Different Causes of Pyrexia of Unknown Origin on Bone Marrow Examination- An Institutional Experience

Authors
Roopali Jandial[1], Ritu Bhagat[2*], Vinod Kumar[3]
[1,2]Demonstrator, Department of Pathology, Government Medical College, Jammu, India
[3]Post graduate Department of Medicine, Government Medical College, Jammu, India
*Corresponding Author
Dr Ritu Bhagat
Department of Pathology, Government Medical College, Jammu, J&K, India

Abstract

Introduction: *Petersdorf and Beeson defined pyrexia of unknown origin (PUO) as a complaint with temperature surpassing 38.3^0 C, developing over a period of at least three weeks, with no possible opinion reached after one week of inpatient investigation. In present study an attempt has been made to find out the causes of PUO based on bone marrow morphology.*

Method & Materials: *All the patients presenting with classical PUO coming to Government Medical College, Jammu, fulfilling the criteria of Petersdorf RG et al whether inpatient or outpatient over a period of two years were included in this prospective study.*

Results: *Out of 76 patients 48 were males and 28 were females. Age of patients varied from 12 years to 70 years. Majority of patients were in the age group of 30-44 years comprising of 45% of total cases. Anemia was seen in nearly 50% of cases of PUO. Most common diagnosis was neoplastic changes, seen in 20% of patients, 16% cases show megaloblastic changes, iron deficiency was seen 10 % cases, reactive myeloid hyperplasia seen in 18% cases, hemophagocytosis in 6% cases, 5% cases show hypocellular marrow. Among infections malaria was the commonest constituting 5.2% cases, Out of total 15 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 40% cases.*

Conclusion: *Bone marrow examination is an important investigation of PUO in arriving at an etiological diagnosis.*

Keywords: *Pyrexia of unknown origin, Bone marrow examination, Malignancy, Hematological.*

Introduction

Petersdorf and Beeson defined pyrexia of unknown origin (PUO) as a complaint with temperature surpassing 38.3^0 C, developing over a period of at least three weeks, with no possible opinion reached after one week of inpatient investigation.[1] The range of diseases causing PUO not only seems to be determined by geographical factors, but time also plays a vital role.[2] Bone marrow examination plays an important role in early diagnosis of core cause for PUO and is a best tool for picking hematological and non hematological disorders in any age group.[3,4]

In developing countries afford ability is a limitation; so bone marrow examination has become the ultimate modality for early diagnosis of pyrexia of unknown origin. Variable response of the bone marrow depends upon etiology either infective or non-infective, as a result infections and systemic diseases can be studied by analysis

of morphology & etiology and helps in the management of patients with PUO.

This prospective study is conducted to find out the spectrum of diseases causing PUO in Jammu region. In present study an attempt has been made to find out the causes of PUO based on bone marrow morphology.

Method & Materials

All the patients presenting with classical PUO coming to Government Medical College, Jammu, fulfilling the criteria of Petersdorf RG et al[1] whether inpatient or outpatient over a period of two years were included in this prospective study. Detailed clinical history, physical examination and various relevant investigations were noted from the case records. Preliminary investigations include routine urine examination, haemogram, peripheral blood smear for malarial parasites, liver function tests, urea & creatinine, widal test, mantoux test and chest x ray. Bone marrow aspiration had been done after taking an informed consent from the patient. Mostly posterior superioriliac spine was the site preferred under local anesthesia using lumbar puncture needle of 16G. The aspirate smears were stained with Giemsa stain. The parameters studied were cellularity of marrow particles; status of all series of hematopoietic cells increase in plasma cells presence and type of granulomas and any other associated features seen including hemophagocytosis.

Results

A total of 76 patients of PUO who underwent bone marrow aspiration over a period of two years were included in our study. Out of 76 patients 48 were males and 28 were females, with a M:F ratio of 1.7:1. Age of patients varied from 12 years to 70 years. Out of 76 patients, there were 56 adults patients and 09 children (<14 years). Majority of patients were in the age group of 30-44 years comprising of 45% of total cases followed by 15-29 years, 33% cases. Age distribution is shown in **table 1**.

