FREQUENCY OF BONE MARROW INVOLVEMENT IN PYREXIA OF UNKNOWN ORIGIN

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Abstract

Background and Objectives: This study has been conducted to highlight the frequency of involvement of bone marrow in Pyrexia of unknown origin (PUO) and delineate the existing spectrum of diseases involved in PUO. The results would facilitate the clinician in making the right choice of patient for bone marrow biopsy.

Methods: A total 121 cases of pyrexia of unknown origin were included in the study. Patients with known systemic illness, hematological disorders, who had taken radiotherapy or chemotherapy or with known malignant disorders were excluded to avoid selection bias. Bone marrow was aspirated from posterior iliac crest in all the patients along with trephine biopsy using disposable trephine biopsy needle of 11 gauge. Wright-Geimsa stain was used to stain the smears prepared from concentrated marrow cells. The involvement of bone marrow was categorized into four major etiologies of PUO and assessed by observing bone marrow aspirate along with trephine biopsy slides using light microscopy.

Results: The mean age was 34.72 ± 14.66 years with minimum and maximum age 18 and 65 years. .Out of 121 patients, a total of 94 (77.7%) cases showed involvement of bone marrow and 27(22.3%) cases showed no involvement. Post stratification Chi-square test revealed significant. P-value: 0.000.

Conclusion: Our results identified a large number of cases of PUO with involvement of bone marrow which can serve as a diagnostic aid in further workup. We believe that implementing invasive procedures such as bone marrow biopsy can help to find the underlying cause and prevent the delay in diagnosis of such patients.

Keywords: Pyrexia of unknown origin, Bone marrow examination, clinical decision-making, chronic diseases, clinicians

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The most crucial step in management of the patient is diagnosis. Many a times, patients present with vague symptoms and chronic history which do not point to the right diagnosis. Baseline investigations are helpful to a certain extent but certain advanced techniques have to be employed to reach to a final diagnosis. Bone marrow biopsy is one of these investigations which enable a clinician to reach the final diagnosis and serves as a helpful tool in staging, prognostication and determination of therapeutic response in various diseases.

More than 200 distinct disease have been studied to produce chronic relapsing fever, which have caused hurdles in reaching a conclusive diagnosis. The proportion of patients in each category varies depending upon the geographic distribution, age group, the span of febrile illness and presence or absence of any underlying disease.[4] There are four major categories of PUO: infective, inflammatory, neoplastic and miscellaneous. Infectious diseases (40%), neoplastic disorders (20%), and connective tissue disorders (15%) are ultimately attributed to the majority of the cases of PUO worldwide. Infectious diseases are still very common in

developing countries due to poor hygiene and lack of awareness amongst general population. The clinicians usually investigate these four major categories to delineate a diagnosis in cases of PUO where cause remains vague.[5]

Many a times, patients present with cytopenia, lymphadenothy and organomegaly which are sings of an underlying hematological disorder. The role of bone marrow biopsy becomes extremely important when imaging and other diagnostic procedures come out inconclusive.[6]

Although bone marrow biopsy is an invasive and painful procedure but it can give valuable information in the diagnosis of difficult patients.[7] Early diagnosis of these patients can be done using bone marrow biopsy in developing countries like ours where affordability is an issue. This study was conducted to highlight the frequency of involvement of bone marrow in PUO and delineate the existing spectrum of diseases involved in PUO. The results would facilitate the clinician in making the right choice of patient for bone marrow biopsy.[8]

METHODS

This was a prospective study conducted in Pathology Department of King Edward Medical University from 30th June 2020 to December 2020. A total 121 cases of pyrexia of unknown origin were included in the study. The minimum sample size was calculated as 121 by using 95% confidence coefficient and 6% absolute precision with suspected 13% involvement of bone marrow.[(9)] Informed consent was taken from all patients for being included in the study.

Patients with known systemic illness, hematological disorders, who had taken radiotherapy or chemotherapy or with known malignant disorders were excluded to avoid selection bias. Bone marrow was aspirated from posterior iliac crest in all the patients along with trephine biopsy using disposable trephine biopsy needle of 11 gauge. Wright-Geimsa stain was used to stain the smears prepared from concentrated marrow cells. Haematoxylin and eosin (H&E) stain was used on decalcified and paraffin embedded biopsy specimens. The involvement of bone marrow was assessed by observing bone marrow aspirate along with trephine biopsy slides using light microscopy and results were recorded on the profoma. Subjective assessment of bone marrow aspirate and trephine biopsy showing abnormal cellularity for age, suppression of trilineage hematopoiesis, infiltration by blast cells, atypical cells, extramedullary cells, hemoparasite, storage cells, fungal or tuberculous infection and granuloma were assessed. Presence of any of these either on aspirate or trephine biopsy was labelled as bone marrow involvement. The patients who showed involvement of bone marrow were further categorized on basis of bone marrow findings into various systemic illnesses. SPSS version 26 was used for data entry and analysis. Qualitative variables such as gender was calculated as frequencies while involvement of bone marrow and subsequent clinical diagnoses were calculated as percentages. Age was analysed into mean and standard deviation. Further stratification for age, gender, duration of pyrexia of unknown origin, bone marrow aspirate, trephine findings and diagnoses was done. Chi-square test was applied and p-value of ≤ 0.05 was taken as significant after post stratification of all the data.

