there may be relative contraindications related to the general condition of the patient or the risk of anesthesia or deep sedation [2].

The primary contraindication is hemophilia and disorders related to hereditary bleeding. Thrombocytopenia is not absolute

contraindication for bone marrow procedure [3]. Marrow smears are the cost effective and high specific diagnostic method in resource limited set up where PCR is not available [4]. The positivity result of bone marrow biopsy is related to the sample size. The World Health Organization (WHO) recommend the minimal adequate length of >1.5 cm [5]. The objective of the study was to measure the sensitivity of bone marrow examination findings among undifferentiated febrile cases in a tertiary care hospital in Nepal.

Methods

The study was conducted in B. P. Koirala Institute of Health Sciences a medical school with a referral hospital in Eastern Nepal. The institute is only the center to perform bone marrow examination in the region. Department of Internal Medicine and Pediatrics performs the marrow procedure whereas the Department of Pathology provides the report on regular basis. A retrospective study was performed from January 2010 till December 2014 evaluating bone marrow reports. Completed request forms and the histopathological reports of the bone marrow specimens were retrieved and reviewed. Request form asked as fever under evaluation, undifferentiated fever,

pyrexia of unknown origin or any form with clinical diagnosis of infectious origin were enrolled in the study. All patients went under bone marrow aspiration and if it were inconclusive then a repeat aspiration and biopsy was performed. Bone marrow aspiration and biopsy were performed from different sites by the clinicians after taking written consent with the standard method under aseptic precautions. For cytological studies trail smear and crush smear were obtained to laboratory. The bone marrow smears fixed in methanol and stained with Romanowsky stain and additional stain like iron and immunocytochemistry as per clinical suspect. Biopsy specimens were received after fixation into 10% formalin. The samples were decalcified for 24 hours followed by tissue processed and thin sectioning. The thin sections (0.4mm) were stained with hematoxylin and eosin and others immunohistochemistry stains as per clinical suspect. The total number individual infectious disease data was obtained from hospital record system. Statistical data was analyzed using SPSS 17 and p-value of <0.05 was considered significant.

Results

During the study period of five years 319 specimens were collected as bone marrow biopsy and 1076 as aspiration. The proportion requested for fever under evaluation, undifferentiated fever, pyrexia of unknown origin or any form with clinical diagnosis of infectious origin were 27% (86) and 66% (714) respectively among the biopsy and aspiration samples. Among the biopsy sample enrolled 71(83%) were requested from Department of Internal Medicine whereas 15 (17%) were from Pediatric Department. Of the aspiration samples, 621 (87%) were from Department of Internal Medicine and 93 (13%) from Pediatric Department. The common sites for marrow examination were posterior superior iliac crest (82%) followed by tibia, (11%) anterior superior iliac crest (5%) and sternum (2%). None of the procedure had any life threatening serious event. Only 39 (45%) biopsy samples and 600 (84%) aspirations were adequate for evaluation. Adequacy of samples were observed in 20% (3/15) pediatric cases and 51% (36/71) adult cases of marrow biopsy whereas 89% (83/93) pediatric cases and 83% (517/621) adult cases of marrow aspiration. Among the total biopsy and aspiration samples received 59% (188) and 72% (779) was adequate for evaluation. (Table 1)

Table 1: Characteristics of bone marrow samples provided to Pathology Department

Characteristics of bone marrow examination	Total bone marrow biopsy sample	Undifferentiated fever bone marrow biopsy sample	Total bone marrow aspiration sample	Undifferentiated fever bone marrow aspiration sample
Total sample received	319	86	1076	714
Number requested on year 2010/2011/2012/2013/2014		22/16/11/17/20		131/146/169/130/138
Female		38 (44.2%)		301 (42.2%)
Pediatric cases		15 (17.4%)		93 (13%)
Adult cases		71 (82.6%)		621 (87%)
Adequate for processing	188 (59%)	39 (45.3%)	779 (72%)	600 (84%)
paediatric samples adequate for processing		3		76
Adult samples adequate for processing		36		524

The mean and median age of the biopsy performed patients was 35 and 31 years respectively. The median length of biopsy was 0.6 cm with ranges of 0.1 to 3.0 cm. The median lengths of inadequate and Adequate sample were 0.4 cm and 0.8 cm respectively. The sensitivity of bone marrow biopsy was 34% (29/86). (Table 2)

Table 2: Characteristics of bone marrow biopsy samples provided to Pathology Department

