Original Research Article

Etiology of Pyrexia of Unknown Origin on Bone Marrow Examination- In a tertiary care centre

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Abstract

Background: Pyrexia of unknown origin (PUO) has been defined by Petersdorf and Beeson as patient complaint of increased body temperature of more than 38.3^{0}C developing over a period of a ≥ 3 week before specific diagnosis including 1 week of investigation in hospital. In the present study, an attempt has was made to find out the causes of PUO based on bone marrow morphological finiding. Bone marrow examination plays an important role in early diagnosis of core cause for PUO and is the best investigating tool for haematological and non-haematological disorders in any age group. **Materials & Method:** It was a prospective study conducted in Department of Pathology, MGM Medical college & LSK hospital, Kishanganj, during the period of September 2019 to august 2021. All patients presenting with classical PUO whether inpatient or outpatient coming to Medical College fulfilling the criteria of Petersdorf RG et al. **Results:** Out of 56 patients, 35 were males and 21 were females. Age of patients varied from 2 years to 70 years. Majority of patients were in the age group of 30-44 years comprising of 32.2% of total cases. Most common diagnosis was neoplastic changes, seen in 30.3% of patients, reactive myeloid hyperplasia was seen in 21.4% cases,14.2% cases show megaloblastic anemia, iron deficiency was seen 3.6 % cases, haemophagocytosis in 5.3% cases, 5.3% cases showed hypocellular marrow. Among infections, malaria was the commonest constituting 5.3% cases. Out of total of 17 cases of neoplastic changes in bone marrow, majority of them were acute myeloid leukaemia seen in 35.3% cases. **Conclusions:** Bone marrow examination is most important investigation of PUO in arriving at an etiological diagnosis. The most common causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, and haemophagocytosis, whereas in adults, the main causes were malignancies, reactive myeloid hyperplasia and megaloblastic anaemia . This study reflect light on the current spectrum of diseases causing pyrexia of unknown origin in this region.

Keywords: Pyrexia of Unknown Origin, Bone Marrow Examination, Malignancy, Acute myeloid leukemia

Introduction

pyrexia of unknown origin (PUO) has been defined by Petersdorf and Beeson as patient complaint of increased body temperature of more than 38.3^{0}C developing over a period of a ≥ 3 week before specific diagnosis including 1 week of investigation in hospital[1]. The diseases ranges causing PUO not only restricted to geographical factors, but time factor also plays a important role[2,3]. Bone marrow examination plays a vital role in early diagnosis of specific cause for PUO and is a best investigating procedure for choosing haematological and non-haematological disorders in any age group [2,4]. The response of the bone marrow varies, depending upon etology either infective and noninfective as resulting from infection and systemic disease can be analysed by morphology & etiology. It can impart great impact in the management of patients with PUO[5].

Materials and Method

It was a prospective study performed at the Department of Pathology, MGM medical college and LSK Hospital, Kishanganj, Bihar. It was conducted for the period of two years started from september 2019 to august 2021. Total number of 56 patients were selected for this study based on the Petersdorf and Beeson criteria[1] and age above ≥2 years and below ≤70 years.

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Patients clinical, radiological and laboratory findings were recorded. Preliminary investigations include complete haemogram, peripheral blood smear for malarial parasites, Widal test, urine rutine examination, liver function tests, urea & creatinine, chest x ray and Mantoux test. Bone marrow aspiration (BMA) were performed after taking informed consent from patient and posterior superior iliac spine was the site preferred under local anaesthesia using bone marrow aspiration needle (Klima and Salah). The aspirate smears were made and stained with Giemsa stain. Periodic Acid Schiff (PAS) and Myeloperoxidase stain were also used for acute leukemia cases. Zeihl-Neelsen (ZN) stain was also performed in suspected case of tuberculosis.

Statistical analysis

Data collected were compiled into MS Excel 2007 to make the dataset and statistical analysis was done.

Results

A total of 56 patients with PUO underwent bone marrow aspiration for a period of two years were included in our study. Out of 56 patients 35 were males and 21 were females, with a M: F ratio of 1.6:1. Age of patients varied from 2 years to 70 years. Out of 56 patients, there were 47 adult patients and 09 children (<18 years).Majority of patients were in the age group of 30-44 years comprising of 32.2% of total cases followed by 45-59 years, 27% cases. Age distribution is shown in table 1.