Table 1: Age distribution of patients with PUO

Age group (years)	No. of cases	Percentage (%)
1-14	09	12
15-29	25	33
30-44	34	45
45-59	05	06
>60	03	04
Total	**76**	**100**

All the patients gave history of prolonged fever ranging in duration from 20 days to 120 days, with an average duration of 30 days. There was history of weight loss in 35 cases, history of diarrhoea in 08 cases, epistaxis seen in 03 cases, history of rash and jaundice seen in 03 cases. Hepatospleenomegaly was seen in 30 cases and lymphadenopathy in 14 cases.

Anaemia was seen in nearly 50% of cases of PUO. It was normocytic normochromic in 70% of cases, macrocytic in 16% cases and microcytic hypochromic in 14% cases.

Various morphological changes were seen in patients with PUO on bone marrow aspiration which are shown in **table 2**. Most common diagnosis was neoplastic changes, seen in 20% of patients, 16% cases show megaloblastic changes, iron deficiency was seen 10 % cases, reactive myeloid hyperplasia seen in18% cases, hemophagocytosis in 6% cases, 5% cases show hypocellular marrow. Normal marrow findings seen 5.3% cases. Among infections malaria was the commonest constituting 5.2% cases, intracellular and extracellular amastigote forms of leishmania donovani were seen in 4% cases and tuberculosis was seen in 2.6% cases. Also 2.6% cases show features of ITP.

**Table 2:** Showing morphological changes in bone marrow

Diagnosis	No. of cases	Percentage(%)
Normal marrow	07	5.3
Neoplastic	15	20
Megaloblastic	12	16
Reactive myeloid hyperplasia	14	18
Iron deficiency	08	10
Hemophagocytosis	05	06
Hypocellular marrow	04	05
Tuberculosis	02	2.6
Leishmaniasis	03	04
Malaria	04	5.2
ITP	02	2.6

Out of total 15 cases of neoplastic changes in bone marrow majority of them were acute myeloid leukemia seen in 40% cases. Acute lymphoid leukemia was the second common diagnosis constituting about 26.6% cases, all of them were seen in children. Chronic myeloid leukemia and multiple myeloma were seen in 13.3% cases each. Myeloid dysplastic syndrome was seen in 6.7% cases. Distribution of malignancy is shown in **table 3.**

Table 3: Showing distribution of malignancies

| Malignancy	No. of cases	Percentage(%)
Acute lymphoid leukemia	04	26.6
Acute myeloid leukemia	06	40
Chronic myeloid leukemia	02	13.3
Multiple myeloma	02	13.3
MDS	01	6.7
Total	**15**	**100**

Among children with PUO most common finding on bone marrow aspiration was acute lymphoid leukemia 04 cases, followed by 03 cases of megaloblasticanemia and 02 cases of hemophagocytosis.
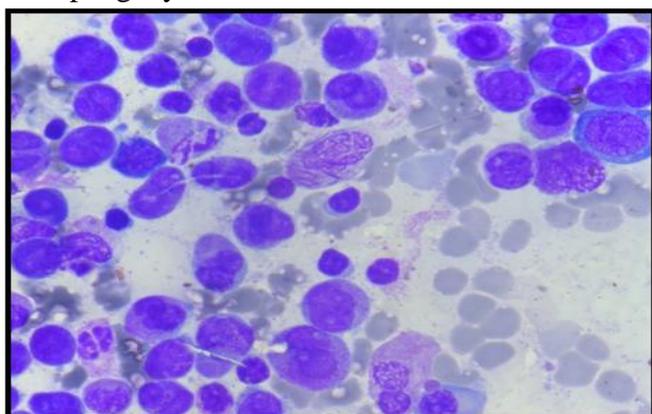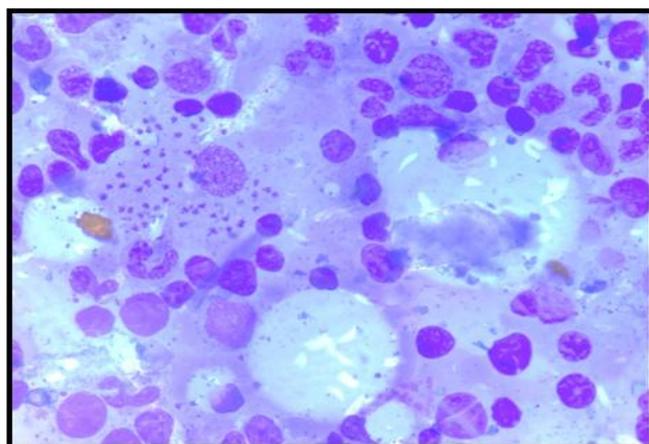

