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**Original Research Article**

# Bone Marrow Findings in Pyrexia of Unknown Origin: A Retrospective Study

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**Abstract**

**Background:** Pyrexia of unknown origin (PUO) remains a challenging clinical entity despite advances in diagnostic modalities. Bone marrow examination is often employed when routine investigations fail to identify the cause, particularly in the presence of hematological abnormalities. This study aimed to evaluate bone marrow findings and their diagnostic contribution in patients with PUO.

**Material and Methods:** A retrospective observational study was conducted in a tertiary care hospital over a three-year period. A total of 92 patients fulfilling standard diagnostic criteria for PUO and who underwent bone marrow examination were included. Demographic details, clinical features, hematological parameters, and bone marrow findings were retrieved from medical records. Bone marrow aspiration with or without trephine biopsy was analyzed, and findings were categorized into infectious, malignant, non-malignant, reactive, and non-specific patterns.

**Results:** The study population showed a male predominance, with most patients presenting in early to middle adulthood. Fever of 7–12 weeks' duration was the most common presentation, frequently accompanied by systemic features such as weight loss, hepatosplenomegaly, and lymphadenopathy. Hematological abnormalities were common, with anemia being the predominant finding, followed by thrombocytopenia, leukocyte count abnormalities, pancytopenia, and bicytopenia. Bone marrow examination revealed infectious etiologies as the most frequent diagnostic category (37.0%), followed by hematological malignancies (22.8%) and reactive marrow changes (20.7%). Granulomatous inflammation suggestive of tuberculosis was the most common infectious finding, while acute leukemia constituted the leading malignant diagnosis. Overall, bone marrow examination established a definitive diagnosis in 59.8% of cases, provided suggestive findings in 30.4%, and was non-contributory in 9.8%.

**Conclusion:** Bone marrow examination plays a significant role in the evaluation of PUO, particularly in patients with associated hematological abnormalities, by enabling identification of infectious and malignant causes and guiding further clinical management.

**Keywords:** Pyrexia of unknown origin; Bone marrow examination; Granulomatous inflammation; Hematological malignancy; Pancytopenia.

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## Introduction

Pyrexia of unknown origin (PUO) remains a persistent diagnostic challenge despite advances in laboratory and imaging techniques. Traditionally defined as a fever exceeding 38.3 °C on several occasions for more than three weeks without an established diagnosis after appropriate evaluation, PUO encompasses a broad spectrum of infective, inflammatory, and neoplastic conditions [1]. Fever of prolonged duration often necessitates a meticulous and systematic workup, yet the underlying cause remains elusive in a significant proportion of patients [2]. Bone marrow examination, incorporating aspiration and trephine biopsy, has been recognized as a valuable investigative modality in patients with PUO, especially when initial non-invasive investigations fail to reveal a diagnosis. It offers the potential to detect hematological malignancies, granulomatous infections such as tuberculosis, hemophagocytic syndromes, and other marrow-infiltrative processes that might not be apparent on peripheral evaluation [3-5]. In particular, bone marrow assessment is considered when patients present with associated hematological abnormalities (e.g., cytopenias) or

clinical features suggestive of reticuloendothelial system involvement, such as hepatosplenomegaly or lymphadenopathy [6].

The diagnostic yield of bone marrow examination in PUO varies across studies, reflecting differences in study populations, prevalence of underlying diseases, and methodological approaches. Some reports suggest that bone marrow evaluation establishes a specific diagnosis in a substantial fraction of cases, while others highlight limitations, especially in immunocompetent cohorts without hematological clues [3]. Nevertheless, incorporating bone marrow assessment into the diagnostic algorithm for PUO can facilitate early identification of critical underlying pathologies, leading to timely and targeted management.

## Material and Methods

**Study Design and Setting:** A retrospective observational study was conducted at a tertiary care teaching hospital in India. The study involved a review of bone marrow examinations performed in patients evaluated for PUO. The institution serves as a referral center, catering to both urban and rural populations, thereby providing a heterogeneous patient cohort.

**Study Population and Sample Size:** All patients who fulfilled the diagnostic criteria for PUO and subsequently underwent bone marrow examination as part of their diagnostic workup were considered eligible for inclusion. PUO was defined as documented fever ≥38.3°C on several occasions, persisting for more than three weeks, with no established diagnosis after appropriate initial evaluation.

During the study period**,** 96 consecutive patients meeting these criteria underwent bone marrow evaluation. After exclusion of incomplete records, 92 cases were included in the final analysis. The sample size was determined by the total number of eligible cases available during the study duration, consistent with the retrospective design.

**Inclusion and Exclusion Criteria:** Inclusion criteria comprised patients of all age groups and both sexes diagnosed with PUO, in whom bone marrow aspiration with or without trephine biopsy had been performed. Exclusion criteria included patients with a previously confirmed cause of fever prior to bone marrow examination, cases with inadequate or poorly preserved bone marrow samples, and records lacking essential clinical or laboratory details required for analysis.