RESULTS

The mean age was 34.72 ± 14.66 years with minimum and maximum age 18 and 65 years. (TABLE 1). Out of 121 patients, a total of 94 (77.7%) cases showed involvement of bone marrow and 27(22.3%) cases showed no involvement. (FIGURE 1) Post stratification Chi-square test revealed significant. (P-value: 0.000). There were 94 patients who showed involvement of bone marrow and were further categorized into benign and malignant disease processes. There were a few patients in which bone marrow did not pinpoint to clear cut diagnosis and were categorized as miscellaneous such as reactive bone marrow changes or megaloblastic anemia. (Table 2). Benign diseases were categorized into infections, granulomatous diseases, storage disor-ders and pure red cell aplasia whereas malignant disea-ses were categorized into Acute leukemia, lymphoma, chronic

leukemia, multiple myeloma, metastatic disea-ses etc. Duration of pyrexia of unknown origin was subcategorized into four groups. (Figure 2). It was compared with various clinical diagnosis to see if there was any association between the two. (Table 3)

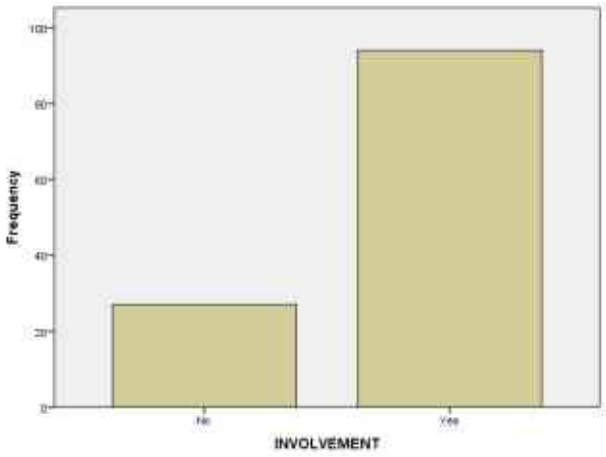

Figure 1: *Frequency Distribution According to involvement of Bone Marrow*

Table 1: *Frequency distribution of involvement of bone marrow with respect to gender*

		Involvement of bone marrow		Total
		NO	YES	
GENDER	Male	16(13.2%)	51(44.6%)	70(57.9%)
	Female	11(9.1%)	40(33.1%)	51(42.1%)
Total		27(22.3%)	94(77.7%)	121(100.0%)

Table 2: *Frequency distribution of benign, malignant and miscellaneous diseases in PUO*

Diagnosis	Male		Female		TOTAL
Benign	18	47%	20	52%	38 (40%)
Malignant	20	60%	13	18%	33 (35%)
Miscellaneous	10	43%	13	56%	23 (24%)
TOTAL					94

DISCUSSION

There were 121 patients with diagnosis of PUO included in our study to determine the frequency of involvement of bone marrow amongst them. Further categorization of patients was done based on their diagnoses. It was a descriptive cross sectional study which was conducted in fully functional tertiary care hospital. 94% of patients who had PUO showed involvement of bone marrow.

The mean age of patients was 34.72 ± 14.66 with majority of patients falling in age group 18-30 years old. Similar study was conducted by Syed NN et al, where the mean age of patients was 33 years[10] and Kumar V et al, 32.3 was the mean age (range, 1-72 years).[11] Zafar A et al, study showed that age of the patients varied from 7 years to 85 years. maximum number of patients were 20-30 years old.[4] This is similar to our findings that most of the cases of pyrexia of unknown origin are reported in >30 years of age. This reflects that age distribution of PUO patients is

Table 3: *Frequency distribution of systemic illnesses according to duration of PUO*

Diagnoses		Duration of PUO							
		< 1 month		1-4 months		4-8 months		8-12 months	
BENIGN	Infections	5	5.3	8	8.5	4	4.2	1	1
	Granulomatous disease	3	3.1	7	7.4	2	2.1	1	1
	Storage disorders	0	0	3	3.1	0	0	0	0
	Pure red cell aplasia	2	2.1	2	2.1	0	0	0	0
MALIGNANT	Acute leukemia	5	5.3	6	6.3	0	0	0	0
	Lymphoma	0	0	2	2.1	1	1	1	1
	Chronic leukemia	0	0	2	2.1	2	2.1	3	3.1
	Aplastic anemia	0	0	3	3.1	2	2.1	0	0
	Myelodysplastic syndrome	0	0	2	2.1	1	1	0	0
	Multiple myeloma	0	0	0	0	1	1	0	0
	Metastatic disease	0	0	0	0	1	1	0	0
	Myelofibrosis	0	0	0	0	1	1	0	0
Total cases		15 (15.95%)		35 (37.2%)		15 (15.95%)		6 (6.3%)	

Number and Percentages given

more or less same amongst various populations.

