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Original Research

Clinico-hematological Portrait of Bone Marrow Infections: Unusual Visitors Unveiled

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Abstract

Background: Bone marrow examination is a crucial diagnostic tool for both hematological and non-hematological disorders, ranging from benign to malignant ones. It is a relatively simple and easy procedure for evaluating pyrexia of unknown origin, as it often leads to an etiological diagnosis. The study aims to evaluate the clinico-hematological profile in various infections infiltrating bone marrow and study the spectrum of morphologic alterations in bone marrow aspirate in various infections.

Methodology: This retrospective observational study was conducted at a tertiary care center in Bihar, India, over a 4.5-year period (June 2019–December 2023). All patients referred to the haematology section for bone marrow aspiration and/or biopsy based on strong clinical and morphological suspicion of infection were included. Cases with inadequate marrow samples or lacking corroborative infection evidence were excluded.

Results: The study included a total of 52casesdemonstratingthe presence of bone marrow infections. Out of 52 cases, bone marrow aspirations were done in all cases, whereas bone marrow biopsy was done in 23(44.2%) cases only. There were 39 (75%) cases of adults and 13 (25%) of children; and the mean age of presentation was 35.3 years (range, 1-72 years).

On clinical examination, anemia was the most common symptom (82.6%), followed by splenomegaly (78.8%). On bone marrow examination, an increase in plasma cells was the most striking finding, accounting for 67.3% (n=35), followed by erythroid hyperplasia and an increased number of macrophages showing features of hemophagocytosis in 50% and 32.6% of cases, respectively. A total of 41 cases showed the presence of Leishmania Donovani (LD) bodies. Granulomas were seen in 09 cases (17.3%), out of which 05(9.6%) cases showed AFB positivity.

Conclusion: Bone marrow examination plays a pivotal role in diagnosing various infectious diseases, particularly in patients presenting with pyrexia of unknown origin, cytopenias, or unexplained hematological abnormalities. Morphological analysis, along with specialized staining techniques, allows the identification of a broad spectrum of infectious agents, spanning from parasites and bacteria to fungi.

Keywords: Bone Marrow; Infections; Granuloma; Hemophagocytosis; Pyrexia of Unknown Origin; Cytopenia.

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Introduction:

Bone marrow examination (BME) is a crucial diagnostic tool for both hematological and non-hematological disorders, covering benign and malignant etiologies. [1] It is a relatively simple and safe procedure, especially valuable in evaluating pyrexia of unknown origin, as it often leads to an etiological diagnosis. Persistent anemia unresponsive to therapy and other peripheral cytopenias are the most common indications for BME, sometimes revealing infections that were not clinically suspected.[2]

Bone marrow infections may be evaluated by conducting both morphological and etiological assessments. Morphologically, different infectious agents may produce similar lesions, while a single pathogen can cause a diverse set of marrow changes. Routine stains like Leishman and Giemsa help indetecting viral inclusions, parasites (Leishmania, Toxoplasma, Microfilaria), and fungi (Histoplasma, Cryptococcus), whereas special stains such as Ziehl-Neelsen (ZN) and periodic acid-Schiff (PAS) assist in identifying Mycobacterium and certain fungi.[3] The literature focusing on the diagnostic utility of BME in infections is sparse and mostly remains underexplored. Therefore, a retrospective study was conducted to assess the role of BME alongside clinico-hematological analysis, aiming to establish its diagnostic value.

Bone marrow examination in infections may directly identify pathogens or reveal reactive changes indicative of infection. However, such changes are sometimes nonspecific and may overlap with malignancies or autoimmune disorders. [4,5] This study focuses on the clinico-hematological profile and infection-related bone marrow changes. To the best of our knowledge, there is a lack of available literature regarding the pattern and distribution of various bone marrow infections in Bihar. Recognizing these reactive patterns can raise suspicion of infection, prompting further microbiological evaluation or additional diagnostic tests. The study aims to highlight the spectrum of morphological features in bone marrow aspirates that should alert pathologists to a possible infectious etiology. This study aimed to evaluate the clinico-hematological profile in various infections infiltrating the bone marrow and to study the spectrum of morphologic alterations in bone marrow aspirate in various infections.