**Data Collection:** Relevant data were retrieved from laboratory registers, pathology reports, and hospital medical records. Extracted variables included demographic details (age and sex), duration of fever, associated clinical features, baseline hematological parameters, and bone marrow findings. No patient identifiers were recorded, and confidentiality was strictly maintained.

**Bone Marrow Examination:** Bone marrow aspiration was performed from the posterior superior iliac spine under aseptic precautions. In selected cases, a trephine biopsy was obtained concurrently to enhance diagnostic yield. Aspirate smears were routinely stained with May–Grünwald–Giemsa stain. Special stains such as Ziehl–Neelsen, Periodic Acid–Schiff, and reticulin stain were applied where indicated, based on cytomorphological suspicion.

Bone marrow findings were categorized into infectious, hematological malignancy–related, non-malignant hematological disorders, reactive changes, and normal or nonspecific marrow patterns. A final interpretation was made by experienced pathologists, integrating cytological and histological features.

**Statistical Analysis:** Data were entered into a spreadsheet and analyzed using standard statistical software. Continuous variables were summarized as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. The diagnostic contribution of bone marrow examination in establishing a specific etiology of PUO was assessed descriptively. No inferential statistical testing was planned, as the primary objective was to evaluate patterns and diagnostic yield.

## Results

The demographic and clinical profile of the study population is summarized in Table 1. Patients represented a wide age range with a male predominance, and most presented with fever of intermediate duration. Systemic manifestations such as weight loss, hepatosplenomegaly, and lymphadenopathy were frequently observed, indicating multisystem involvement in a considerable proportion of cases.

Baseline hematological abnormalities were common, as detailed in Table 2. Anemia emerged as the most prevalent finding, while varying degrees of leukocyte and platelet count derangements were also observed. Notably, a significant subset of patients demonstrated pancytopenia or bicytopenia, reinforcing the rationale for bone marrow evaluation in the diagnostic workup of PUO.

The spectrum of bone marrow findings is outlined in Table 3. Infectious conditions constituted the largest diagnostic category, followed by hematological malignancies and reactive marrow changes. A smaller proportion of cases showed

non-malignant hematological disorders or non-specific marrow findings. The distribution highlights the heterogeneity of underlying etiologies encountered in PUO.

Among infectious causes identified on bone marrow examination (Table 4), granulomatous inflammation suggestive of tuberculosis predominated. Hemophagocytic lymphohistiocytosis and parasitic infestations such as leishmaniasis were also notable contributors, while fungal infections accounted for a smaller share. These findings underscore the relevance of marrow examination in detecting infections that may evade routine diagnostic modalities. The range of hematological malignancies diagnosed is presented in Table 5. Acute leukemias formed the most frequent malignant category, followed by myelodysplastic syndromes and lymphomas with marrow involvement. Less commonly, plasma cell dyscrasias and chronic leukemias were identified, reflecting the diverse neoplastic conditions that may manifest primarily with prolonged fever.

The overall diagnostic contribution of bone marrow examination is depicted in Table 6. In a majority of patients, marrow evaluation led to the establishment of a definitive diagnosis, while in others it provided suggestive but non-specific findings that guided further investigations. A limited proportion of cases yielded no contributory information, emphasizing both the strengths and limitations of bone marrow examination in the evaluation of PUO.

**Table 1: Demographic and Clinical Characteristics of Study Population (n = 92)**

| Variable | Frequency / Mean ± SD |
|---|---|
| **Age (years)** | 38.6 ± 17.4 |
| **Age group (years)** | |
| ≤20 | 14 (15.2%) |
| 21–40 | 32 (34.8%) |
| 41–60 | 28 (30.4%) |
| >60 | 18 (19.6%) |
| **Sex** | |
| Male | 54 (58.7%) |
| Female | 38 (41.3%) |
| **Duration of fever (weeks)** | |
| 3–6 | 29 (31.5%) |
| 7–12 | 41 (44.6%) |
| >12 | 22 (23.9%) |
| **Associated symptoms** | |
| Weight loss | 39 (42.4%) |
| Hepatosplenomegaly | 27 (29.3%) |
| Lymphadenopathy | 18 (19.6%) |

**Table 2: Hematological Profile of Patients with PUO (n = 92)**

| Parameter | Mean ± SD | Abnormal cases n (%) |
|---|---|---|
| Hemoglobin (g/dL) | 9.8 ± 2.1 | 68 (73.9%) |
| Total leukocyte count ($\times 10^3/\mu L$) | 7.6 ± 3.9 | 31 (33.7%) |
| Platelet count ($\times 10^3/\mu L$) | 168 ± 74 | 36 (39.1%) |
| Pancytopenia | — | 24 (26.1%) |
| Bicytopenia | — | 19 (20.7%) |