Male patient were seen in majority in our study i.e. 70(57.9%) with a male to female ratio of 1.3:1. One study conducted by Hajiabdolbaghi M et al, also showed 79% male population.[12] In another study conducted by Gandapur, A. S., there were 66% males while male to female ratio 2:1.[13]

Involvement of bone marrow in PUO was 94% in our study which is similar to another study conducted by Khattak et al, who obtained final diagnoses in 83% of the cases of PUO.[15] Similarly, Wright et al, studied the most frequent invasive procedure performed to diagnose PUO was bone marrow biopsy, yielding a diagnosis in 42%.[16] In contrast to our study, Hong, F. S. et al, concluded that diagnosis was made in only 13.7% patients of PUO, finding either malignant disorders or granulomatous inflammation.[6] Arya A et al, determined that bone marrow examination contributed to final diagnosis in (17%) cases.[5] Diagnostic yield of bone marrow biopsy was 27% in another study carried out by Ben BS et al, in patients of PUO.[17] This concludes that involvement of bone marrow alone cannot be labelled as underlying cause of PUO. It should always be interpreted in light of supportive investigations.

Our study included patients who presented with 3 weeks duration of pyrexia of unknown origin to >8 months of PUO. It was <1 month in (15.95%) cases, 1-4 months in 37.2% cases, 4-8months in 15.95% cases and >8months in 6.3% which shows that majority of patients who had PUO presented with 4-8 months duration of illness. The median duration of fever was 66.5 days i.e. 2 months in study conducted by Ben-Baruch S et al.[18]

Bone marrow involvement have been described in various infectious and systemic diseases resulting in various morphological changes which can be attributed to PUO.[19] In our study, majority of patients suffering from PUO had infections (19%), granulomatous inflammation (13.8%) followed by acute leukemia, megaloblastic changes and chronic leukemia. Whereas 27 patients showed no involvement of bone marrow. Elisabeth et al and Netherlands studied same group of 167 patients and found infection as a leading cause (26%) whereas neoplasm and non-infectious inflammatory disease (13% & 24% respectively). 5% cases were classified as miscellaneous and 30% of cases remained undiagnosed.[20] In contrast to findings observed in our study, Vinod Kumar et al. found malignant disease to be most frequent cause of PUO in bone marrow i.e. (20%)[19]

Benign disease processes was the most frequent finding in our study i.e. (38%). Infectious diseases (19%) were most common amongst all the benign diseases followed by chronic granulomatous inflammation (14%) while storage disorders (3.1%) and pure red cell aplasia (4.1%) were also found.

Malignant diseases accounted for 35% of all cases. Acute leukemia 11 cases (33 %) followed by chronic leukemia 07 cases (21%), Aplastic anemia 05 cases (15%) , Lymphoma 04 cases (12%) each, multiple myeloma 02 cases (6%) whereas Myeloid dysplastic syndrome, Myelofibrosis and metastases was seen in 01 case (3%) each as shown in Table 3. Similar findings were observed in a study conducted in Karachi by where acute leukemia (23.3%) as the most common etiology of PUO.[21] In contrast to our study, Fatima et al. found Lymphoma (27%) cases as the most common etiology of PUO in bone marrow biopsy followed by Myeloproliferative neoplasms (18%).[22]

Hypersplenism (4.2%) was seen in our patients whereas it was not found in any other similar studies conducted in Pakistan before.[23]

We did not establish any significant association between gender and involvement of bone marrow (p-value:0.867). Similarly, Naito T et al, determined that there was no correlation between gender and the final diagnosis of PUO (P-value: 0.916)

CONCLUSION

Bone marrow examination is an important procedure to identify etiological diagnosis in PUO. Our results identified a large number of cases of PUO with involvement of bone marrow which can serve as a diagnostic aid in further workup. We believe that implementing invasive procedures such as bone marrow

biopsy can help to find the underlying cause and prevent the delay in diagnosis of such patients. It can reduce the morbidity and definitely mortality of the patient and can facilitate in prompt management of disease.

Conflict of Interest *None*

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