E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.02.623

Research Article

Diagnostic Utility of Bone Marrow Examination in Pyrexia of Unknown Origin: A Prospective Study from a Tertiary Care Centre

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Received: 11.09.25, Revised: 05.10.25, Accepted: 15.11.25

ABSTRACT

Background: Pyrexia of unknown origin (PUO) remains a significant diagnostic challenge in clinical practice due to its diverse aetiologies and nonspecific clinical presentation[1–3]. Bone marrow examination should be considered early in the diagnostic algorithm of PUO. Despite advances in imaging and laboratory investigations, a considerable proportion of cases remain undiagnosed after initial evaluation. Bone marrow examination is a minimally invasive diagnostic procedure that can provide valuable insights into infectious, haematological, and inflammatory causes of PUO, particularly in resource-limited settings[4–6].

Objective: To evaluate the diagnostic utility of bone marrow aspiration and trephine biopsy in patients presenting with PUO.

Methods: This prospective observational study was conducted on 80 patients presenting with PUO at a tertiary care centre. All patients underwent bone marrow aspiration and trephine biopsy under aseptic precautions. Smears were stained with Leishman stain, and biopsy sections were stained with Hematoxylin and Eosin (H&E). Special stains, including Ziehl–Neelsen (ZN) and Periodic acid–Schiff (PAS), were applied where indicated[13–15]. Clinical and laboratory data were recorded, and results were analyzed using descriptive statistical methods.

Results: Bone marrow examination established a definitive diagnosis in 62% (50/80) of cases. Infectious etiologies were the most common, accounting for 40% of cases, with granulomatous inflammation observed in 25% and tuberculosis confirmed by acid-fast bacilli positivity in 15% of cases[6,16]. Non-infectious causes included haematological malignancies (12.5%) and hemophagocytic lymphohistiocytosis (10%)[21–23]. The predominance of infectious causes was statistically significant ($p < 0.05$). A considerable proportion of cases (37.5%) remained inconclusive.

Conclusion: Bone marrow examination is a safe, cost-effective, and highly valuable diagnostic modality in the evaluation of PUO. It offers a high diagnostic yield, particularly in detecting infectious and haematological causes[17,18]. Early utilisation can significantly reduce diagnostic delay and improve clinical outcomes, especially in developing countries where infectious diseases are prevalent[5–7].

Keywords: Pyrexia of unknown origin, Bone marrow examination, Tuberculosis, Granulomatous inflammation, Hemophagocytic lymphohistiocytosis, Diagnostic yield.

INTRODUCTION

Pyrexia of unknown origin (PUO) is a commonly encountered clinical condition that poses significant diagnostic difficulty. It is classically defined as fever exceeding 38.3°C lasting for more than three weeks without a diagnosis after appropriate initial evaluation[1,2]. Despite advancements in diagnostic technologies, establishing the exact aetiology remains challenging in a subset of patients[3].

The causes of PUO are diverse and include infections, malignancies, autoimmune disorders, and miscellaneous conditions[4]. The distribution of these causes varies across geographical regions. In developed countries, malignancies and autoimmune conditions are more common, whereas in developing countries like India, infectious diseases—particularly tuberculosis—remain the predominant cause[5–7].

Disseminated tuberculosis often presents with nonspecific clinical features, making diagnosis difficult[6]. Haematological malignancies such as leukaemia and lymphoma may also present with prolonged fever without obvious clinical findings[8].

The evaluation of PUO requires a systematic approach including detailed history, clinical examination, laboratory investigations, imaging, and invasive procedures where

necessary[9]. However, even after extensive workup, some cases remain undiagnosed.

Bone marrow examination is a valuable diagnostic tool that provides direct insight into the hematopoietic and reticuloendothelial systems. It is minimally invasive, cost-effective, and particularly useful in detecting infections, malignancies, and inflammatory conditions not evident on routine evaluation[10–12].

