Original article

The role of bone marrow biopsy in patients with pyrexia of unknown origin

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ABSTRACT

Background: Pyrexia of unknown origin (PUO) is a major complication which remains undiagnosed. Different diagnostic test were used to arrive at final investigation. Bone marrow biopsy (BMB) plays a vital role in diagnosis of PUO. The objective of current study was to determine the role of bone biopsy in diagnosing various types of causes of pyrexia of unknown origin.

Patients and methods: A prospective cross-sectional study was conducted from 1st September 2018 to 28th February 2019 at Department of Hematology, Combined Military Hospital Lahore, Pakistan. The data of 120 patients who were remained undiagnosed for at least 1 week were enrolled. Standard procedures were used to obtain the biopsy specimens and bone marrow aspiration was sent for microbiological examination. All the demographic information was kept on a structured self-designed proforma. Data was entered and analyzed using SPSS v.24.

Results: Out of 120 patients recruited in the study there were 67 (55.8%) were from age group 16 to 35 years, were males (65.8%) and 65.0% patients were suffering from fever for more than 3 days. The majority of the participants (30%) were diagnosed with infections, fever due to reactive changes (10.0%), acute leukemia (14.2%), lymphoma (11.7%), chronic leukemia (10.0%), aplastic anemia (4.2%), multiple myeloma (2.5%) and 11.7% patients were undiagnosed

Conclusion: In the diagnosis of pyrexia of unknown origin, morphological and histological investigation of bone marrow plays a vital role. However, if it is combined with other diagnostic modalities such as radiological, microbiological, and serological examinations, the efficiency of diagnosis can be improved.

Keywords:

Bone marrow culture (BMC), Pyrexia of unknown origin PUO, Blood culture (BC)

INTRODUCTION

Pyrexia of unknown cause (PUO) refers to an elevated body temperature of >38.3°C (100.9°F) that persists for more than 3 weeks and has no definite cause despite adequate investigation.[1] A series of investigations into PUO reveals signs of infection, autoimmune illness, cancer, and other potential causes.[2] The etiology of PUO varies greatly depending on age, gender, and geographic location.

When clinicians are unable to identify the reason of the fever despite using a variety of invasive and noninvasive diagnostic procedures, a bone marrow examination is recommended to determine the true cause of the pressure ulcer.[3] However, in a few cases, the etiology is unidentified, and a bone marrow study is ineffective in determining the cause.[4]

In patients with PUO, a bone marrow biopsy (BMB) can be used to diagnose HIV infection. [5] However, the effectiveness of BMB in diagnosing PUO in individuals with a healthy immune system is still limited. Bone marrow biopsy is considered a quick testing approach based on clinical decision for mycobacterial infections or hematologic malignancies. A bone marrow biopsy, in particular, revealed that the known cause of PUO is existence of lymphoma.[6]

Until a definitive diagnosis is made, treatment of PUO should be carefully considered. Few limitations were placed on the use of steroids and antibiotics because they mask the symptoms of the underlying disease. The purpose of this study was to see if bone marrow biopsy could be used to identify pyrexia of unknown origin. Therefore, the purpose of this study was to determine the role of bone marrow biopsy in diagnosing various causes of pyrexia of unknown origin.

Conflict of interest: The authors declared no conflict of interest exists.

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PATIENTS AND METHODS

A prospective cross sectional study was conducted from 1st September 2018 to 28th February 2019 at Department of Hematology, Combined Military Hospital Lahore, Pakistan; after approval of Ethical Review Board. The data of 120 patients aged above 15 years, fever >38.3°C (101°F) remained undiagnosed for at least 1 week of outpatient visits or as an inpatient were collected from pathology department and the internal medicine unit of the hospital Patients with nosocomial fever, HIV infection, or a history of hematologic malignancy were excluded from the research, as were those on steroids (>10 mg/day) or other immunosuppressants for at least 2 weeks, or those receiving treatment for a malignancy were also excluded from study. Sample size was calculated to be 120 based on the prevalence of most frequent finding total 120 patients were included and sample size was calculated by reactive changes in the histopathological analysis of pyrexia as 27.5% (reference) with 95% confidence interval, margin of error as 8% using the following formula: $n= (Z_{(1-\alpha/2)}^{*2}\ p(1-p))/d^{*2}$

A written Informed consent was taken from the participants. A Jamshidi needle was used to perform all biopsies at the posterior iliac crest. Biopsy pieces were decalcified in 3% nitric acid after being stored in formaline for 24 hours. Tissue processing, paraffin embedding and sectioning, staining with haematoxylin and eosin (H&E), and reticulin staining were all performed as usual. If necessary, special stains such as PAS and ZN were used and also according to specific stains were applied. The morphological details of all the bone marrow trephine sections were studied and analyzed. All the demographic information was kept on a structured self-designed proforma. Data was entered and analyzed using SPSS v.24. Quantitative variables were presented in the form of Mean±SD and for categorical variables frequency and percentages were used.

