

## **The diagnostic usefulness of bone marrow examination and bone marrow culture in patients with pyrexia of unknown origin**

### **Abstract**

#### **Introduction**

Bone marrow cultures (BMCs) are usually obtained in the diagnosis of pyrexia of unknown origin (PUO). In the effort to identify the cause of systemic infection, BMCs are often performed in addition with blood cultures (BCs) and cultures of other body fluids and tissues. The practice of performing BMC and Blood cultures is long-standing, but the medical importance is questionable. Given the importance of cost effectiveness, such practices must be assessed on the basis of their cost-benefit to patient outcomes. In this study we compared the value of BMC with BC and studied the usefulness of the histopathological features of bone marrow trephine biopsy specimens in detecting the cause of systemic infections in selected patient population with PUO.

**Objective:** To determine the usefulness of bone marrow culture for the diagnosis of different causes of pyrexia of unknown origin.

**Study Design:** Descriptive Cross-sectional study

**Place and Duration of Study:** This study was conducted at Peoples University of Medical and Health Sciences for Women Nawabshah Pakistan from June January 2020 to January 2021.

**Materials and Methods** A total 150 patients were included in this study who fulfilled the criteria of pyrexia of unknown origin. The bone marrow aspiration, biopsy, and

blood cultures specimens were obtained using standard techniques and bone marrow culture send for microbial analysis.

**Results:** 1.5% of patients had hematomas, one diagnosed with Behcet disease, other patients with acute leukemia. The bone marrow aspiration results exhibited that 23 patients (15.3%) diagnose with a hemophagocytic syndrome where 3 cases of infection, 3 cases with hematological malignant disorder, and 7 cases with hemophagocytosis, and repercussion of bone marrow aspiration diagnosed 5 acute leukemia and 2 with visceral leishmaniasis. The usefulness of BMB was determined through an odd ratio of few parameters including thrombocytopenia with odd ratio 4.59 and 95% CI (1.07-8.4), anemia odd ratio 3.17, and CI (1.09-12.92) were considered most associated factors for the usefulness of BMB. BMC in 13 (8.66%) patients out of 150 were found with bacterial growth and 2 (1.33%) cases with bacterial growth were observed in blood culture. There was no fungal and mycobacterial growth observed. In the BMC analysis 2 cases of *E. coli*, 3 cases with *Staphylococcus aureus*, 2 cases of *Enterococcus sps.* while 4 cases of *Salmonella typhi* and 2 cases of *Salmonella paratyphi-A* were diagnosed in blood culture analysis.

**Conclusion:** The obtained data indicate that blood culture did not divulge bacterial growth without the bone marrow culture. Therefore bone marrow culture was found to be an important diagnostic modality and correlation was found for thrombocytopenia and anemia. Bone marrow biopsy is deemed a useful method to diagnose pyrexia of unknown origin.

**Key Words:** Bone marrow culture (BMC), Pyrexia of unknown origin PUO, Blood culture (BC)

**Introduction**

Pyrexia of unknown origin (PUO) is defined as higher body temperature more than 38.3° C(100.9 F) that lasts for more than three weeks with no obvious source despite appropriate investigation<sup>1</sup>. The investigation of PUO undergoes through the series of investigations which consists of detection of infection, autoimmune disorder, malignancies and other miscellaneous causes.<sup>2</sup> A wide variation in the etiology of PUO is exist because of age, gender, and regional differences.

A variety of diagnostic methods are known in the medical field to evaluate the F/UO, still the cause of F/UO is obscure which leads to creating difficulty for F/UO guidelines related to treatment of the patients. There is no single golden method available to compare and evaluate the other diagnostic methods. Despite various invasive and non-invasive diagnostic modalities when the clinicians fail to identify the cause of fever then bone marrow examination is preferred to ascertain the actual reason of PUO.<sup>3</sup> But still the cause remain undiagnosed in few cases and bone marrow examination doesn't give an effective response<sup>4</sup>.