Methodology

It was a retrospective 4.5-year observational study conducted at a tertiary care center in Bihar, India, from June 2019 to Dec 2023 (4.5 years). All those patients referred to the Hematology section for bone marrow aspiration and biopsy with strong clinical and morphological suspicion of infections were included in the study. Clinical features that were considered were pyrexia of unknown origin, acute or chronic febrile illness not responding to antipyretics or antibiotics, fever with chills, pallor, and any organomegaly. Those who had no symptoms of fever, pallor, or organomegaly were excluded from the study. All cases where bone marrow aspiration/biopsy were inadequate for opinion and in which there was no supporting evidence of infections were excluded. Ethical clearance was taken from the Institute's ethical committee(1366/IEC/IGIMS/2024).

Sample collection and parameter estimation:

Archival records and slides over a period of 4.5 years of bone marrow aspiration and biopsy were evaluated. Clinical details, biochemical profile, complete hemogram with peripheral blood smears, bone marrow aspiration smears, and bone marrow biopsy slides (wherever available) were reviewed, and data were analyzed. Findings of the Complete blood count from the Sysmex XN-1000 fully automated hematology analyzer were recorded. Peripheral blood smears and bone marrow aspiration smears were stained by Leishman stain, whereas bone marrow biopsy slides were stained by Hematoxylin and Eosin stain. In addition, wherever indicated, Ziehl-Neelsen stain (ZN stain) was also used on bone marrow aspirate smears.

Statistical analysis:

The percentage was calculated from categorical variables. Mean and standard deviation (SD)

were calculated from numerical values. The software used for data analysis was SPSS version 22.

Results:

The study included a total of 52 cases demonstrating the presence of bone marrow infections. Out of 52 cases, bone marrow aspirations were done in all cases, whereas bone marrow biopsy was done in 23(44.2%) cases only.

There were 39 (75%) cases of adults and 13 (25%) of children; and the mean age of presentation was 35.3 years (range, 1-72 years) [Table 1]. The male: female ratio was 2.4:1.

Table 1: showing age-wise distribution of cases.

Age range (in years)	Number of cases (%)
<10 years	05(9.6)
10-20	08(15.3)
21-30	10(19.2)
31-40	16(30.7)
41-50	05(9.6)
51-60	03(5.7)
61-70	02(3.8)
71-80	02(3.8)
>80 years	01(1.9)

The clinical presentation of the cases varied from fever (moderate to high grade) and abdominal pain to non-specific symptoms like generalized weakness and weight loss. Fever was the commonest symptom and was seen in84.6% of the cases (n=44), followed by generalized weakness in 32.6% of cases (n=17) [Table 2].

Table 2: The range of clinical presentations of bone marrow infections.

Clinical presentation	Number of cases	Percentage
Fever	44	84.6
Abdominal pain	18	34.6
Vomiting/diarrhoea	08	15.3

Bleeding manifestations	04	7.69
Generalized weakness	17	32.6
Cough/breathlessness	11	21.1
Weight loss	10	19.2

On clinical examination, anemia was the most common symptom (82.6%), followed by splenomegaly (78.8%). Other significant findings were hepatomegaly, lymphadenopathy, effusion(ascitic/pleural/pericardial), and pallor. The rK39 antigen for leishmaniasis was positive in 78.6% of the cases (n=41), followed by microfilaria antigen in 9.6% (n =005) [Table 3].

Table 3: showing clinical findings and various antigen assays in cases presenting bone marrow infections.

Clinical findings	**Number of cases**	**Percentage**
Splenomegaly	41	78.8
Hepatomegaly	23	44.2
Lymphadenopathy	08	15.3
Effusion (pleural/ pericardial/peritoneal)	06	11.5
Pallor	43	82.6
Antigen assays		
Malarial parasite antigen	02	3.8
Microfilaria antigen	05	9.6
HIV antigen +	04	7.6
rK39	41	78.8
Histoplasma	01	1.9

On peripheral smear examination, anemia was the most common finding seen in 96.1% of the cases (n=50), followed by 67.3 % of cases of pancytopenia (n=35). The most common type of anemia was the microcytic hypochromic type. Other findings were leucopenia, thrombocytopenia, and rouleaux formation. Common hematological findings are summarized in [Table 4].

Table4: Showing hematological findings in various bone marrow infections noted on peripheral blood smear.

Common hematological findings	Number of cases	Percentage
Pancytopenia	35	67.3
Anemia	50	96.1
Leukopenia	31	59.6
Thrombocytopenia	28	53.8
Rouleaux formation	07	13.4
Neutrophilia	05	9.6
Eosinophilia	04	7.6
Lymphocytosis	03	5.7

On bone marrow examination, an increase in plasma cells was the most striking finding, accounting for 67.3% (n=35), followed by erythroid hyperplasia and increased reticuloendothelial activity showing features of hemophagocytosis in 50% and 32.6%of cases, respectively. A total of 41 cases showed the presence of Leishmania Donovani (LD) bodies. Granulomas were seen in 09 cases (17.3%), out of which 05(9.6%) cases showed AFB positivity [Table 5; Figure 1a-1f].

