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Original Article

Effectiveness of Bone Marrow Biopsy for the Diagnosis of Pyrexia of Unknown Cause.

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Abstract

Background: Diagnosis of fever of unidentified cause remains challenging despite the availability of modern diagnostic techniques. Pyrexia of Unknown Origin (PUO) may result from various etiologies, among which infectious diseases are largely responsible. Many diagnostic approaches are currently applied. A detailed history with a complete general physical examination followed by baseline investigations with other specific tests like imaging, microbiological tests, and biopsies is employed to diagnose PUO. This study was designed for the evaluation and effectiveness of bone marrow biopsy in the identification of PUO and highlighted the existing spectrum of diseases involved in PUO.

Methodology: This Cross-sectional study was conducted at Dow University of Health Sciences, Karachi from 2015 to 2018 evaluated the records of patients who had bone marrow aspiration and biopsy Patients included in this study had a history of fever due to an Unfamiliar cause and met the Peters Dorf and Beeson criteria for PUO, i.e. fever for more than 3 weeks before diagnosis. Informed consent was taken from all patients.

Results: We analyzed the medical histories of 67 patients (48 males and 19 females) who were recommended bone marrow biopsy and aspiration for the assessment of PUO. The mean age was 38 years. The most common clinical symptoms found in patients of PUO were fever, hepato-splenomegaly followed by abdominal pain and weight loss. Anemia was the most common hematological parameter found in this study. The most frequent diagnosis in biopsies of PUO patients was Non-Hodgkins Lymphoma in about 25% of patients.

Conclusion: Certain laboratory and clinical parameters can detect major hematological diseases like malignancies when bone marrow biopsy is used for the workup of pyrexia of unknown origin. Bone marrow biopsy should be regarded as a constitutive part of the workup and diagnosis of pyrexia of unknown origin in conjunction with clinical findings.

Keywords

Pyrexia of Unknown Origin, Bone Marrow Biopsy, Bone Marrow Aspirate.

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Introduction

Various medical conditions are not necessarily related to each other but share the common symptom of long-standing fever unexplained after baseline tests. These conditions fall under the umbrella term of "Pyrexia of unknown origin." With advancements in diagnostic methods, treatment modalities and medical technology, the presentation of PUO and physicians' approach for its management is evolving continuously. With time and changing demographics, the epidemiology of conditions causing PUO also continues to change. Despite the presence of modern diagnostic techniques, diagnosis of PUO is still a difficult challenge[1]. PUO was mainly characterized through the well-known Peters Dorf and Beeson, who defined it as a body temperature of more than 38ºC for a duration longer than three weeks before diagnosis[2]. Durack and Street revised the original definitions of PUO in 1991[3]. PUO is further categorized into HIV-associated PUO, nosocomial PUO and neutropenia PUO[4]. Fever of unknown origin is associated with a diverse spectrum of diseases[5,6] such as malignancy, infections, inflammatory diseases and other miscellaneous etiologies[7]. It has been shown in many studies that infections such as abscesses, endocarditis, tuberculosis, UTIs and others are frequently associated with PUO[8]. It has been reported in a study that bone marrow biopsy and culture and blood culture give better diagnostic outcomes in mycobacterial, fungal and HIV diseases[8].

Bacterial, fungal and parasitic infections are the major causes of PUO[9]. Among bacteria, organisms that cause osteomyelitis, endocarditis and abscesses are easy to culture, whereas intracellular organisms like Rickettsia can be diagnosed serologically. Typhoid fever, tuberculosis and brucellosis, although difficult to culture, can be cultured[9]. Malaria and Visceral leishmaniasis are known parasitic causes of PUO[9]. Pulmonary and disseminated fungal infections are also known to cause PUO [9].

