ORIGINAL RESEARCH

Investigating the cause of Pyrexia of unknown origin using bone marrow examination

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ABSTRACT
Aim: Investigating the cause of Pyrexia of unknown origin using bone marrow examination. **Materials and Method:** Total number of 100 patients were selected for this study based onthe Petersdorf and Beeson criteria and age above ≥2 years and below ≤70 years. 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 marrowaspiration (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. **Results:** All the patients had prolonged fever, ranging from 3 weeks to 2 months. There was history of weight loss in 42 cases, history of diarrhoea in 7 cases, epistaxis seen in 12 cases, history of rash and jaundice seen in 7 cases. Hepatosplenomegaly was seen in 45 cases and lymphadenopathy in 19 cases. Various morphological changes were seen in cases with PUO on bone marrow aspiration. Most common diagnosis was neoplastic changes, seen in 30% of cases, 14% cases show megaloblastic changes, 3.6% cases of iron deficiency was seen, 21% cases of reactive myeloid hyperplasia seen, haemophagocytosis seen in 5% cases, 6% cases show hypo cellular marrow. Among infections tuberculosis, malaria, Leishmaniasis and seen in 2%, 5% and 4%respectively. Normal marrow findings seen in 9%. Out of total 30 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 36.67% cases. Acute lymphoid leukemia was the second common diagnosis constituting about 30% cases, all of them were seen in pediatric age group. Chronic myeloid leukemia and multiple myeloma were seen in 16.67% and 3.33% cases respectively. Myeloid dysplastic syndrome was seen in 13.33% cases. **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.

Keywords: PUO, Bone marrow, Anaemia

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INTRODUCTION

Pyrexia of unknown origin (PUO) has been defined by Petersdorf and Beeson as patient complaint of increased body temperature of more than 38.3^0C developing over a period of a ≥3 week before specific diagnosis including 1 week of investigation in hospital[1]. The diseasesranges 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. Total number of 100 patients were selected for this study based on the Petersdorf and Beeson criteria[1] and age above ≥2 yearsand below ≤70 years. Patients clinical, radiological and laboratory findings were recorded.

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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 100 patients with PUO underwent bone marrow aspirationfor a period of two years were included in our study. Out of 100 patients 70 were males and 30 were females, with a M: F ratio of 2.33:1. Age of patients varied from 2 years to 70 years. Out of 100 patients, there were 80 adult patients and 20 children (<18 years).Majority of patients were in the age group of 30-44 years comprising of 32% 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	14	14
15-29	21	21
30-44	32	32
45-59	27	27
>60	6	6
Total	100	100

All the patients had prolonged fever, ranging from 3 weeks to 2 months. There was history of weight loss in 42 cases, history of diarrhoea in 7 cases, epistaxis seen in 12 cases, history of rash and jaundice seen in 7 cases. Hepatosplenomegaly was seen in 45 cases and lymphadenopathy in 19 cases. Anaemia was seen in almost 52% of cases of PUO. It was normocytic normochromic in 62% of cases, macrocytic in 25% cases and microcytic hypochromic in 17% cases.

Table 2: Morphological Changes in Bone Marrow

Diagnosis	No. of Cases	Percentage
Neoplastic	30	30
Megaloblastic	14	14
Iron deficiency	4	4
Reactive myeloid hyperplasia	21	21
Haemophagocytosis	5	5
Tuberculosis	2	2
Leishmaniasis	4	4
Malaria	5	5
Normal marrow	9	9
Hypocellular marrow	6	6

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% of cases, 14% cases show megaloblastic changes, 3.6% cases of iron deficiency was seen, 21% cases of reactive myeloid hyperplasia seen , haemophagocytosis seen in 5% cases, 6% cases show hypo cellular marrow. Among infections tuberculosis, malaria, Leishmaniasis and seen in 2%, 5% and 4%respectively. Normal marrow findings seen in 9%.

Table 3: Distribution of Malignancies

Malignancy	No. of Cases	Percentage
Acute myeloid leukemia	11	36.67
Acute lymphoid leukemia	9	30
Chronic myeloid leukemia	5	16.67
MDS	4	13.33
Multiple myeloma	1	3.33
Total	30	100

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Out of total 30 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 36.67% cases. Acute lymphoid leukemia was the second common diagnosis constituting about 30% cases, all of them were seen in pediatric age group. Chronic myeloid leukemia and multiple myeloma were seen in 16.67% and 3.33% cases respectively. Myeloid dysplastic syndrome was seen in 13.33% cases. Distribution of malignancy is shown in table 3.