Table 1: Age Distribution numbers and percentage of Patients with PUO

Age Group (Years)	No. of Cases	Percentage (%)
1-14	8	14.2
15-29	12	21.4
30-44	18	32.1
45-59	15	26.7
>60	3	5.6
Total	56	100.0

All the patients had prolonged fever, ranging from 3 weeks to 2 months. There was history of weight loss in 24 cases, history of diarrhoea in 04 cases, epistaxis seen in 07 cases, history of rash and jaundice seen in 04 cases. Hepatosplenomegaly was seen in 25 cases and lymphadenopathy in 11 cases. Anaemia was seen in almost 50% of cases of PUO. It was normocytic normochromic in 60% of cases, macrocytic in 24% cases and microcytic hypochromic in 16% cases.

Table 2: Morphological Changes in Bone Marrow

Diagnosis	No. of Cases	Percentage(%)
Neoplastic	17	30.3
Megaloblastic	08	14.2
Iron deficiency	02	03.6
Reactive myeloid hyperplasia	12	21.4
Haemophagocytosis	03	05.3
Tuberculosis	01	01.8
Leishmaniasis	02	03.8
Malaria	03	05.3
Normal marrow	05	09.0
Hypocellular marrow	03	05.3

Various morphological changes were seen in cases with PUO on bone marrow aspiration shown in table 2.
Most common diagnosis was neoplastic changes, seen in 30.3% of cases, 14.2% cases show megaloblastic changes, 3.6% cases of iron deficiency was seen, 21.4% cases of reactive myeloid hyperplasia seen , haemophagocytosis seen in 5.3% cases, 5.3% cases show hypo cellular marrow. Among infections tuberculosis, malaria, Leishmaniasis and seen in 1.8%, 5.3% and3.8%respectively. Normal marrow findings seen in 9%.

Table 3: Distribution of Malignancies

Malignancy	No. of Cases	Percentage (%)
Acute myeloid leukemia	6	35.3
Acute lymphoid leukemia	5	29.4
Chronic myeloid leukemia	3	17.6
MDS	2	11.8
Multiple myeloma	1	05.9
Total	17	100%

Out of total 17 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 35.3% cases. Acute lymphoid leukemia was the second common diagnosis constituting about 29.4% cases, all of them were seen in pediatric age group. Chronic myeloid leukemia and multiple myeloma were seen in 17.6% and 5.9% cases respectively. Myeloid dysplastic syndrome was seen in 11.8% cases.
Distribution of malignancy is shown in table 3.
Among pediatric age group with PUO most common finding on bone marrow aspiration was acute lymphoid leukemia 05 cases(55.5%), followed by 03 cases (33.4%) haemophagocytosis and 01 cases (11.1%) of iron deficiency anemia.

Discussion

Pyrexia of unknown origin (PUO) is defined as unexplained fever for more than 3 weeks, where no etiology could be found after extensive routine investigations[1]. For diagnosis of PUO multidisciplinary approach and battery of tests are required. In present study an attempt was made to diagnose the causes of PUO based on bone marrow morphology alone[5].
In our study, the various causes of PUO were identified that is neoplastic lesion, reactive myeloid hyperplasia megaloblastic anaemia, normal marrow, haemophagocytosis, hypo cellular marrow, iron deficiency anaemia followed by infections like tuberculosis, malaria and leishmania.
In our study most common cause of PUO is Neoplasstic lesion followed by reactive myloid hyoerplasia and megaloblastic anemia. Other studies showed infections is the most common cause followed by neoplasm and collagen vascular disease[6,7,8]. Elisabeth et al, showed infection as most common cause (26%) followed by neoplasm and non-infectious inflammatory disease (13% & 24% respectively). In our study 30.3% cases showed haematological malignancies in their bone marrow. Most common neoplasm among them was acute myloid leukemia, 06 cases (35.5 %), Second common was Acute lymphoid leukemia 05 cases (29.4%), all cases were seen in children followed by Chronic myeloid leukemia 3 cases (17.6%), Myeloid dysplastic syndrome constituted 02 case (11.8%) and multiple myeloma 1 case (5.9) shown in table 3. Similar study done by Haq SA et al[9] showed leukaemia is commonest malignancy causing PUO. Study done by De Kleijn et al[3], showed neoplasm constituted 12.6% of total cases. 66.66% of total neoplastic cases were haematological malignancies. Hodgkin disease was the commonest neoplasm (35.7%). Knokaert et al[10] and colleagues, showed 7% cases were malignancy as a cause of PUO. Three percent cases were from Haematological malignancy and 4% cases were from solid tumors. Among the haematological malignancies commonest was AML constituted, 3 cases (50%). Multiple myeloma constituted only 1 case (16.66%) and 2 cases (33.33%) were from Hodgkin disease. Results of these studies were similar from our study.
In our study, megaloblastic anaemia was the second most common cause (16%) of pyrexia of unknown origin in adult. This was in concordance with study done by Davidson S et al[2,11] where it occurred in 22% of patient, Davidson related the degree and frequency of fever to the severity of anaemia
In our study reactive myeloid hyperplasia constituted 12 cases (21.4%). Reactive myeloid hyperplasia was non-specific morphological change of bone marrow due to response of various inflammatory and infective conditions. Bone marrow responds to