Many diagnostic approaches published in studies for PUO show etiological variation, but no study illustrates the definite cause of PUO[10,11]. It is difficult for many patients to bear the cost of multiple tests; therefore, bone marrow biopsy can be a subsequent modality for the rapid and early diagnosis of PUO, as bone marrow demonstrates multiple changes resulting from infectious and systemic diseases and can easily be detected by morphology. A comprehensive history with a complete physical examination followed by baseline investigations with other specific tests such as imaging, microbiological tests and biopsies is the protocol followed in the diagnosis of PUO[10, 12]. Our study investigated the contribution of bone marrow aspiration and biopsy to identify PUO and highlighted the existing spectrum of diseases involved in PUO.

Methodology

It is the Cross-sectional study in which we analyzed the records of sixty-seven patients who underwent bone marrow aspiration and biopsy from 1st January 2015 to 31st December 2018 at the DUHS. The ethical review board of Dow University of Health Sciences approved this study (Reference no. IRB-1293/DUHS/Approval/2019). Patients recruited in this study had a history of PUO. Patients had to meet the Peters Dorf and Beeson criteria of PUO, i.e. fever of greater than 3 weeks interval before diagnosis. Bone marrow biopsy and aspiration was done for the assessment of PUO. Patients with leucopenia and those who underwent transplantation were excluded from this study.

Routine analysis of peripheral blood smear was done along with bone marrow aspiration and biopsy. Standard methods and number of techniques were followed during the procedure bone marrow aspiration and biopsy. Bone marrow biopsy samples were taken from the posterior iliac crest under local anesthesia. Smears of bone marrow aspirate and biopsy were stained with Giemsa and H&E (Haematoxylin and Eosin). Bone marrow biopsy specimens were decalcified by HCL and formic acid 9%, which is then fixed in 10% formalin. For further studies, bone marrow smears were additionally stained with Leishman, Myeloperoxidase and Periodic Acid Schiff stain (PAS). Zeihl Nelson (Z.N.) stain was also done in

suspected tuberculosis cases. As it was a cross-sectional study, data were assembled, and the results were analyzed. All demographic details were noted. A detailed analysis of medical history, physical examination and Haematological features was conducted. Data were analyzed on SPSS version 22.0.

Results

We analyzed the medical histories of 67 patients who were suggested for bone marrow biopsy and aspiration to assess PUO. All patients fulfilled the Peters Dorf and Beeson criteria for PUO. There were 48 (71%) males and 19 (29%) females in this study, with a mean age of 38.

Clinical Attributes

Nearly 95% of patients recruited in this study had a history of fever from 24 to 64 days with a mean of 45.33 weeks, followed by abdominal pain in 18%, weight loss in 33% of cases.

Hematological Parameters

About 28 patients had microcytic and hypochromic anemia with a lower hematocrit, MCV and MCHC. WBC counts in these patients were between 0.06 x 10^9/L to 22.4 x 10^9/L, whereas platelet counts ranged from 5.74 x 10^9/L to 256 x 10^9/L. Anemia was seen in 54% of cases. In 22% of patients on the blood film, Pancytopenia was noticed, followed by depression in one and two cell lines in 36% and 27% of cases, respectively. All clinical sign and symptoms were shown in table 1.

Table 1: Clinical attributes of patients

Clinical Signs and Symptoms	n(%)
Fever	64(95)
Abdominal pain	12(18)
Weight loss	22(33)
Dyspnoea	3(4.5)
Cough	6(9)
Epistaxis	6(9)
Jaundice	3(4.5)
Hepato-spleenomegaly	14(21)
Lymphadenopathy	2(3)
Anaemia	36(54)
Leucopoenia	24(36)
Leucocytosis	4(6)
Thrombocytopenia	18(27)
Pancytopenia	15(22)

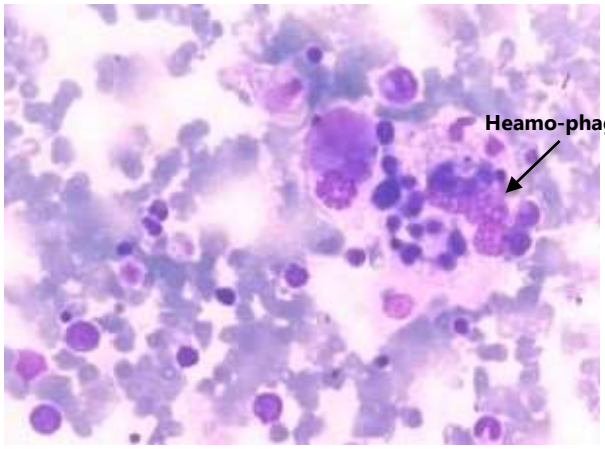

Figure 1: Bone marrow aspiration smear (Leishman stain x100) shows hemophagocytosis within macrophages.