Table 5: showing the spectrum of bone marrow findings in various bone marrow infections.

Bone marrow findings	Number of cases (Percentage)
Erythroid hyperplasia	26(50)
Plasmacytosis	35(67.3)
Increased hemophagocytic activity	17(32.6)
Increased eosinophils and its precursors	09(17.3)
Lymphocytosis	04(7.6)
Presence of LD bodies	41(78.8)
Presence of granuloma AFB positive AFB negative	09(17.3) 05(9.6) 04(7.6)
Presence of Histoplasma	01(1.9)
Malarial parasite	02(3.8)
Presence of Microfilaria	05(9.6)

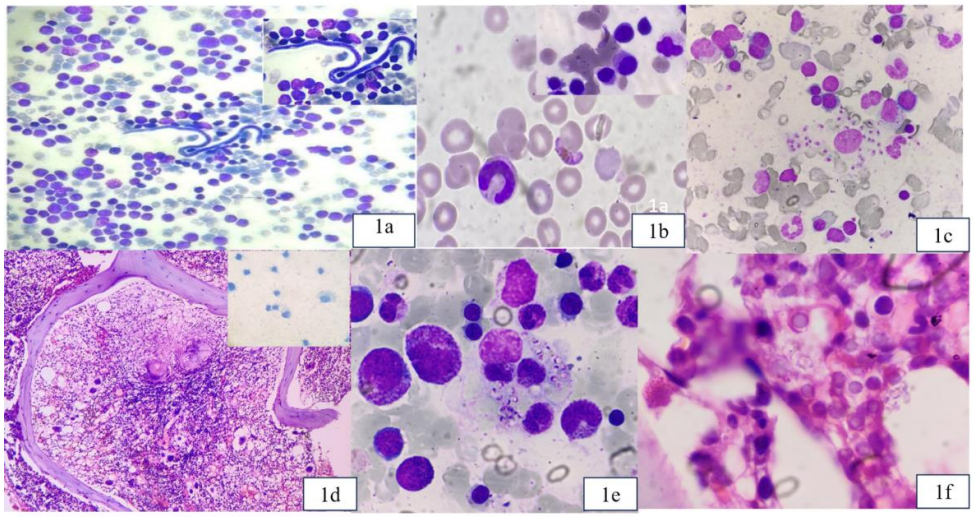

Fig 1a: Microphotograph showing presence of microfilaria in a bone marrow aspirate(Leishman stain; 40X). The inset shows the same under an oil immersion lens.

Fig 1b: Microphotograph showing the presence of a gametocyte of Plasmodium falciparum (Leishman stain; 40X). The inset shows the same under an oil immersion lens.

Fig 1c: Microphotograph showing the presence of LD bodies in a bone marrow aspirate (Leishman stain;100X)

Fig 1d: Microphotograph showing the presence of well-formed granuloma (H&E stain; 40X). The inset shows AFB-positive bacilli (ZN stain; oil immersion lens)

Fig. 1e: Microphotograph of bone marrow aspirate showing Histoplasma capsulatum (Leishman stain;1000X)

Fig 1f: Microphotograph of bone marrow biopsy showing the presence of Histoplasma capsulatum (H &E;100X)

Discussion:

Bone marrow examination (BME) is an essential diagnostic tool in evaluating patients with pyrexia of unknown origin (PUO) and pancytopenia.[6] Given its ability to provide direct evidence of infections or associated reactive changes, it serves as a valuable investigative modality, particularly when peripheral blood findings are inconclusive. Although various infections manifest with distinct morphological changes in the bone marrow, comprehensive studies evaluating the full spectrum of infectious agents affecting the marrow remain limited.