RESULTS

Out of 120 patients recruited in the study there were 67(55.8%) were from age group 16 to 35 years, 28.3% were in between 36 to 55 years of age and only 15.9% were above 56 years. Majority of the patients were males (65.8%) and females were 41 (34.2%). There were 16.7%, 46.6%, 26.7% and 10.0% patients underweight, normal, overweight and obese respectively. 24.2% patients were inpatient and 75.8% patients were from outpatient visits. 35.0% patients were suffering from fever for less than 3 days and 65.0% patients were suffering from fever for more than or equal to 3 days (Table 1).

Table 1: Demographic information of patients

Variables	Frequency	Percentage
Age		
16-35 years	67	55.8
36-55 years	34	28.3
56-75 years	19	15.9
Gender		
Male	79	65.8
Female	41	34.2
BMI		
Underweight	20	16.7
Normal	56	46.6
Overweight	32	26.7
Obese	12	10.0
Patient Status		
Inpatient	29	24.2
Outpatient	91	75.8
Duration of fever		
<3 days	42	35.0
≥3 days	78	65.0

Table 2: Diseases diagnosed on bone marrow biopsy of patients suffering from pyrexia

Causes	Frequency	Percentage
Infections	36	30.0
Marrow showing reactive changes	12	10.0
Granulomatous inflammation	7	5.7
Acute leukemia	17	14.2
Lymphoma	14	11.7
Chronic leukemia	12	10.0
Aplastic anemia	5	4.2
Multiple myeloma	3	2.5
Undiagnosed	14	11.7

Diagnosis based on bone marrow biopsy showed the distribution of different diseases. The majority of the participants i.e. 30% were diagnosed with infections, 12 (10.0%) were having fever due to reactive changes, 7 (5.7%) patients having granulomatous inflammation, 17 (14.2%) patients were diagnosed with acute leukemia, 14 (11.7%) patients were having lymphoma, 12 (10.0%) patients were having chronic leukemia, 5 (4.2%) patients were diagnosed with aplastic anemia, 3 (2.5%) patients were diagnosed with multiple myeloma while 14 (11.7%) patients were undiagnosed (Table 2). The figure depicted the distribution of diagnosed causes with respect to gender. There were 22 males and 14 females diagnosed with infections. With regard to marrow showing reactive changes there were 8 males and 4 females, while for granulomatous inflammation the majority of males were diagnosed and there was only 1 female. Patients diagnosed with acute leukemia were 12 males and 5 females. Majority of the males were diagnosed with lymphoma i.e. 10 and females were 4 in number. There were 7 males and 5 females diagnosed with chronic leukemia while for aplastic anemia there were 3 males

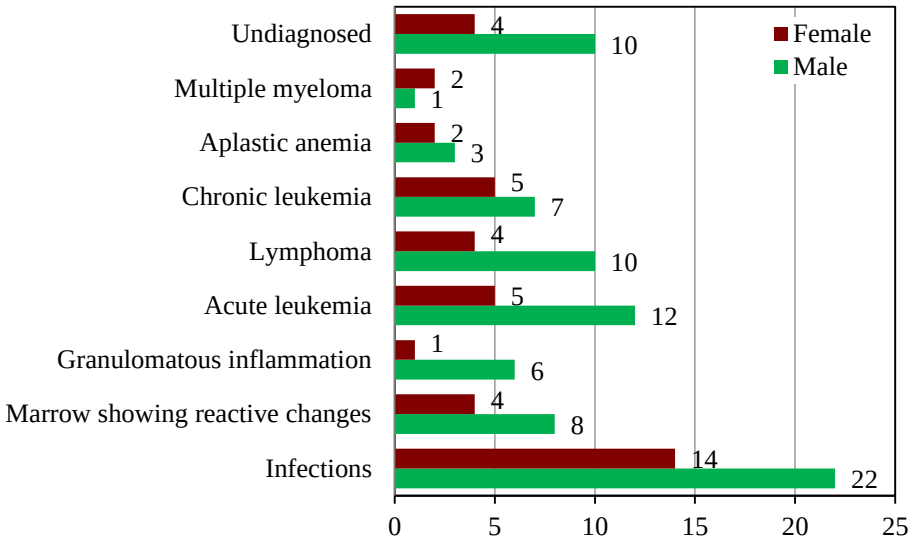

Figure 1: Distribution of diagnosed causes of pyrexia with respect to gender

and 2 female patients. Only 3 patients were diagnosed with multiple myeloma among those 1 was male patient and remaining were female patients. Overall 14 patients remained undiagnosed; majority of the male patients remained undiagnosed i.e. 10 and 4 patients were female (Figure 1).