This study was conducted to assess the diagnostic utility of bone marrow examination in patients presenting with PUO.

MATERIAL AND METHODS

This prospective observational study included 80 patients with PUO who underwent bone marrow aspiration and trephine biopsy under aseptic conditions at the Department of Pathology, Dr. KNS Memorial Institute of Medical Sciences, from December 2023 to December 2024. Sample size was determined based on feasibility during the study period.

Inclusion criteria included patients with fever >38.3°C for more than three weeks and no diagnosis after initial evaluation[13]. Patients with known infections, malignancies, or those already receiving treatment were excluded.

After obtaining informed consent, detailed clinical and laboratory data were recorded. Bone marrow aspiration and biopsy were performed from the posterior superior iliac spine using a Jamshidi needle[14].

Smears were stained with Leishman stain, while biopsy sections were stained with H&E. Special stains including Ziehl-Neelsen (ZN) and Periodic acid–Schiff (PAS) were used where indicated[15].

Data were analysed using descriptive statistical methods. Diagnostic yield was calculated, and a p-value <0.05 was considered statistically significant.

The study was approved by the Institutional Ethics Committee (IEC), and all procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

RESULTS

Bone marrow examination contributed significantly to diagnosis, with an overall diagnostic yield of 62%. Infectious aetiologies accounted for 40% of cases, including granulomatous inflammation in 25% (Figure 2) and tuberculosis confirmed by acid-fast bacilli in 15% (Figure 1). Non-infectious causes comprised 22.5% of cases, including haematological malignancies (12.5%) (Figure 3) and hemophagocytic lymphohistiocytosis (10%) (Figure 4). The predominance of infectious causes was statistically significant ($p < 0.05$). A total of 37.5% of cases remained inconclusive.

Table 1. Distribution Of Bone Marrow Findings In PUO

Diagnosis	Cases (n=80)	Percentage
Granulomatous inflammation	20	25.0%
Tuberculosis (AFB positive)	12	15.0%
Haematological malignancy	10	12.5%
Hemophagocytosis (HLH)	8	10.0%
Inconclusive	30	37.5%

Statistics: Data were analyzed using SPSS software (version 25.0; IBM Corp). Categorical variables were expressed as frequencies and percentages. The Chi-square test was applied to assess statistical significance. A p-value <0.05 was considered statistically significant.

DISCUSSION

Pyrexia of unknown origin continues to pose a diagnostic challenge due to its heterogeneous aetiologies and nonspecific clinical presentation. In this study, bone marrow examination demonstrated a diagnostic yield of 62%, which is comparable to previous studies reporting yields between 50–70%[17,18].The diagnostic yield of 62% in the present study is comparable to studies by Chandra et al. (60%) and Jain et al. (65%), reinforcing the utility of bone marrow examination in PUO.

Granulomatous inflammation was the most frequently observed finding, consistent with studies conducted in regions where tuberculosis is endemic[6,19]. Bone marrow granulomas may be seen in various conditions; however, tuberculosis remains the most likely cause in developing countries.

AFB positivity confirmed tuberculosis in 15% of cases(Figure 1).Bone marrow examination is particularly useful in diagnosing extrapulmonary tuberculosis, which often presents with vague clinical features[20].

Haematological malignancies accounted for 12.5% of cases(Figure 3). Bone marrow examination plays a critical role in diagnosing

these conditions and facilitates early initiation of therapy[21,22].

Hemophagocytosis was observed in 10% of cases (Figure 4). HLH is a severe condition that is often underdiagnosed due to nonspecific presentation. Bone marrow examination is essential for its diagnosis[23–25].

Geographical variation significantly influences the aetiology of PUO, with infections predominating in developing countries and malignancies more common in developed regions[7,8].

The findings of this study highlight the importance of early bone marrow evaluation in PUO, particularly in tuberculosis-endemic regions

CONCLUSION

Bone marrow examination is a valuable, safe, and cost-effective diagnostic modality that should be considered early in the evaluation of PUO.

