Original Article

Diagnostic Utility of Bone Marrow Biopsy/ Bone Marrow Culture in Pyrexia of Unknown Origin: A Ten-Year Retrospective Analysis

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ABSTRACT

OBJECTIVE: This study was carried out to assess the diagnostic utility of Bone Marrow Biopsy and Bone Marrow Culture in patients with PUO.

METHODOLOGY: This retrospective cross-sectional study was conducted at Fauji Foundation Hospital, Rawalpindi. The clinical, laboratory and radiological records from January 2012 - December 2021 were retrieved from our hospital management information system for this study. Data from 63 patients with PUO were analyzed according to Petersdorf criteria.

RESULTS: Out of 63 patients with PUO, BMB was diagnostic in 25 (39.68%) patients. The leading cause of PUO was infectious disorders (mycobacterium tuberculosis, visceral leishmaniasis, malaria), followed by inflammatory disorders and hematological malignancies. In 38 (60.31%) patients, BMB could not detect any underlying pathology. BMC showed growth in only 03(4.76%) patients, and the diagnostic yield of BMC was meagre.

CONCLUSION: BMB is essential in establishing a diagnosis in patients with PUO. Infectious diseases are the leading cause of PUO, and BMC should not be included as a routine investigation in the initial evaluation of a patient with PUO.

KEYWORDS: Pyrexia, Bone marrow biopsy, Bone Marrow Culture, PUO, Bone Marrow Aspirate, Mycobacterium Tuberculosis

INTRODUCTION

Pyrexia of unknown origin (PUO) remains a diagnostic challenge even in this era of advanced diagnostic technology[1]. A prolonged fever of 38.3C or higher for a minimum period of 3 weeks is unexplained after all the preliminary diagnostic investigations are called PUO. The definition has been revised with some additional changes; however, a revised minimum testing criterion is required.[1] The approach to a patient with PUO has been evolving with time[1]. It is estimated that patients with PUO make up about 03% of the total hospital admissions. In a study done, 2.9% of hospitalized patients had PUO[2].

The diagnosis of PUO is based on extensive laboratory testing that puts a very high financial burden on already strained healthcare systems. The complexity of interpreting the tests increases in case of multiple tests[2].

Clinicians still struggle to reach a conclusive diagnosis in patients with PUO despite many tests, from imaging studies to serology[3]. There is a lot of unnecessary and invasive testing in patients with PUO to reach a final diagnosis; sometimes, these laboratory tests can be misleading[3].

Clinicians should be well aware of the diagnostic test's utility and interpretation. One of the tests being advised in patients with PUO is Bone marrow biopsy (BMB); as it is an invasive procedure, it should be carefully thought out and planned[4].

BMB most commonly diagnoses diseases in patients with PUO, including infection, inflammation and neoplasia. BMC can also assist in showing any underlying bacterial, viral and fungal infections[5]. Literature on the yield of BMB and Bone marrow cultures (BMC) is limited, and there is a lack of local data on the outcome of BMB/BMC[16]. It is estimated that half of the patients with PUO are undiagnosed despite all the current advances in diagnostic tests[6-9].

Pakistan is a resource-poor country with a significant burden on the healthcare sector; most of the population belongs to lower social strata, so recommending diagnostic tests with a lower utility can put a financial toll on the patient. Unnecessary tests with low yields should be avoided. This study was carried out to assess the diagnostic utility of BMB and BMC in PUO.

METHODOLOGY

This retrospective cross-sectional study was conducted at the Department of Pathology, Fauji Foundation Hospital, Rawalpindi / Foundation University Islamabad, Pakistan. We retrospectively analyzed data of 63 patients who fit the criteria for PUO according to Petersdorf[10] and underwent BMB and BMC as part of the diagnostic workup between January 2012 - December 2021. The ethical committee of Fauji Foundation Hospital approved this study in November 2021 (Ref No. 587/RC/FFH/RWP).

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We retrieved the records through our hospital management information system (Medix) for the clinical, laboratory and radiological patients. All these patients had undergone a preliminary minimal diagnostic workup deemed mandatory for the diagnosis of PUO.

Inclusion Criteria

1. Age 18-70
2. Fever ≥38.0□ for ≥14 days
3. No diagnosis after 01 week of investigations
4. Inpatients only

Exclusion Criteria

1. Age < 18 years
2. Outpatients
3. Patients who had underlying diseases such as immunodeficiency and known malignancies

For a complete blood count (CBC), 3ml was drawn and done on the hematology analyzer Sysmex XE 2100. Peripheral smears were stained with Leishman stain. BMB was done from the posterior superior iliac crest under aseptic techniques. Local anaesthesia (Lidocaine) was given at the site before the procedure. 0.5 ml of blood was drawn for bone marrow aspirate (BMA) and BMC. Bone marrow trephine biopsy was done using disposable trephine needles, while bone marrow aspirate was done using disposable spinal needles. BMA slides were stained with Leishman stain, while bone marrow histopathology slides were stained with H&E after fixation into 10% formalin and decalcification process. In cases where there is suspicion of tuberculosis Zeihl -Neelsen (ZN), a stain was also performed.

