ROLE OF BONE MARROW EXAMINATION IN CASES OF PYREXIA OF UNKNOWN ORIGIN

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ABSTRACT

BACKGROUND

PUO refers to cases having prolonged fever the cause of which cannot be ascertained despite all diagnostic investigations. Pyrexia of unknown origin was best defined by Petersdorf and Beeson in 1961 after a study as "a temperature of 38.3^0C (101^0F) or greater on several occasions for more than 3 weeks duration and failure to reach a diagnosis despite 1 week of inpatient investigations". The diagnostic spectrum of PUO is changing over time and PUO remains a diagnostic challenge. Bone marrow examination plays an important role in early diagnosis of underlying cause for pyrexia of unknown origin and can influence the management of patients.

MATERIALS AND METHODS

It is a one-year prospective study. A total of 360 aspirations were done, of which 82 aspirations were performed for PUO as a part of diagnostic work up.

RESULTS

Bone marrow examination of 82 patients presenting as pyrexia of unknown origin was performed. Of a total of 82 cases, 52 cases (63.4%) were males and 30 cases (36.5%) were females. In children, 7 cases (3.7%) had acute lymphoblastic leukaemia followed by 4 cases (14.8%), showing haemophagocytosis while 3 cases showed megaloblastic changes (11.1%). 4 cases showed reactive changes only. In adults, neoplasm was seen in majority of cases 13 cases (23.6%), followed by megaloblastic anaemia in 12 cases (22%) 9 cases were reported as reactive changes followed in frequency by iron deficiency anaemia 5 cases, while mixed deficiency was seen in 2 cases. Atypical marrow infiltration, aplastic marrow and infectious aetiology (falciparum and leishmaniasis) were also seen in few cases.

CONCLUSION

Bone marrow examination is an adjuvant part of investigation of PUO in arriving at an aetiological diagnosis and subsequent treatment. The most frequent causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, haemophagocytosis, whereas in adults, the main causes were malignancies, megaloblastic anaemia, iron deficiencies anaemia and infection.

KEYWORDS

PUO, Bone Marrow Aspiration.

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BACKGROUND

PUO refers to cases having prolonged fever and the cause of which cannot be ascertained despite all diagnostic investigations .Pyrexia of unknown origin was best defined by Petersdorf and Beeson in 1961 after a study as "a temperature of 38.3^0C (101^0F) or greater on several occasions for more than 3 weeks duration and failure to reach a diagnosis despite 1 week of inpatient investigations."[1] Durack and Street (1991) proposed a new classification of PUO.[2] PUO is now defined as persistent fever higher than 101 F for 3 weeks and failure to make a diagnosis with 3 outpatient visits or 3 days of inpatient investigations. There are 4 subclasses of PUO classic PUO, HIV associated PUO, Nosocomial PUO and PUO in neutropenic patient.

The diagnostic spectrum of PUO is changing over time and PUO remains the diagnostician's challenge.[1] Bone marrow examination plays an important role in early diagnosis of underlying cause for pyrexia of unknown origin and is a best tool for picking haematological and non-haematological disorders in children and adults[3,4] and can influence in the management of patients.

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MATERIALS AND METHODS

It is a 1-year prospective study conducted in the haematology section of Pathology Dept., Govt. Medical College, Jammu from July 2017 to June 2018. Patients (both males and females) presenting with fever fulfilling the criteria of pyrexia of unknown origin (PUO) were included in the study.

The total no of bone marrow aspirations done during the said period were 360, of which 82 aspirations were

performed for PUO as a part of diagnostic work up. Preliminary tests like peripheral smears for malaria, urine examination, liver function tests, Widal test, Mantoux test were performed in all the cases before labelling them as PUO. Relevant clinical, radiological and laboratory findings were also recorded.

Bone marrow aspiration (BMA) and biopsy were performed from posterior iliac crest after taking informed consent.

Aims and Objective

To find out causes of PUO, to demonstrate the utility of the bone marrow and assess its contribution to the final diagnosis in PUO cases.

RESULTS

Bone marrow examination of 82 patients presenting as pyrexia of unknown origin was performed. Of a total of 82 cases, 52 cases (63.4%) were males and 30 cases (36.5%) were females with male to female ratio of 1.7:1

The age range of patients was 9 months to 68 years and the mean was 37 years. Of the total 82 patients, 27 cases (33%) were children (0-14 years) and 55 cases (67%) were adults.