S.N.	Characteristics of Bone marrow biopsy	Undifferentiated fever sample (N=86)
1	Mean age of the patient	34 years
2	Median age of the patient	31 years
3	Bone marrow biopsy	
	a. Median length of the biopsy	0.6 cm
	b. Range of length of the biopsy	0.1 cm -3 cm
	c. Mean length of the biopsy	0.72 cm
	d. Median length of inadequate sample	0.4 cm
	e. Mean length of inadequate sample	0.53 cm
	f. Median length of adequate sample	0.8 cm
	g. Mean length of adequate biopsy	0.91cm
4	Bone marrow findings	

a. Normal marrow	10
b. Abnormal marrow	29

Out of 714 aspiration samples of undifferentiated fever 16% (114) could not be reported due to poor sample. Among the reported 10.2% (73/714) were normal findings. Majority of aspirations were hypercellular (54.6%) as well as increased myeloid to erythroid ratio (43.1%). Leishmania donovani was detected among 51.7% aspiration samples collected for evaluation. (Table 3)

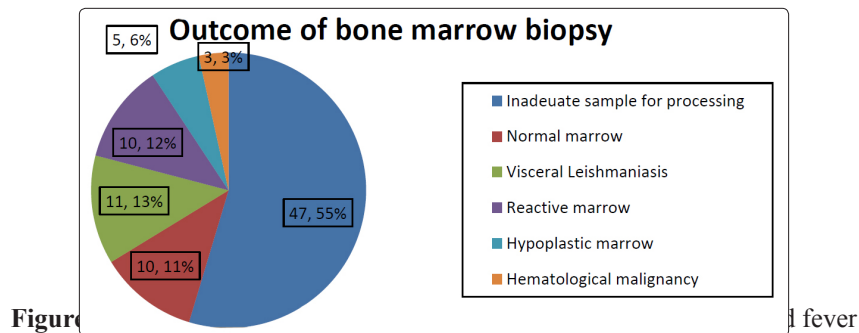
Table 3: Characteristics of bone marrow aspiration samples provided to Pathology Department

S.N.	Characteristics of bone marrow aspiration samples	Undifferentiated fever sample (N=714)
1	Mean age of the patient	39 years
2	Median age of the patient	34 years
3	Bone marrow aspiration findings	
	a. Marrow fragment less than 3	114
	b. Marrow fragment more than or equal to 3	600
4	Cellularity	
	a. Hypocellularity/Normal@/Hypercellularity	137/73/390
	b. M/E ratio; Normal#/Increased/Reversal	174/308/118
	c. Plasma cells; less than 2% /3% to 10% /more than 10%	439/154/7
	d. Hemoparasites	369

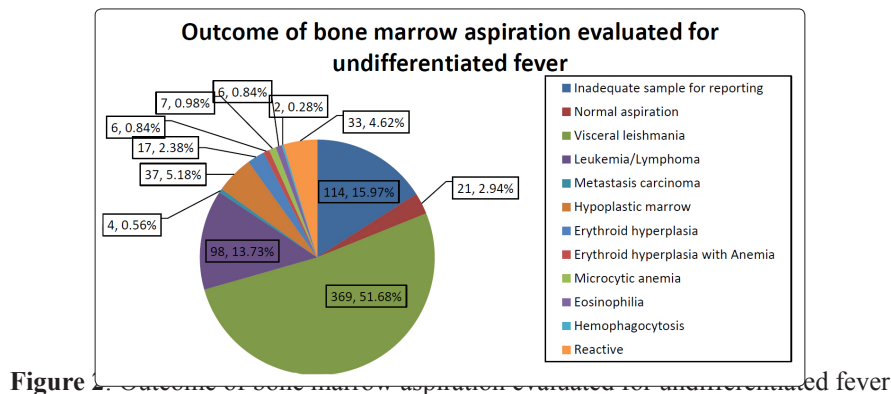
@ Normal cellularity has been defined as marrow cell percentage equal or more than 100 - the age of patient in years

#Normal M/E is 3:1 to 15:1

Majority of biopsy samples (55%) were inadequate for evaluation however among the adequate samples the most common finding was visceral leishmaniasis (13%) then reactive marrow (12%), hypoplastic marrow (6%) and hematological malignancy (3%). (Figure 1)



Among the reported sample the most common diagnosis were visceral leishmaniasis (51.7%) followed by 13.7% hematological malignancy, 5.2% hypoplastic marrow, 4.6% reactive marrow and 1.8% anemia. (Figure 2)



Bone marrow biopsy added the diagnosis of visceral leishmaniasis to 380 (53%). The sensitivity of bone marrow aspiration and aspiration or biopsy was 95% and 98% respectively. (p value of 0.03) (Table 4)