inflammation by increased release of cells from post mitotic reserve pool caused by TNF& IL-1 and associated with an increase in numbers of more immature granulocytes. Severe sepsis lead to granulocytic hyperplasia with or without maturing cells. Toxic granules may be seen in the cytoplasm of the granulocytes[12].

In our study, megaloblastic anaemia was the Third most common cause 8 cases (14.2%) of PUO in adult. This was similar with study done by Davidson S et al [11] showed in 22% of patient. McKee LC et al[13] showed fever in megaloblastic anaemia is because of increased activity of megaloblastic marrow, and fever was present in 40% of patients. Some studies shown that cause of pyrexia in megaloblastic anaemia is exactly not known but chance could be due to a defect in oxygenation to the regulatory centres of temperature in the brain secondary to anaemia due to vitamin B12 and folate deficiency[11,13,14,15].

In present study hypocellular marrow is seen in 03 cases (5.3%). Various drugs, toxins, chemicals, radiation or immune disorders and infection were involved in aetiology of hypocellular marrow. Only bone marrow examination was not sufficient to find out the exact cause of hypoplastic marrow. In case of hypoplastic marrow, bacterial and fungal infections were secondary to neutropenia. Haemophagocytosis was seen in 03 cases (5.3%) in the present study. Bhagat R et al[2] showed haemophagocytosis was seen in 05 cases (6%). Viruses such as Parvovirus-B19, Herpes virus, EBV CMV and HIV are commonly associated with haemophagocytosis[2].

Mirdha BR et al[16] showed in his study malaria in the bone marrow of 8 of 120 cases with PUO. Three cases were Plasmodium falciparum and 5 cases were Plasmodium vivax. In present study 2 cases were plasmodium vivax and 1 case was plasmodium falciparum. The common used laboratory method for diagnosis of malaria is microscopic examination of Romanowsky's stained thin and thick peripheral blood film. Diagnostic bone marrow examination is often performed when a patient have suspected infection with persistent fever. Microscopic examination of the blood film for malaria surveys do not always detect chronic, low-grade infection due to either scanty parasitaemia or the patient's immunity. Till date it is understood that complete consensus on routine diagnostic use of bone marrow for the malaria diagnosis have not been achieved due to its inherent limitations. But, examination of bone marrow still has a important place in the investigation of patients with suspected malaria[16]. In our study, Leishmaniasis was detected in 02 cases (3.8%). Bhagat R. et al[2] showed 3 cases (4%) of leishmaniasis in her study. In our study only one case of tuberculosis(1.8) was detected on bone marrow aspiration with presence of epithelioid cell granuloma and area of caseous necrosis and presence of acid fast bacilli in Zeihl-Neelsen stained smear. Similar result also shown by Bhagat R et al[2] that is 1case of tuberculosis (1.75%).

Conclusion

Bone marrow examination is an important investigation for etiological diagnosis of PUO. Overall most common causes of pyrexia of unknown origin were Neoplastic pathology. However most frequent cause in children were acute lymphoblastic leukemia and haemophagocytosis. Whereas in adults, the main causes were malignancies, reactive myeloid hyperplasia and megaloblastic anaemia. This study reflect light on the current spectrum of diseases causing pyrexia of unknown origin in this region.

Conflict of Interest: Nil Source of support: Nil

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