Age Group (years)	No. of Cases	Percentage
1-14 yrs	27	32.9%
15-30 yrs	18	21.9%
30-65 yrs	30	36.5%
>65 yrs	07	8.5%
Total	82	100%

Table 1. Age Distribution

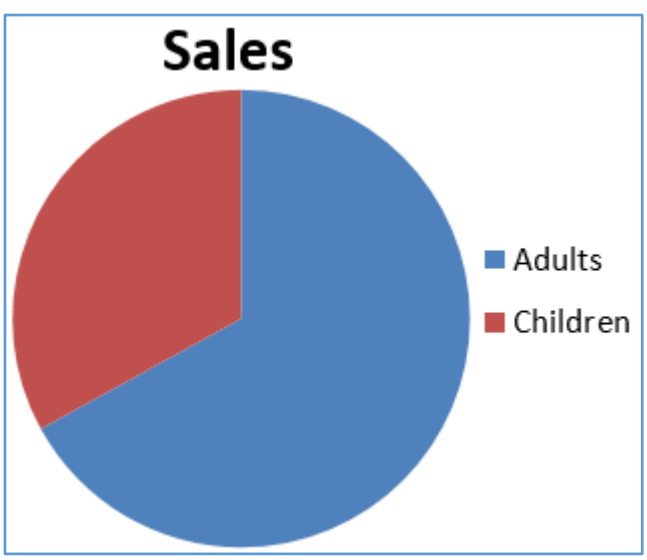

Figure 1. Distribution of PUO amongst Adults and Children

Diagnosis	No. of Cases	Adults	Children
Normal	04(4.8%)	03(5.4%)	01(3.7%)
Reactive hyperplasia	13(16%)	09(16.3%)	04(14.8%)
Neoplastic	20(24.3%)	13(23.6%)	07(26%)
Megaloblastic change	15(18%)	12(22%)	03(11.1%)
Iron deficiency	07(8.5%)	05(9.3%)	02(7.4%)
Mixed change	04(4.8%)	02(3.6%)	02(7.4%)
Hemophagocytosis	04(4.8%)	0	04(14.8%)
Hypocellular marrow	02(2.4%)	02(3.6%)	0
Aplastic marrow	03(3.6%)	02(3.6%)	01(3.7%)
Falciparum	02(2.4%)	02(3.6%)	0
Leishmaniasis	01(1.2%)	0	01(3.7%)
Tuberculosis	02(2.4%)	02(3.6%)	0
ITP	02(2.4%)	0	02(7.4%)
Marrow with atypical infiltrate	03 (3.6%)	03(5.4%)	0
Total	82	55	27

Table 2. Results of the Morphological Diagnosis of PUO Patients in 82 Cases

In children, 7 cases (3.7%) had acute lymphoblastic leukaemia followed by 4 cases (14.8%) showing haemophagocytosis while 3 cases showed megaloblastic changes (11.1%). 4 cases showed reactive changes only. Idiopathic thrombocytopenic purpura, iron deficiency anaemia and mixed deficiency anaemia were observed in 2 cases each, while only 1 case showed normal marrow.

In adults, neoplasm was seen in majority of cases 13 (23.6%), followed by megaloblastic anaemia in 12 cases (22%) 9 cases were reported as reactive changes followed in frequency by iron deficiency anaemia 5 cases, while mixed deficiency was seen in 2 cases. 3 cases showed atypical infiltration (metastatic) in the marrow. Hypocellular marrow and aplastic marrow were seen in 2 cases each. Among the infectious aetiology, 2 cases each of falciparum and tuberculosis were.

Types of Malignancies	No
Acute lymphoid leukaemia	07(35%)
Acute myeloid leukaemia	06(30%)
Chronic myeloid leukaemia	04(20%)
Multiple myeloma	02(10%)
MDS	01(5%)
Total	20(100%)

Table 3. Distribution of Malignancies

In children, all the (7) cases were of Acute lymphoid leukaemia whereas in adults, 6 cases were reported as Acute myeloid leukaemia, 4 cases as Chronic myeloid leukaemia, multiple myeloma in 2 cases and 1 case of MDS.

DISCUSSION

It is difficult to compare patients presenting with PUO because of the large number of causes. Although diagnosis of PUO requires multidisciplinary approach, bone marrow studies should be considered significant in evaluating patients having pyrexial illness.

In our study, the causes of PUO in descending order of frequency were neoplasm, megaloblastic anaemia, iron deficiency anaemia followed by haemophagocytosis, hypocellular marrow, infections like tuberculosis, malaria and leishmania. This is in contrast to other studies where infections constituted the most common cause followed by neoplasm and collagen vascular disease[5,6,7] Another study conducted by Elisabeth et al and Netherlands about FUO in 167 patients, showed infection as a leading cause (26%) followed by neoplasm and non-infectious inflammatory disease (13% & 24% respectively). Miscellaneous cause accounted 5% and 30% of cases were undiagnosed despite every effort.[8]

In the present study 24% showed haematological malignancies in their bone marrow. Most common neoplasm was ALL, 7 cases (35% all cases in children). Second in frequency was AML 6 cases (30%) followed by CML 4 cases (20%). Multiple myeloma accounted in 2 cases (10%) and, MDS constituted 1 case (5%) as shown in table. This is similar to a study by Haq SA et al where leukaemia constituted the commonest malignancy causing PUO.[9] In a prospective multicentric study in 167 patients with PUO by De Kleijn et al and colleague, neoplasm constituted 12.6% of total cases. Haematological malignancies were 66.66% of total neoplastic cases. Hodgkin disease was the commonest neoplasm (35.7%)[8] In the study of Knokaert et al and colleagues, 7% cases were malignancy as a cause of PUO. Haematological malignancy constituted 6 cases (3%) and solid tumours constituted 8 cases (4%). Among the haematological malignancies AML was the commonest, 3 cases (50%). Multiple myeloma constituted 1 case (16.66%) and Hodgkin disease 2 cases (33.33%).[10] The results of these studies were concordant to our study.

In this study, megaloblastic anaemia was found to be the second common (22%) cause of pyrexia of unknown origin in adult. This is similar to study by Davidson's where it occurred in 22% of patients[11] Davidson related the degree and frequency of fever to the severity of anaemia. According to McKee LC et al. fever in megaloblastic anaemia is due to increased activity of megaloblastic marrow, and fever was present in about 40% of patients.[12]

In the present study pyrexia of unknown origin caused due to atypical infiltrate or metastatic infiltration were 3.6% while in another study it was found to be 6.5%.[13]

In the present study, 10% adults showed reactive changes and 5% children showed reactive changes. This is in contrary to a study conducted before where in children 10% showed reactive changes.[14] In one of the study, reactive hyperplasia in children was 12%.[15]

In the present study Hemophagocytosis was seen in 4 cases (14.8%) all in children less than 1 year. Familial hemophagocytic lymphohistiocytosis develop early in life; about 70% present at less than 1m year of age.[16]

In our study, 5 cases of infectious aetiology were detected. 2 cases of tuberculosis of which one was AFB positive in a clinicopathologic analysis of 58 cases, by Bodem CR et al, 4 cases had tuberculosis with granuloma in the bone marrow, but only 2 of 4 cases showed AFB positively**.**[17]

Mirdha BR et al identified malaria in the bone marrow of 8 of 120 cases with PUO. Five cases were Plasmodium vivax and 3 cases were Plasmodium falciparum.[18] In present study two cases was diagnosed to have malaria in the bone marrow and both were Plasmodium falciparum. Bone marrow examination still has a valuable place in the investigation of patients with suspected malaria[18] and diagnostic bone marrow examination is often performed when a patient with suspected infection has persistent fever.

In this study, Leishmaniasis was detected in 1 case (3.7%) in a 12-year-old child. Study has been carried out showing the sensitivity of bone marrow being equivalent to splenic aspirates for diagnosing leishmaniasis.[19]

CONCLUSION

Bone marrow examination is an adjuvant part of investigation of PUO in arriving at an aetiological diagnosis. The most frequent causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, haemophagocytosis, whereas in adults, the main causes were malignancies, megaloblastic anaemia, iron deficiency anaemia and infection. This study will help to know the current spectrum of diseases causing pyrexia of unknown origin in this region.

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