Table 4: Sensitivity of Aspiration and Aspiration or Biopsy for visceral leishmaniasis

	Aspiration	Aspiration or Biopsy	P value
Proportion of positive VL test (Demonstration of LD bodies)	369/389	380/389	0.03

When aspiration was compared with biopsy there were statistical differences between the proportion of samples with inadequacy, abnormal reports, demonstration of LD bodies, hematological malignancy and reactive marrow. (Table 5)

Table 5: Comparison between proportion of different component test between aspiration and biopsy

	Aspiration (n=714)	Biopsy (n=86)	P value
Proportion of inadequate sample for reporting	114	47	0.0
Proportion of positive abnormal test among the undifferentiated fever	579	29	0.0
Proportion of positive VL test (Demonstration of LD bodies)	369	11	0.0
Proportion of hematological malignancy	98	3	0.007
Proportion of reactive marrow	33	10	0.006
Proportion of hypoplastic marrow	37	5	0.8

Discussion

Bone marrow examination is common procedure in BPKIHS with no case report of life threatening complication with more than 1000 procedures during year 2010 to 2014. More than two third of the aspirations and one fourth of biopsy samples of the patient presented to the hospital were undiagnosed case of fever. Majority of the samples were adult population and male gender. Similar age and gender distribution was observed at another tertiary care hospital in Nepal by Jha A et al [5].

About one fifth bone marrow was taken from sites other than of the posterior superior iliac crest however the study by Jha A et al reported posterior superior iliac crest as the only site for marrow examination [5]. The adequacy of the samples for reporting was 59% for biopsy and 72% for aspirations. (P value 0.0) The differences could be because biopsy demands more invasive procedure than aspiration i.e. biopsy sample is conformed only by removing the needle hence if the preceding biopsy has inadequate sample patient need to be inserted the needle again. Among the pediatric case 20% biopsy and 82% of aspiration were adequate for reporting. Among the adult cases 51% of biopsy and 84% of aspiration were adequate for reporting. Adequacy of sample depends upon the length of biopsy provided [4]. Low proportion of adequacy of pediatric sample could be because of smaller biopsy sample size as compared to adults. This could be the reason for having median length of adequate sample 0.8cm as compared to inadequate sample 0.4cm in this study.

The median age for aspiration and biopsy was 34 and 31 years which was comparable to similar other study [5]. The sensitivity of bone marrow biopsy was 34% (29/86). Similar results were observed on bone marrow biopsy by Hot A et al (23.7%), Benito N et al (37.9%) and Quesada NE et al (42%) [6-8]. The most common infectious etiology detected by marrow biopsy was Visceral Leishmaniasis (12%). Hematological malignancy, reactive

marrow and hypoplastic marrow was found in 3%, 12% and 6% of biopsy sample respectively. The aspiration has the highest yield for Visceral Leishmaniasis (52%). This could be because for all clinical suspect of Visceral Leishmaniasis at first the patient went under aspiration and if result were negative a repeat aspiration and biopsy was done. So the bone marrow biopsy has additional 3% (11) benefit of confirmatory diagnosis of Visceral Leishmaniasis. (p value 0.03) The most common diagnosis on marrow examination was Visceral Leishmaniasis reason being all the clinical suspect cases of Visceral Leishmaniasis were referred to only this center and Visceral Leishmaniasis being ministry priority program. The sensitivity of Visceral Leishmaniasis by marrow examination was more than 95% in this study. Similar result has been reported by Mauro et al with the sensitivity of 96.6% by the bone marrow examination [3]. The other findings of aspiration were 13.7% hematological malignancy, 5.2% hypoplastic marrow, 4.6% reactive marrow and 1.8% anemia. Aspiration also revealed eosinophilia, erythroid hyperplasia, metastasis and hemophagocytosis each entity less than 1%. The diagnosis was similar as compared to Jha A et al [1] however the proportion of cases were not similar for the common diagnosis like visceral leishmaniasis and hematological malignancy. This could be due to climatic variation of the two medical schools and the differences in the sample size. Infective pathology most commonly Mycobacterium species was commonly diagnosed among fever of unknown origin patients on bone marrow evaluation by Hot A et al, [6] Benito N et al, [7][Quesada NE et al [8] and Riley et al [9]. These studies were carried out in developed nation however patients were immune compromised which could be the reason for such findings. However a study carried by Ahemad et al comparing bone marrow of non HIV population found the infective etiology less than 10% of marrow sample. Addition of biopsy among inconclusive aspiration increases the yield for Visceral Leishmaniasis and Hematological malignancy with statistical significance.

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