Bone marrow biopsy is useful to identify the immunodeficiency (HIV) infection in patients with PUO<sup>5</sup>. Research by Mourad et al claims that physicians' choice is a keen object to perform bone marrow biopsies. The histological findings of bone marrow biopsies constitute the most common diagnosis method of F/UO. Though, the effectiveness of BMB in patients with a strong immune system is not yet so useful to diagnose the PUO. For mycobacterial infection or hematological malignancies bone marrow biopsy is consider to be an expeditious testing method based on clinical decisions. Notably, bone marrow biopsy provided a clear clue of the occurrence of lymphoma, a well-known cause of pyrexia of unknown origin<sup>6</sup>.

The management of PUO should be considered very carefully until a final diagnosis has been established. Few restrictions were imposed regarding the recommendation of steroids and antibiotics as it masked the symptoms of actual disorder. The present study aims to determine the usefulness of bone marrow biopsy and its culture to diagnose the pyrexia of unknown origin.

**Objective:** To determine the usefulness of bone marrow culture for the diagnosis of different causes of pyrexia of unknown origin.

### **Materials and Methods**

It was a cross-sectional study carried out at Peoples University of Medical and Health Sciences for Women Nawabshah Pakistan from June January 2020 to January 2021. This study was conducted after taking approval of Ethical committee of institute. The data of 150 patients were collected from the internal medicine unit and pathological department of the hospital. 150 patients were selected who met the inclusion criteria (having PUO defined as having an illness with reported increase in body temperature from 38.3 degree centigrade at multiple times, which remains undiagnosed for at least 1 week of investigations) and were observed through the laboratory tests, bone marrow examination, and microbial analysis as a part of this study. Informed consent was taken from the patients who were included in the study. Patients who were diagnosed on 3<sup>rd</sup> day of reporting the illness were excluded from the study.

### **Microbial analysis**

The standard method was used to procure the bone marrow aspirates culture specimens, inoculated in culture medium for the bacterial, fungal, and acid-fast microorganism. Samples were inoculated at temperature 35°C for five days thereafter gram staining was performed to evaluate the organism. The subculture of the specimens on specific media depends upon the gram staining morphology. The culture for mycobacteria was inoculated on particular culture medium BACTEC (Becton, Dickinson Company), incubate at 37°C for 6 weeks and then growth was evaluated by using instrument. The same procedure was used for each patient to assess the diagnostic usefulness of bone marrow culture in identify the underlying cause of PUO<sup>7</sup>.

### **Statistical analysis**

The statistical calculations were performed using the SPSS version 23. Independent samples t-test was applied for the comparison between two categories first in which bone marrow biopsy was diagnostically useful and second in which it was not diagnostically useful. 95% confidence intervals and odd ration were also measured in the models. P-values of less than 0.05 considered to be significant.

### **Results .**

A total of 100 patients were included in this study who fulfilled the inclusion criteria.the age of patients ranges from 25 to 70 years.mean age of males was 58.6% and females was 41.15 in study population.

The obtained result of patients with pyrexia of unkown origin indicated a very low statistically P value of >0.05.

Among them 57% had infective etiology , followed by acute leukemia ,lymphoma and other disorder as described in Table 1.

Table 2 summarize that only 7 number of cases had positive bone marrow culture while 6 cases had positive of both blood and bone marrow culture and 44 cases showed no growth.

Bone marrow culture and blood culture showed 26.7% salmonellatyphi growth while 17.8% showed mycobacterial tuberculosis growth and only 3.5% showed psudomonas growth.

**Table:1. Summary of clinical diagnosis.**

DIAGNOSIS	NUMBER OF CASEs
Infections	57
Granulomatous disease	03
Acute leukemia	12
Lymphoma	11
Chronic leukemia	09
Aplastic anemia	01
Multiple myeloma	02
Metastatic disease	02
Total cases	100

**Table:2. Summary of Bone marrow and Blood culture Results.**

<b>Total no of cases</b>	<b>Bone marrow only</b>	<b>Blood culture only</b>	<b>Both</b>	<b>No growth</b>
<b>100</b>	<b>07</b>	<b>43</b>	<b>06</b>	<b>44</b>