Bone marrow aspiration findings

On examination of bone marrow aspiration of these cases of PUO, hypercellular, hypocellular and acellular marrow pattern were evaluated in 28, 7 and 3 patients, respectively. Hyperplasia of erythroid precursors was seen in 14 patients, followed by myeloid precursors in 13 patients. Reactive plasmacytosis and an increase in histiocytes were observed in 26 cases (38.9%) on bone marrow aspiration. Moreover, eosinophilic precursors, hemophagocytosis and pseud-Gaucher cells were the additional findings on bone marrow aspiration. Amastogote form of Leishmania Donovan was seen in one case shown in figure 1.

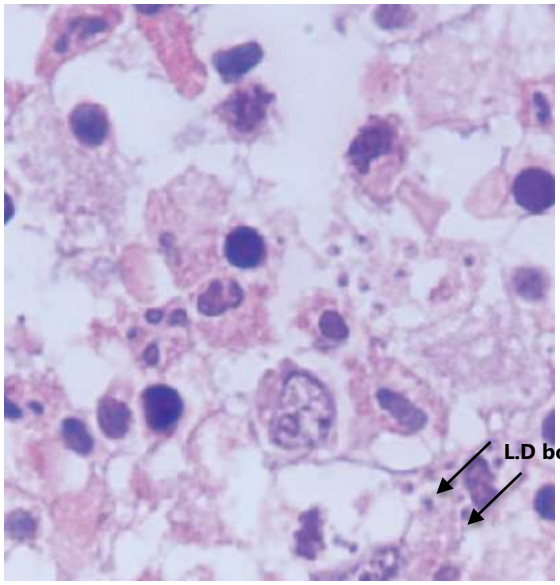

Figure 2: Photomicrograph showing L.D. body in a trephine biopsy (H&E) section.

All biopsies were adequate and showed a similar pattern of hematopoiesis as observed in their corresponding aspiration. A case that showed L.D. Body on aspiration, its corresponding trephine showed an increase in histiocytes with fewer L.D. Bodies as shown in Figure 2.

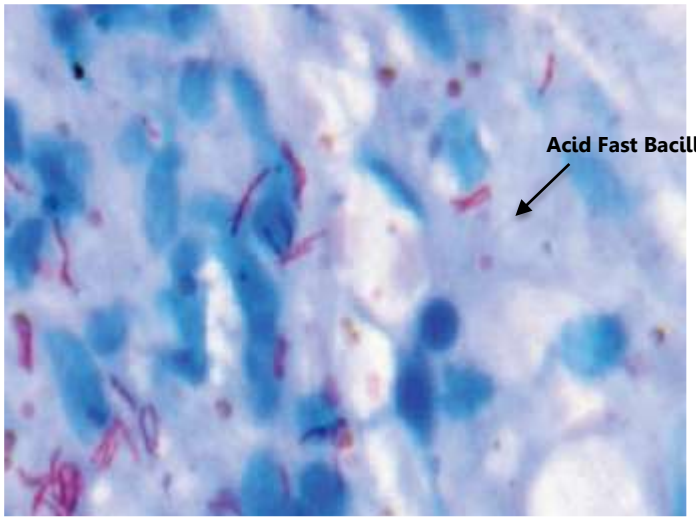

Figure 3 shows a photomicrograph of bone marrow aspirate (Ziehl- Nelson staining x1000) showing acid-fast bacilli.