BMC was obtained from all patients regardless of their symptoms. All three cultures were received, i.e. bacterial, mycobacterial, and fungal cultures. BMC specimens were inoculated in the standard anaerobic bottle and placed on the Organon Teknika BacT/ ALERT system for 05 days at 35°C. The specimen bottle was removed when growth was identified. Then gram stain was done and subcultured on the appropriate media after observing morphology on the gram stain, gram-positive cocci were subcultured on blood agar, and gram-negative cocci and rods were subcultured on MacConkey agar.

BACTEC 13 A bottle (after vaccination) held for six weeks at a temperature of 37 C was used for mycobacteria BMC. BACTEC 460 was used to evaluate the specimen's growth, and if it yielded, a growth acid-fast stain was performed.

Trypticase soy blood agar and chocolate agar plate were used for bacterial culture of BM specimens. Blood-brain heart infusion agar plate was used for fungal culture. The BMB specimen was fixed in formalin solution, decalcified, processed and finally embedded in paraffin. Sections of 3 to 4 urns were made for bone marrow trephine specimens, and H&E was used to stain it. The biopsy specimens were stained for fungi and acid-fast bacilli using the Gomori methenamine silver and ZN stains.

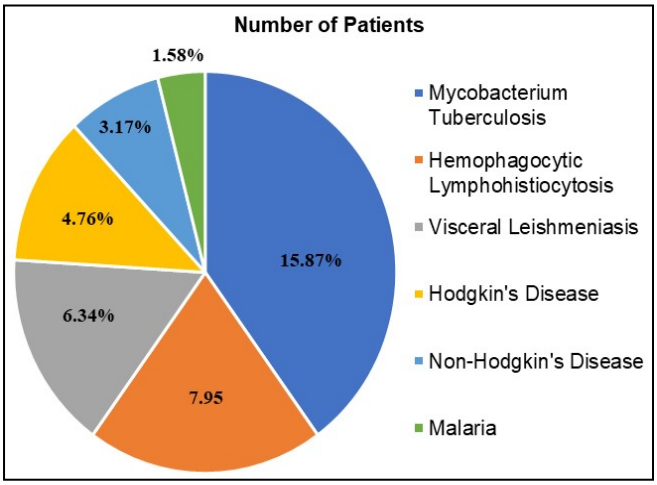
Mean±SD were reported for quantitative variables, and frequency and percentages were given for categorical variables, i.e. gender, BMB and BMC diagnosis. Statistical analyses were performed using SPSS version 25.0.

RESULTS

During the ten years study period, 2,710 BMB were performed from January 2012-December 2021. Eighty -one patients underwent BMB and BMC for PUO. Sixty-three patients were selected after applying the inclusion and exclusion criteria. Of these 63 patients, 41(65%) were females, and 22 (35%) were male. The mean age of the patients was 41, with an SD of ±5 years

Out of these 63 patients, three underwent biopsy twice, as the biopsy was inconclusive after the first bone marrow, and the patients' fever persisted. The outcome of BMB in patients with PUO is shown (**Figure I**).

Figure I: Yield of bone marrow biopsy in patients with pyrexia of unknown origin



In 25 (39.68%) patients, BMB was found to be an underlying cause of the patient's fever.

For most patients with PUO, the underlying cause was an infectious disorder, including mycobacterium tuberculosis, visceral leishmaniasis, secondary hemophagocytic lymphohistiocytosis, and malaria. In 38 (60.31%) patients, BMB could not detect any underlying pathology.

BMC showed growth in only 03 (4.76%) patients. The diagnostic yield of BMC was found to be very low. The culture of mycobacterium tuberculosis failed; similarly, there was no fungal growth. The results of BMC are shown in (**Table I**).

Table I: Yield of bone marrow culture

Yield of Bone Marrow Culture	Number/Percentage of Patients
Salmonella Typhi	01(1.58%)
Enterococcus Coli	01(1.58%)

DISCUSSION

BMB is done as part of the workup for PUO[11]. At the same time, BMC can be done to rule out underlying bacterial, fungal or tuberculous infection[11].

In this study, only 25 (39%) patients had a diagnostic BMB, while in 38(60.31%) patients, BMB could not detect any underlying pathology. BMC showed growth in only 03 (4.76%) patients, and the diagnostic yield of BMC was meagre. Our study was in agreement with previous national and international studies.