**Table:3. Comparison of Bone marrow culture and Blood culture isolates results.**

<b>ISOLATES</b>	<b>BMC only</b>	<b>BC only</b>	<b>BMC+BC</b>	<b>Number of cases</b>	<b>Percentage (%)</b>
<i>Mycobetrium tuberculosis</i>	3	3	4	10	17.8%
<i>Salmonella typhi</i>	2	12	1	15	26.7%
<i>E.coli</i>	1	10	-	11	19.6%
<i>Staph.aureus</i>	1	5	1	7	12.5%
<i>Klebsella</i>	-	3	-	3	5.3%
<i>Psudomonas</i>	-	2	-	2	3.5%
<i>Actinobacter</i>	-	2	-	2	3.5%
<i>Enterobacter</i>	-	6	-	6	10.6%

## Discussions

The emerging trends in use of precise diagnostic techniques for diagnosing PUO is still insufficient to abolish the uncertainty of its causes with PUO. Therefore bone marrow examination deemed a may be very helpful method for diagnosis of PUO<sup>8</sup>. Larson EB and colleagues described yield strength of BMB for the diagnose of pyrexia of unknown origin.<sup>9</sup> Jha A reported that bone marrow biopsy revealed 19.25% cases of hematological malignancy, 54.55% cases of neoplasm, 18.97% cases of myeloma, and one case of thrombocytopenia as the diagnosis of patients suffering from PUO<sup>10</sup>.

De Kleijn et al demonstrated the usefulness of BMB in patients without hematological disorders<sup>11</sup>. Henter et al reported that bone marrow biopsy represented 11 cases of hemophagocytosis and 20 cases with onset of hemophagocytic lymphohistiocytosis at initial stages of life where 70% patients were less than 21 years of age.<sup>12</sup> Farhi DC and colleagues describe the role of The previous history of the bone marrow biopsy in mycobacterium infection.<sup>13</sup> Bodem CR and colleagues During the pathological assay 4 cases diagnosed tuberculosis along with granuloma in the bone marrow and acid-fast bacillus was detected in 3 cases.<sup>14</sup>

An investigation about bone marrow examination for underlying fever in both immunocompetent and non-competent patients indicated that malignancy was found in two cases, granuloma in three and mycobacterial infection in three patients.<sup>15</sup> To obtain a more precise response to identifying the causes of marrow granuloma patients would go through the second biopsy after the specific therapy. The prospective study of Bleeker-Rovers et al<sup>16</sup> failed to contribute in FUO diagnosis

through BMB. For diagnosis, they used fludeoxyglucose F 18 positron emission tomography (FDG-PET), one of the expensive methods used for investigating bone marrow involvement in malignant diseases, such as Hodgkin disease<sup>17</sup>. It can help understand the source and root cause of FUO. Many other studies observed that the levels of eosinophils in bone marrow increased in case of normal morphology while peripheral blood did not show any eosinophilia. The reason might be a delay present between the eosinophil formations and transport from marrow to blood. Eosinophilia has an association with various helminthic infections, drugs, allergic diseases, and endocrine disease<sup>18</sup>. However, in this study, no other issue was identified.

An earlier literature study about the etiology of PUO reports tuberculosis in 15.8% cases with the detection of acid fast bacilli in all cases. The history of fast-acid bacilli infected patients could be elucidated with outcomes of bone marrow biopsy that provide the information of 25% cases identified with organism and such patients diagnose tuberculosis<sup>19</sup>.

Another finding of this study was the long term follow up a response of patients to corticosteroids use, it did not show any positive impact and none of the effects was noticed through the bone marrow examination. For example, if we obtained any confirmation data after the bone marrow examination when a patient taking steroids. Then we should add the other studies as evidence in support of this point. Although, the literature review confirmed that there was confined data on bone marrow culture evaluation for the diagnosis of Pyrexia of unknown origin especially in immunocompetent patients<sup>20</sup>.

As we have concluded the non-efficacious bone marrow culture outcomes with a very useful diagnostic yield.

**Conclusion:** The evaluation of bone marrow examination provides a frequent and accurate diagnosis which helps to construct the guideline and recommendation for improvement of the patient's condition. The bone marrow biopsy and aspiration should be conducted in patients with a long duration of fever without any apparent reason. Physicians should have awareness about the history of patients with periodic fever. A significant correlation existed in hematologic finding and the output of bone marrow examination.

#### COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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