Findings in Parasitic Infections

A study conducted by Dhingra KK et al. on visceral leishmaniasis (kala-azar) highlighted several significant bone marrow changes.[7] These included hypercellularity, increased lymphocytes and plasma cells, marrow granulomas, hemophagocytosis, myelodysplasia, and gelatinous transformation. Such findings should alert pathologists to search for *Leishmania donovani* (LD) bodies, especially in patients from non-endemic areas within tropical regions. Early detection is crucial, as visceral leishmaniasis, if

left untreated, can lead to severe complications, including secondary infections and multi-organ failure.[8]

Similarly, a retrospective analysis by Shaikh MS et al. at Aga Khan University Hospital (AKUH) in Karachi, Pakistan, reviewed 35 parasite-positive bone marrow specimens. The study found a median patient age of 22 years (range: 1-75), with 60% (n=21) being male. The most frequently detected parasites were *Plasmodium falciparum* (22 cases) and *Plasmodium vivax* (12 cases), with one case of mixed infection. The predominant parasitic stages identified were gametocytes and trophozoites, observed in both peripheral blood and bone marrow smears.[9] In our study as well, gametocytes were the most frequently encountered stage in bone marrow aspirates seen in two cases, presenting with a high parasite density. These findings underscore the importance of BME in malaria diagnosis, particularly in cases of severe or complicated malaria where peripheral smears may show low parasitemia.

A study by Daneshbod Y et al. on bone marrow findings in kala-azar further corroborated these observations.[10] The most common findings included granulomas, intracellular and free LD bodies, plasma cells with or without inclusions, eosinophilia, free-floating cytoplasmic bodies, granular bodies, and erythroid hyperplasia. These diverse morphological alterations highlight the varied impact of *Leishmania* infection on the bone marrow microenvironment. [10-13] In our study, LD was seen in 78.8% of cases, highlighting the endemicity of this parasite in our region.

Bone Marrow Changes in HIV and Opportunistic Infections

Infections in immuno-compromised patients, such as those with HIV, present unique challenges. A study by Kumar et al. (2020) investigated 16 diagnosed HIV cases where BME was performed.[14] Opportunistic infections were identified in two cases: one with tuberculosis and another with LD bodies.The remaining HIV-positive cases exhibited reactive changes, including plasmacytosis and histiocytic prominence. These findings suggest that bone marrow alterations in HIV patients are not always infection-specific but may indicate immune dysregulation. Besides *Leishmania*, marrow plasmacytosis can be associated with bacterial, viral, and autoimmune conditions.

Filariasis and Its Bone Marrow Manifestations

Filariasis, a neglected tropical disease affecting over 120 million people globally, is often overlooked in bone marrow studies.[15] In endemic areas, peripheral blood eosinophilia serves as a useful but non-specific screening marker. In our study, five cases (9.6%) demonstrated microfilariae in bone marrow aspirates. A study by Aggarwal et al. also reported two cases of filariasis associated with mild eosinophilia.[16] These findings emphasize the need for heightened awareness of filarial infections, particularly in endemic regions, as their diagnosis can significantly impact patient management and treatment strategies.

Tuberculosis and Other Bacterial Infections

Tuberculosis remains a major infectious cause of PUO worldwide. 45% of PUO cases diagnosed through BME were due to tuberculosis. Gupta et al. reported that the key bone marrow findings in tuberculosis arethe presence of granulomas, giant cells, necrosis, and the presence of acid-fast bacilli (AFB) using Ziehl-Neelsen (ZN) staining. Such features strongly suggest tuberculosis, even in cases where peripheral blood or radiological investigations fail to confirm the diagnosis. In our study, granuloma was seen in 17.3% cases with 9.6% AFB positivity. [17-19]

Fungal Infections in Immunosuppressed Patients

Fungal infections are another important consideration, particularly in immunosuppressed individuals. In our study, one case of *Histoplasma capsulatum* infection was identified in a renal transplant recipient. Previous studies estimate the prevalence of fungal infections in bone marrow specimens to be around

7%.[18] Given the rising incidence of opportunistic fungal infections, especially in patients receiving immunosuppressive therapy, bone marrow examination can serve as a crucial diagnostic adjunct. We had only one case of Histoplasma capsulatum in a renal transplant patient who was immunocompromised.

Importance of Bone Marrow Trephine Biopsy

While bone marrow aspirations provide cytological details, trephine biopsy offers additional insights into marrow architecture, cellularity, and distribution. This is particularly useful in detecting focal lesions such as granulomas, lymphoid aggregates, or metastatic deposits. In cases where aspiration yields inconclusive results, trephine biopsy can help establish a definitive diagnosis.[19]

Conclusion

Bone marrow examination plays a pivotal role in diagnosing various infectious diseases, particularly in patients presenting with pyrexia of unknown origin, cytopenias, or unexplained hematological abnormalities. Morphological analysis, along with specialized staining techniques, enables the identification of a wide range of infectious agents, encompassing from parasites bacteria to fungi. Additionally, bone marrow findings can provide indirect evidence of systemic infections, guiding further diagnostic investigations. Given its diagnostic utility, BME should be considered an essential tool in the comprehensive evaluation of hematological and infectious diseases.

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