Figure 1: Showing acute leukemia having myeloblast and Auer rods (Leishman;40X)
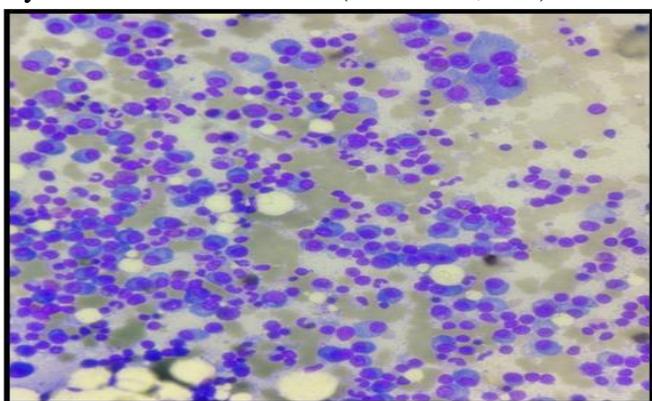
Figure 2: Showing multiple myeloma having immature and mature plasma cells in bone marrow (Leishman;10X)
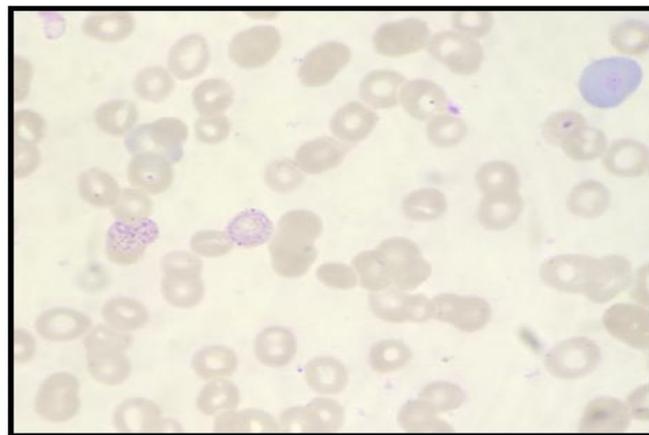
Figure 3: A peripheral blood film showing Plasmodium vivax trophozite and ring form (Leishman;100X)

Figure 4: Bone marrow microphotograph showing extracellular amastigote forms of Leishmania Donovani bobies (Leishman;100X)

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.[5] Different infections, hematological and non hematological malignancies are well differentiated on bone marrow examination, cultures and trephine biopsy results.[6] Though bone marrow aspiration and trephine biopsy is a painful procedure but the diagnosis made by this can be life saving in many patients.[7,8]

A variety of morphologic changes in the bone marrow have been described in various infectious and systemic diseases resulting in PUO.[9] These changes may be features of acute inflammation (interstitial edema, vascular congestion, hemorrhage, ischemic necrosis or suppurative necrosis) or chronic inflammation with granuloma formation, reactive lymphoid hyperplasia, plasmacytosis, histiocytosis or fibrosis.[9]

In our study, the various causes of PUO were neoplasm, megaloblastic anemia, iron deficiency anemia, reactive myeloid hyperplasia 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.[10,11,12] Another study conducted by Elisabeth et al and Netherlands about FUO in167 patients, showed infection as a leading cause (26%) followed by neoplasm and non-infectious inflammatory disease (13% & 24% respectively). Miscellaneous causes accounted 5% and 30% of cases were undiagnosed despiteevery effort.[13]

In our study 20% cases showed haematological malignancies in their bone marrow. Most common neoplasm among them was Acute lymphoid leukemia, 04 cases (26.6 %) all cases were seen in children. Second common was Acute myeloid leukemia 06 cases (40%) followed by Chronic myeloid leukemia and multiple myeloma 02cases (13.3%) eachand Myeloid dysplastic syndrome constituted only 01 case (6.7%) as shown in **table 3**. These findings are similar to study done by Haq SA et al[14] where leukaemia constituted the commonest malignancy causing PUO. In a study done by De Kleijnet al[13], which was a prospective multicentric study of 167 cases of PUO, neoplasm constituted 12.6% of total cases. Haematological malignancies were 66.66% of total neoplastic cases. Hodgkin disease was the commonest neoplasm (35.7%). In the study done by Knokaert et al[15] 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 only1 case (16.66%) and Hodgkin disease 2 cases (33.33%).The results of theses studies were similar to our study.