DISCUSSIONS

Bone marrow biopsy plays a vital role in diagnosis of pyrexia of unknown origin (PUO). A series of investigations into PUO reveals signs of infection, autoimmune illness, cancer, and other potential causes.[2] The use of accurate diagnostic procedures for identifying PUO is becoming more common. The use of bone marrow biopsy is an important diagnostic tool for diagnosis of PUO. However different diagnostic approaches were used but the current study only utilizes the bone marrow biopsy. The objective of current study was to determine the role of bone marrow biopsy in diagnosing various types of causes of pyrexia of unknown origin. A bone marrow examination may be a very useful approach for diagnosing PUO.[8] The yield strength of BMB was described by Larson EB and colleagues for the diagnosis of pyrexia of uncertain origin.[9]

The results of current study revealed that the majority of the participants i.e. 30% were diagnosed with infections, 12 (10.0%) were having fever due to reactive changes, 7 (5.7%) patients having granulomatous inflammation, 17 (14.2%) patients were diagnosed with acute leukemia, 14 (11.7%) patients were having lymphoma, 12 (10.0%) patients were having chronic leukemia, 5 (4.2%) patients were diagnosed with aplastic anemia, 3 (2.5%) patients were diagnosed with multiple myeloma while 14 (11.7%) patients were undiagnosed.

A prospective study was conducted on 57 patients of pyrexia of unknown origin. 42% cases reported specific diagnosis in which megablastic anemia was more common followed by hypoplastic anemia, tuberculosis and malaria. The most common hematological malignancy was multiple myeloma.[10]

In a prospective multicentric analysis of 167 patients undertaken De Kleijn et al at the Netherlands' FUO study group, infection was the primary cause (26%), followed by neoplasm and non-infectious inflammatory illness (13% and 24%, respectively). Miscellaneous causes accounted for 5% of cases, and despite best efforts, 30% of cases remained misdiagnosed.[11]

Another study conducted on BMB found that 20 cases of hemophagocytic lymphohistiocytosis and 11 cases of hemophagocytosis in the early stages of life, with maximum patients being under 21 years of age.[12] A study was conducted on mycobacterium infection by conducting BMB. The results revealed that the patient's age ranged between 25-46 years with 73% leukopenia, 45% thrombocytopenia and pancytopenia. BMB shows significant results in mycobacterium tuberculosis infection.[13]

The results of a study conducted revealed that, four cases were diagnosed with tuberculosis, acid-fast

bacillus and granuloma in the bone marrow during the pathological examination.[14] During a bone marrow test for underlying fever in both immunocompromised and non-compromised patients, the malignancy was identified in two patients, mycobacterial infection and granuloma in 3 patients, according to another research.[15]

A study conducted by Zafar and colleagues on the bone marrow findings of PUO showed that there were 30 males and 10 females in current study. Chronic granulomatous inflammation, atypical mononuclear infiltrate, aplastic anaemia, hypocellular marrow, and visceral leishmaniasis were the most common histopathological findings in patients, followed by chronic granulomatous inflammation, atypical mononuclear infiltrate, aplastic anaemia, hypocellular marrow, and visceral leishmaniasis.[16]

In a previous research of the pathogenesis of PUO, 15.8% tuberculosis was found, with acid fast bacilli found in among all of them. The history of fast-acid bacilli infected patients can be explored using the results of bone marrow biopsy, which reveal that 25% of cases are infected with the organism, and these patients are diagnosed with tuberculosis.[17]

Despite the fact that the review of literature revealed that for the diagnosis of pyrexia of unknown origin there are limited number of data available for evaluating bone marrow cultures analysis., especially in immunocompetent patients, the review of literature also revealed that there are few researches were available which define the usefulness of bone marrow cultures for the diagnosis of PUO.[18]

CONCLUSION

In the diagnosis of pyrexia of unknown origin, morphological and histological investigation of bone marrow plays a vital role. Bone marrow examination leads to more useful and precise diagnosis, which helps in developing guidelines and recommendations to improve the patient's condition. In patients who have had a long-term fever for no apparent reason, a bone marrow biopsy and aspiration should be performed. However, if it is combined with other diagnostic modalities such as radiological, microbiological, and serological examinations, the efficiency of diagnosis can be improved.

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