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, hypocellular marrow, iron deficiency anaemia followed by infections like tuberculosis, malaria andleishmania.

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. Out of total 30 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 36.67% cases. Acute lymphoid leukemia was the second common diagnosis constituting about 30% cases, all of them were seen in pediatric age group. Chronic myeloid leukemia and multiple myeloma were seen in 16.67% and 3.33% cases respectively. Myeloid dysplastic syndrome was seen in 13.33% cases. 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 fromsolid tumors. Among the haematological malignancies commonest was AML constituted, 50%. Multiple myeloma constituted only 20% and 30% were from Hodgkin disease. Results of these studies were similar from our study.

In our study, megaloblastic anaemia was the second most common cause (14%) 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 theseverity of anaemia. .

In our study reactive myeloid hyperplasia constituted 21 cases (21%). 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 thegranulocytes[12].

In our study, megaloblastic anaemia was the Third most common cause 14 cases (14%) 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 anaemiadue to vitamin B12 and folate deficiency[11,13,14,15].

In present study hypocellular marrow is seen in 6 cases (6%). 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 5 cases (5%) in the present study. Hayakawa K 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 3 cases were plasmodium vivax and 2 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 dueto 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

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suspected malaria[16]. In our study, Leishmaniasis was detected in 4 cases (4%). Hayakawa K et al[2] showed 3 cases(4%) of leishmaniasis in her study. In our study only 2 case of tuberculosis(2%) 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 Hayakawa K 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.

REFERENCES

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report of 100 cases. Medicine (Baltimore) 1961;40(1):130.
2. Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review. Am J Med Sci. 2012;344(4):307–316.
3. De Kleijn EM, Vandenbroucke JP, Van der Meer JW. Fever of unknown origin (FUO). I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76(6):392-400.
4. Kumar S, Rau AR, Naik R, et al. Bone marrow biopsy in Non- Hodgkin's lymphoma: a morphological study. Ind J Pathol Microbiol 2009;52(3):332-8.
5. Jha A, Sarda R. Value of Bone marrow Examination in Pyrexia of unknown origin. J Pathol Nep. 2013;3(6):447-51.
6. Arnow PM, Flaherty JP. Fever of unknown origin. Lancet 1997;350(9077):575-80.
7. Root RK, Petersdorf RG. Fever of unknown origin. In: Root RK, Waldvogel F, Corey L, et al, eds. Clinical infectious diseases. A practical approach. New York: Oxford Medical Publications 1999: p. 459-69.
8. Ben-Baruch S, Canaani J, Braunstein R, Perry C, Ben-Ezra J, Polliack A, Naparstek E, Herishanu Y. Predictive parameters for a diagnostic bone marrow biopsy specimen in the workup of fever of unknown origin. Mayo Clin Proc. 2012;87(2):136–142.
9. Haq SA, Alam MN, Hossain SM, et al. A study of prolonged pyrexia in Dhaka. Bangladesh Med Res Counc Bull 1996;22(1):33-42.
10. Knockaert DC, Vanneste LJ, Vanneste SB, et al. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med 1992;152(1):51-5.
11. Davidson S. Clinical picture of pernicious anaemia prior to the introduction of liver therapy in 1926 and Edinburg subsequent to 1944. Br Med J 1957;1(5013):241-3.
12. Bain BJ, Clark DM, Lampert IA. Bone marrow pathology: infection and reactive changes. 2nd edn. Oxford: Blackwell Science 1996: p. 51-87.
13. Mckee LC Jr. Fever in megaloblastic anemia. South Med J 1979;72(11):1423-4.
14. Singanayagam A, Gange N, Singanayagam A, et al. Folate deficiency presenting as pyrexia: a case report. Cases Journal 2008;1(1):275.
15. Jones RV, Payne RW. The occurrence of fever in anemia. Practitioner 1960;184:618-20.
16. Mirdha BR, Samantray JC, Mishra B, et al. Bone marrow examination for identifying Malariain fever of unknown origin. J Assoc Physicians India 1999;47(2):177-

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