Its high diagnostic yield, particularly in identifying infectious and hematological causes, makes it indispensable in resource-limited settings.

Histomorphological Images Figure 1: Bone marrow smear stained with Ziehl–Neelsen stain showing acid-fast bacilli (AFB) as slender red rods against a blue background (oil immersion, 1000×), consistent with tuberculosis.

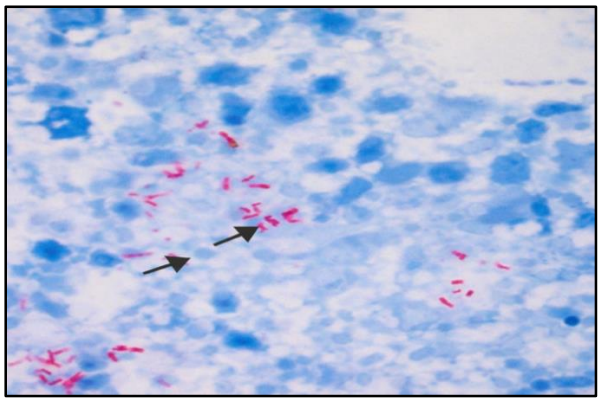


Figure 2. Bone Marrow Aspirate Showing Well-Formed Epithelioid Granuloma with Surrounding Hematopoietic Cells (Leishman Stain, 40x).

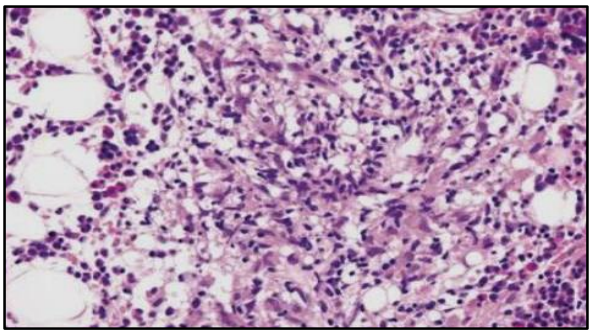


Figure 3. Bone Marrow Aspirate Showing Numerous Blast Cells With High Nuclear-Cytoplasmic Ratio Suggestive Of Acute Leukaemia (Leishman Stain, 40x).

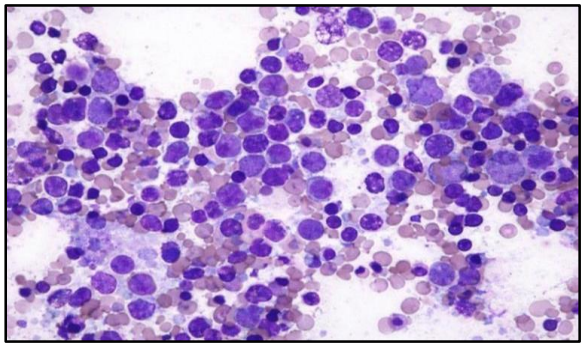
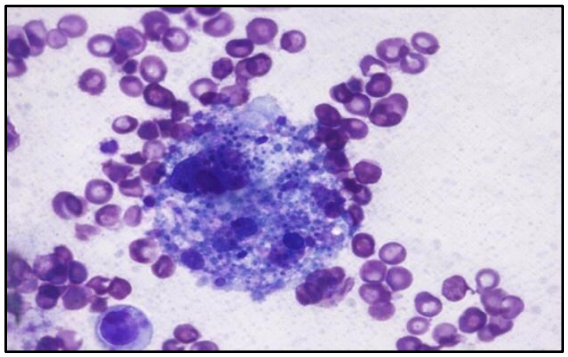


Figure 4. Bone Marrow Macrophage Demonstrating Hemophagocytosis with Engulfed Hematopoietic Cells, Consistent With HLH (Leishman Stain, 40x).



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