**Table 3: Bone Marrow Findings in PUO Patients (n = 92)**

| Bone marrow diagnosis | Number (%) |
|---|---|
| Infectious etiology | 34 (37.0%) |
| Hematological malignancy | 21 (22.8%) |
| Reactive marrow changes | 19 (20.7%) |
| Non-malignant hematological disorders | 9 (9.8%) |
| Normal / non-specific findings | 9 (9.8%) |
| **Total** | **92 (100%)** |

**Table 4: Spectrum of Infectious Etiologies Detected on Bone Marrow Examination (n = 34)**

| Infectious diagnosis | Number (%) |
|---|---|
| Granulomatous inflammation (suggestive of tuberculosis) | 18 (52.9%) |
| Hemophagocytic lymphohistiocytosis | 7 (20.6%) |
| Leishmaniasis | 5 (14.7%) |
| Fungal infections | 4 (11.8%) |
| **Total** | **34 (100%)** |

**Table 5: Hematological Malignancies Identified on Bone Marrow Examination (n = 21)**

| Malignancy | Number (%) |
|---|---|
| Acute leukemia | 8 (38.1%) |
| Myelodysplastic syndrome | 5 (23.8%) |
| Lymphoma with marrow involvement | 4 (19.0%) |
| Multiple myeloma | 3 (14.3%) |
| Chronic leukemia | 1 (4.8%) |
| **Total** | **21 (100%)** |

**Table 6: Diagnostic Yield of Bone Marrow Examination in PUO (n = 92)**

| Outcome | Number (%) |
|---|---|
| Definitive diagnosis established | 55 (59.8%) |
| Suggestive but non-specific findings | 28 (30.4%) |
| No contributory findings | 9 (9.8%) |

## Discussion

In the present retrospective study, bone marrow examination demonstrated utility in elucidating the underlying etiologies of PUO, consistent with findings from previous clinical investigations. Prior research has shown that bone marrow evaluation can contribute to establishing specific diagnoses in a subset of patients with prolonged fever, particularly when hematological abnormalities are present [7]. In a large cohort of non-immunocompromised patients with prolonged febrile illness, bone marrow biopsy contributed to diagnosis in nearly one-quarter of cases, with hematological malignancies and granulomatous processes identified among the principal causes. Thrombocytopenia and anemia were noted as significant predictors of a diagnostic bone marrow specimen in this context, underscoring the importance of associated hematologic features in guiding its use [8].

The role of bone marrow examination extends to detecting infectious causes that may be difficult to diagnose by peripheral investigations alone. Studies have highlighted that marrow evaluation can reveal mycobacterial and other infective infiltrates, particularly in populations where tuberculosis and leishmaniasis are endemic. Although the absolute yield for infectious diagnoses may vary with regional disease prevalence and patient characteristics, marrow examination often complements other microbiological and imaging modalities in comprehensive PUO workups [9].

Furthermore, comparative studies that included both aspiration and trephine biopsy have demonstrated that trephine biopsy significantly enhances diagnostic yield over aspiration alone, especially in identifying granulomatous inflammation, fungal infections, and infiltrative hematologic disorders [10]. Despite its utility, bone marrow culture has shown limited incremental value in routine PUO evaluation among immunocompetent patients. Evidence suggests that routine marrow cultures rarely yield additional diagnostic information beyond histopathological examination, particularly after prior negative blood and body fluid cultures. This observation indicates that culture techniques should be selectively applied rather than used indiscriminately in all PUO cases [11,12]. Moreover, prospective studies from tertiary care settings support the integration of bone marrow examination with other targeted investigations, such as imaging and serological tests, to enhance overall diagnostic accuracy [13,14].

The findings from the current study align with existing literature in affirming that bone marrow examination, particularly with trephine biopsy, holds clinical value in specific PUO populations. Identification of hematological malignancies, granulomatous infections, and hemophagocytic phenomena through marrow analysis can critically influence patient management. The decision to perform bone marrow evaluation should be individualized, taking into account clinical presentation, hematological abnormalities, and the likelihood of marrow-infiltrative pathology, to optimize diagnostic yield and resource utilization.

## Conclusion

Bone marrow examination is a useful and informative investigation in patients with PUO,

providing a definitive diagnosis in a substantial proportion of cases. Infectious etiologies, particularly granulomatous lesions, were the most frequently identified causes, followed by hematological malignancies, emphasizing the role of bone marrow evaluation in detecting both infective and neoplastic disorders underlying prolonged fever. Even when findings were non-specific, bone marrow assessment contributed to clinical decision-making by narrowing diagnostic possibilities, supporting its inclusion as a valuable tool in the diagnostic workup of PUO when routine evaluations fail to establish a cause.

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