In our study, megaloblastic anemia was the second most common cause (16%) of pyrexia of unknown origin in adult. This was in concordance with study done by Davidson Set al[16] where it occurred in 22% of patient, Davidson related the degree and frequency of fever to the severity of anemia. According to McKee LC et al[17] fever in megaloblastic anemia is due to increased activity of megaloblastic marrow, and fever was present in about 40% of patients.

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 anemia due to vitamin B12 and folate deficiency.[16,17,18,19] There was 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.

In present study hypocellular marrow is seen in04 cases (5%). Various drugs, chemicals, toxins, infection, radiation or immune disorders were involved in etiology of hypocellular marrow. Bone marrow examination alone was not sufficient to point out the cause of hypoplastic marrow. In patients with hypoplastic marrow, bacterial and fungal infections were common secondary to neutropenia.

Hemophagocytosis was seen in 05 cases (6%) in the present study. Viruses such as Herpes virus, Parvovirus-B19, CMV, EBV, and HIV are most commonly associated with hemophagocytosis. Although bacteria such as Salmonella, E.coli, Brucella, Legionella, and parasites such as Toxoplasma, Leishmania, and Malaria are also responsible for hemophagocytosis.[20,21,22,23]

Mirdha BR et al[24] identified malaria in the bone marrow of 8 of 120 cases with PUO. Five cases were Plasmodium vivax and 3 cases were Plasmodium falciparum. In present study 04 cases of plasmodium vivax were diagnosed on bone marrow. The commonly used laboratory method for diagnosis of malaria in this part of world is microscopic examination of Romanowsky's stained thin and thick peripheral blood film. However, its sensitivity is directly proportional to the microscopic skill, screening time and staining. However diagnostic bone marrow examination is often performed when a patient with suspected infection has persistent fever. Malaria surveys based on microscopic examination of the blood film do not always detect chronic, low-grade infection due to either scanty parasitemia or the patient's immunity. It is understood that till date complete consensus on routine diagnostic use of bone marrow for the diagnosis of malaria have not been achieved due to its inherent limitations. But, bone marrow examination still has a valuable place in the investigation of patients with suspected malaria.[24]

Reactive myeloid hyperplasia constituted 14 cases (18%). This condition was non-specific morphological change of bone marrow in response to various inflammatory and infective conditions. No specific etiological agents were identified. Bone marrow responds to inflammation by accelerated release of cells from post mitotic reserve pool caused by IL-1 & TNF and associated with an increase in numbers of more immature granulocytes. Severe bacterial infections lead to granulocytic hyperplasia with or without maturing cells. Toxic granules may be evident in the cytoplasm of the granulocytes.[25] Bone marrow culture in association with bone marrow morphology would be more useful in suspected infectious etiology.[26]

In our study, Leishmaniasis was detected in 03 cases (4%). Study has been carried outshowing the sensitivity of bone marrow being equivalent to splenic aspirates for diagnosing leishmaniasis.[27]

Conclusion

Bone marrow examination is an important investigation of PUO in arriving at an etiological diagnosis. The most frequent causes of pyrexia of unknown origin observed in children were acute lymphoblastic leukaemia, megaloblastic anemia and haemophagocytosis, whereas in adults, the main causes were malignancies, megaloblastic anaemia and reactive myeloid hyperplasia. This study will help to know 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;40:1-30.
2. De Kleijn EM, Vanderbroucke JP, Vander Meer JW. Fever of unknown origin (FUO). I. A prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine 1997; 76:392-400.
3. Zehnder JL. Bone marrow aspiration and biopsy: Indications andtechnique. Website: http://www.uptodate.com/contents/bone-marrowaspiration-and-biopsy-indication-and-tec....] Retrieved on 15th April
4. