FREQUENCY OF DIFFERENT CAUSES OF PYREXIA OF UNKNOWN ORIGIN ON BONE MARROW EXAMINATION IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To determine the frequency of underlying causes of pyrexia of unknown origin on bone marrow examination.

Study Design: Descriptive study.

Place and Duration of Study: The study was carried out at Hematology department (pathology) of Army Medical College, National University of Sciences and Technology (NUST) and Military Hospital Rawalpindi (during the period of one year) from Jan 2012-Dec 2012.

Material and Methods: Total of 94 patients reporting with pyrexia of unknown origin at MH Rawalpindi underwent bone marrow examination. Bone marrow aspiration procedure was done from posterior superior iliac spine in patients older than one year while tibial tuberosity was used in patients less than one year of age. Lumbar puncture needle of 16 G was used for bone narrow aspiration and trephine biopsy was done by using 11 G trephine biopsy needle.

Results: In children, commonest causes observed were acute lymphoblastic leukaemia in 7 (23.3%), marked haemophagocytosis in 4 (13.3%) and visceral leishmaniasis in 4 (13.3%) patients. In adults, commonest causes included megaloblastic anaemia in 13 (20.3%), lymphoproliferative disorders in 8 (12.5%) and hypersplenism in 5 (7.8%) patients.

Conclusion: This study concludes that causes of pyrexia of unknown origin vary with age of the patient. The most frequent causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, marked haemophagocytosis, and visceral leishmaniasis where in adults main causes were megaloblastic anaemia, lymphoproliferative disorders and hypersplenism.

Keywords: Leishmaniasis, Hypersplenism, Pyrexia of unknown origin.

INTRODUCTION

Pyrexial diseases are commonly worldwide, involving all age groups and both genders[1]. The term pyrexia of unknown origin refers to cases having prolonged fever and their cause remains undetermined even after taking detailed history, examination and investigations.

Pyrexia of unknown origin was best defined by Petersdorf and Beeson in 1961 after a study as "a temperature of 38.3^{0}C (101^{0}F) or greater on several occasions for more than 3 weeks duration and failure to reach a diagnosis despite 1 week of inpatient investigations"[2]. The most common causes include infections, collagen vascular diseases and malignancies.

The diagnosis of patient with pyrexia of unknown origin is challenging but detailed history and examination renders great significance in diagnostic plan[3,4]. 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 hematological and non hematological disorders in children and adults[5,6].

In developing countries like Pakistan where patients cannot afford the expense of multiple tests; bone marrow examination has become the ultimate modality for early diagnosis of pyrexia of unknown origin. Number of studies have been done both at international and national level, showing infections as a highlighted cause of pyrexia of unknown origin[7,8]. Variation is seen among the causes revealing change in its

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aetiology with age, gender, time of the study and geographical location[9,10,11]. No study depicting the definitive cause of pyrexia of unknown origin has yet been carried out in our setup. This study will help to know the current spectrum of diseases causing pyrexia of unknown origin in Pakistan.

MATERIAL AND METHODS

It is a cross-sectional study conducted at Hematology (Pathology) Department, Army Medical College, National University of Sciences and Technology (NUST) and Military Hospital, Rawalpindi from Jan 2012-Dec 2012. Males and females presenting with fever fulfilling the criteria of pyrexia of unknown origin, given by Petersdorf and Beeson[2] were included in this study and those with nosocomial and HIV infection were excluded. Total number of bone marrow biopsies done during this period were 408. Ninety four bone marrow aspiration were performed to reach the definitive underlying cause for pyrexia of unknown origin. Urine examination, peripheral blood smear for malarial parasites, liver function tests, urea & creatinine, widal test, mantoux test and chest x ray were preliminary tests done in all patients before labelling them as cases of pyrexia of unknown origin. Bone marrow aspiration procedure was done from posterior superior iliac spine in patients older than one year and tibial tuberosity was used as a site for procedure in patients less than one year of age. Bone marrow aspiration was done by using lumbar puncture needle of 16 G and trephine biopsy was done by using 11 G trephine biopsy needle. The information was gathered from the records saved in the official departmental registers. Data had been entered on a specifically designed proforma and results analyzed using SPSS version 20.

Descriptive statistics were used to describe the data. Frequency and percentages were calculated for qualitative variables like different signs, causes of pyrexia of unknown origin and mean and standard deviation (SD) were calculated for quantitative variable like age. Chi-square test was applied to compare the frequencies of various diseases in children and adults. p value < 0.05 was considered significant.

RESULTS

Total of 408 patients had gone through the process of bone marrow examination during the period of study. Ninety four patients among them were evaluated for pyrexia of unknown origin. Twenty one patients (22.3%) required trephine biopsy for final diagnosis where as rest were diagnosed by bone marrow aspiration. Males were 81 in number (86.2%) and females were 13 (13.8%). Age range of patients was 4 months to 78 years and the mean was 32.9 years. The range of duration for pyrexia of unknown origin was 22 to 400 days with the mean of 95.69 days.

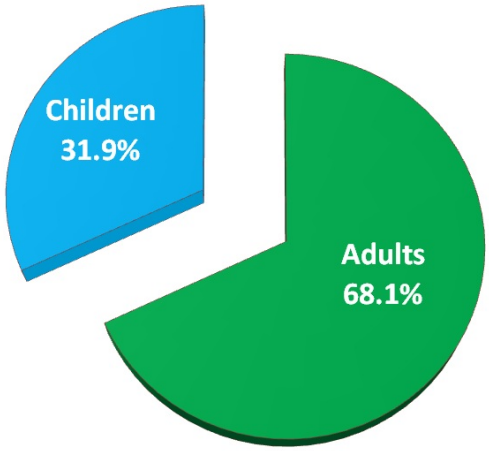

Figure-: Age distribution in cases of pyrexia of unknown origin.

Splenomegaly was present in 38 patients (40.4%) that was the commonest sign followed by hepatomegaly (31.9%) and lymphadenopathy (12.8%). Thirty patients (31.9%) had pancytopenia which was obvious on blood picture followed by depressed one cell line in 22 patients (23.4%) and bicytopenia in 16 patients (17%) where in the rest of 32 patients (27.7%) the blood picture was normal.

Of the total of 94 patients, 30 (31.9%) were children (0-14 years) and 64 (68.1%) were adults (14-90 years) (fig). In children, 7 (23.3%) had

acute lymphoblastic leukaemia followed by 4 (13.3%) having marked haemophagocytosis and same frequency and percentage for visceral leishmaniasis. Idiopathic thrombocytopenic purpura, megaloblastic anaemia and acute myeloid leukaemia were observed in 2 (6.7%) patients each (table).

In adults 13 patients (20.3%) had megaloblastic anaemia followed by lymphoproliferative disorders in 8 patients (12.5%), hypersplenism in 5 patients (7.8%) marrow showing atypical infiltrate and acute myeloid leukaemia in 4 patients (6.3%), anaemia of chronic disorders in 3 patients (4.7%) (table-1).

In this study statistically significant variation among different causes of pyrexia of unknown origin in children and adults was observed in cases of acute lymphoblastic leukaemia (*p*-value 0.002), marked haemophagocytosis (*p*-value 0.003), visceral leishmaniasis (*p*-value 0.018) and lymphoproliferative disorders (*p*-value 0.043). Rest of the causes also showed variations but were statistically insignificant (table-1).

Table-: Variation of different causes of pancytopenia in children and adults.

Disease	Children (n=30)	Adults (n=64)	*p*-value
Acute lymphoblastic leukaemia	7 (23.3%)	2 (3.1%)	0.002
Marked haemophagocytosis	4 (13.3%)	0 (0%)	0.003
Visceral leishmaniasis	4 (13.3%)	1 (1.6%)	0.018
Lymphoproliferative disorders	0 (0%)	8 (12.5%)	0.043
Hypersplenism	0 (0%)	5 (7.8%)	0.116
Megaloblastic anaemia	2 (6.7%)	13 (20.3%)	0.092
Leukopenia with marked basophilic stippling	1 (3.3%)	0 (0%)	0.142
Lymphoblastic lymphoma in leukemic phase	1 (3.3%)	0 (0%)	0.142
Gaucher's disease	1 (3.3%)	0 (0%)	0.142
Marrow showing atypical infiltrate	0 (0%)	4 (6.2%)	0.162
Chronic myeloid leukaemia	0 (0%)	2 (3.1%)	0.328
Leukamoid reaction consistent with infective process	0 (0%)	2 (3.1%)	0.328
Chronic myelomonocytic leukaemia	0 (0%)	2 (3.1%)	0.328
Hypocellular marrow	0 (0%)	2 (3.1%)	0.328
Idiopathic thrombocytopenic purpura	2 (6.7%)	2 (3.1%)	0.428
Red cell aplasia	0 (0%)	1 (1.6%)	0.491
Polycythemia rubra vera	0 (0%)	1 (1.6%)	0.491
Myelofibrotic variant of myelodysplastic syndrome	0 (0%)	1 (1.6%)	0.491
Multiple myeloma	0 (0%)	1 (1.6%)	0.491
Plasmacytosis	0 (0%)	1 (1.6%)	0.491
Aplastic anaemia	0 (0%)	1 (1.6%)	0.491
Bone marrow showing reactive changes	3 (10%)	4 (6.2%)	0.518
Anaemia of chronic disorder	1 (3.3%)	3 (4.7%)	0.762
Acute myeloid leukaemia	2 (6.7%)	4 (6.2%)	0.938
Mixed deficiency anaemia	1 (3.3%)	2 (3.1%)	0.957
Iron deficiency anaemia	1 (3.3%)	2 (3.1%)	0.957

DISCUSSION

Comparison of patients with pyrexia of unknown origin is difficult because of the large number of possible causes and the influence of

numerous factors on the various diagnostic categories. Literature review has shown that bone marrow studies should be considered significant in evaluating patients having long duration of pyrexial illness[12]. Different infections, hematological and nonhematological malignancies are well differentiated on bone marrow examination, cultures and trephine biopsy results[13]. Though bone marrow aspiration and trephine biopsy is a painful procedure but the diagnosis made by this can be life saving in many patients[14,15]. The current study has highlightened different types of underlying causes for pyrexia of unknown origin in children and adults in our setup.

In this study, megaloblastic anaemia was found to be the most common (20.3%) cause of pyrexia of unknown origin in adults contrary to the study carried out in Pakistan where chronic disorders were on the top 20.1%[16]. Case reports are there which show that megaloblastic anaemia can present as pyrexia of unknown origin[17]. Studies have shown that however the cause of pyrexia in megaloblastic anaemia is not exactly 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 B 12 and folate deficiency[17-20]. There is one other proposed mechanism for pyrexia in megaloblastic anaemia suggesting increased bone marrow activity to be responsible for the pyrexia but the exact mechanism is still not known.

The lymphoproliferative disorders were the second leading cause for pyrexia of unknown origin in this study and it goes in favour of study conducted in Eastern India[7] where it was also the second top cause for pyrexia of unknown origin and it contradicts with the studies conducted in Pakistan[16] and North India[21,22].

Hypersplenism is also among the common causes (7.8%) of pyrexia of unknown origin in this study which goes against one of the study conducted before in Pakistan where no patient was found to have hypersplenism[16]. In this study pyrexia of unknown origin caused due to atypical infiltrate or metastatic infiltration were 6.3% which have almost the same percentage (6.5%) as found in one other study[16].They were suggested immunohistochemistry for definitive diagnosis.

In this study acute lymphoblastic leukaemia was found to be the commonest cause (23.3%) of pyrexia of unknown origin in children which contradicts with one of the study where infections were the commonest cause (enteric fever being the commonest)[23]. Visceral leishmaniasis and marked haemophagocytosis were found to be the second commonest cause of pyrexia of unknown origin in contrary to one other study where infections were the leading cause[23]. Study has been carried out showing the sensitivity of bone marrow being equivalent to splenic aspirates for diagnosing leishmaniasis[24].

6.3% adults showed reactive changes in contrary to a study conducted before[8] where in children 10% showed reactive changes which is almost the nearby percentage (12%) as shown in one of the other study[23].

CONCLUSION

This study concludes that causes of pyrexia of unknown origin vary with age of the patient. The most frequent causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, marked haemophagocytosis, and visceral leishmaniasis where in adults main causes were megaloblastic anaemia, lymphoproliferative disorders and hypersplenism.

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