Hot A et al.[5] reported a 23% diagnostic yield of BMB in patients with PUO. The primary diagnoses were malignant hematological diseases followed by tuberculosis, visceral leishmaniasis, systemic macrocytosis and disseminated granulomatosis[5]; our study agreed with this study but primarily showed infectious diseases as the leading cause of PUO. BMC had no conclusive yield in this study and did not assist in identifying the cause of fever[5]. The diagnostic result of BMB in a study by Hong FS et al.[12] was 13.7%. The authors suggested that blood and other tests could have led to these diagnoses without BMB[12]. This study showed a limited diagnostic role compared to ours, likely because of the smaller sample size and comparatively younger age groups. In a study by Gupta R et al., [13] BMB was diagnostic in 76% of patients with PUO. The higher yield compared to our study was most likely due to the larger sample size of that study. A study done by Bharuthram N 2019[6] agreed with our research with a BMB diagnostic yield of 23.5% of patients[6]. Quseda AE et al.[7] study was based on patients with HIV AIDS having PUO; in this study, 31.6% of patients showed granulomas. The yield of BMC was 21%, which was higher than our study as this study comprised only immunocompromised patients.

In a study by Ahmad S 2003[8] on immunocompromised patients, the cause of fever was detected in only 08 (16%) patients. Our study showed a higher percentage of patients. The difference from our study was most probably the smaller sample size. Arya A 2017[9] study had a similar yield as our study with a diagnostic yield of 17% on BMB, whereas BMC was found to be sterile in all (100 %) patients and was non-contributory[9]. The authors emphasized that BMC should only be justifiable when blood culture doesn't reveal growth. The diagnostic yield of BMC in immunocompetent patients in the Mourad O 2003[14] study was approximately 0% - 2% compared to ours. The authors do not recommend BMC as a routine test for diagnosing PUO. The authors suggest that the decision to do BMB should be made at the physician's discretion and should vary from patient to patient. BMB in Ben-Brauch et al.[15] study was diagnostic in 26.7% of patients, which agreed with our study. The BMB revealed mostly malignant diseases, i.e. non-Hodgkin lymphoma, myeloproliferative disorder, acute leukaemia, multiple myeloma, myelodysplastic syndrome, solid tumors, hemophagocytic lymphohistiocytosis and granulomatous disease[15]. The authors recommended BMB as an ancillary procedure for establishing a diagnosis of PUO. In a Memon WR et al. study, [16] BMC showed bacterial growth in 8.6 % of patients, but no fungal or mycobacterial growth was observed. In the BMC analysis, 2 cases of Enterococcus coli, 3 cases of Staphylococcus aureus and 2 cases of Enterococcus species were detected[16], similar to our study. A study by Oliver SAC et al.[17] included primarily immunocompromised patients; only one patient showed growth of methicillin-resistant Staphylococcus Aureus on BMC, while two patients showed growth of staphylococcus epidermidis. This study concluded that BMC has a meagre yield and is not justifiable as a first-line procedure in patients with PUO and should be done only when BC and initial investigations do not give any significant clue. Hot A et al.[5] also showed a minimal value of BMC in the workup of PUO in immunocompetent patients.

In a single centre retrospective study by Sharvit G et al., [18] 03 out of 105 patients showed a conclusive yield on BMC, i.e. Mycobacterium avium and a microbiologically unclassifiable fungal infection in one patient. This study showed only limited value of BMC in immunocompetent patients.

BMC is still being taken for diagnosing patients with PUO, but the limited diagnostic yield is questionable. The cost-benefit analysis should be kept in mind with the consumption of available resources, the test's clinical utility, and the turn-around time for reporting[16].

We conclude BMB is a crucial tool in reaching a diagnosis in patients with PUO. However, as it is an invasive procedure, a careful analysis of patients' clinical data and predictive factors should be done to decide whether a patient needs a BMB/BMC with the possibility of finding any underlying diagnosis. Indiscriminate use of BMB as a routine diagnostic tool for PUO should be discouraged.

Our study has filled the gaps in the existing knowledge and added additional value. Our results showed infectious disorders as the leading cause of PUO, and this finding would undoubtedly assist clinicians in investigating and managing patients with PUO. The current study would catalyze building the foundation of future studies to explore infective disorders as the foremost cause of PUO. Our study suggests blood culture and other preliminary investigations should be interpreted in light of the patient's clinical condition before proceeding for BMC as it is an invasive procedure with a meagre yield. As a culture of MTB failed in our study, it is suggested that clinicians should not rely on BMC to diagnose MTB. By reducing the number of BMCs, the cost and hospital resources can be cut down. Our study recommends that BMB be carried out only when other non-invasive tests do not reveal a conclusive diagnosis to reduce unnecessary BMBs.

The limitation of this study was its retrospective study

design, single-centre analysis and relatively limited sample size. A larger prospective study design with regular follow-up of the patients is warranted.

CONCLUSION

A high frequency of infectious diseases was detected in BMB patients with PUO. BMC should not be included as a routine investigation in the initial evaluation of a patient with PUO because of its low yield. BMB contributes towards establishing a diagnosis in patients with PUO.

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AUTHOR CONTRIBUTIONS

Khaliq S: Design, study concept and manuscript writing
Ali H: Data collection and data analysis, Editing

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