Granulomas were also observed on trephine, in which 4 (6%) cases were diagnosed with tuberculosis. Acid-fast bacilli were observed in one case only, as shown in Figure 3.

The clinical outcome of sixty-four patients was shown in Table 2, whereas three remain undiagnosed. Hematological malignant disorders were the most common diagnosis, followed by infectious diseases. These five patients have infectious origins like leishmaniasis and tuberculosis.

Table 2: The final diagnosis of patient

Diagnosis	n(%)
Acute Lymphocytic Leukaemia	8(12)
Acute Myeloid Leukaemia	9(13.5)
Non-Hodgkin's Lymphoma	17(25)
Hodgkin's Lymphoma	7(10)
Myelodysplastic syndrome	6(9)
Myeloproliferative diseases	12(18)
Tuberculosis	4(6)
Leishmaniasis	1(1.5)
No diagnosis	3(4.4)

Discussion

PUO is a condition fever for more than 2 weeks without identification of etiology after extensive routine workup. A wide variety of causes influences the diagnosis of PUO, which makes PUO difficult to compare their patients suffering from it. In this study, we assessed and compared the effectiveness of bone marrow biopsy in the diagnosis of PUO. As bone marrow biopsy is a highly invasive and painful procedure, it is not considered a first-line tool for the diagnosis of PUO. A study by Mourad et al. did not suggest bone marrow biopsy as a routine test for PUO[10]. There is no standard gold test for PUO diagnosis against which other diagnostic tests can be several hematological and bone marrow morphological changes have been observed in systemic and infectious disease-causing PUO such as necrosis, reactive lymphoid hyperplasia, hemorrhage, plasmacytosis, congestion, histiocytosis, edema, granuloma formation and fibrosis[13]. In this study, anemia was the most frequent hematological alteration in our study[14], followed by leucopenia, thrombocytopenia, pancytopenia, and leucocytosis consistent with the Basu et al. and by Vilalta-Castel et al[15]. Inflammatory, neoplastic or infectious changes were also seen in bone marrow biopsies in our study disease, which were also suggested by Gupta et al[13,16].

In our study, tuberculosis and leishmaniasis were found in 4 and 1 patient, respectively. Hong et al. and Basu et al. also demonstrated granuloma and caseous necrosis in tuberculosis cases on bone marrow aspiration and biopsies in their cases, which was also consistent with our findings[14,17]. Z.N. stain was seen positive in one case only. We also found amastigote form of Leishmania donovani body (L.D.) body, plasmacytosis and hemophagocytosis in the case of leishmaniasis, which was also revealed in previous studies[16, 18]. Our study also demonstrated that most cases diagnosed by bone marrow biopsy were mostly hematological malignant neoplasm's which were consistent with the findings of Ben-Baruch et al. and Hot et al[1,18]. Bone marrow biopsy should be done as an initial investigation in patients with the major hematological disorder, which is suspected to be an aggressive neoplasm and needs immediate-early therapeutic interventions that may relieve the patients. Malignant tumour related pyrexia of unknown origin has a high mortality rate within five years[19]. Due to the invasive nature and inadequate yield, bone marrow biopsy should not be used extensively for the workup of pyrexia of

unknown origin. Therefore, because of certain laboratory and clinical manifestations, physicians should suggest bone marrow aspiration and biopsy for better prospects in diagnosing pyrexia of unknown origin.

Conclusion

Despite the presence of advanced techniques, it is very difficult to reach a definitive diagnosis of PUO. This study indicates certain laboratory and clinical parameters that can detect major hematological diseases like malignancies when bone marrow biopsy is used to workup of pyrexia of unknown origin. Bone marrow biopsy should be regarded as a constitutive part of the workup and diagnosis of pyrexia of unknown origin in conjunction with clinical findings. Furthermore, it can be used for rapid diagnosis when other diagnostic modalities fail to show an appropriate cause for pyrexia of unknown origin. In the future, more researches and global data are needed to better define the role of bone marrow biopsy in pyrexia of unknown origin.

Conflicts of Interest

None.

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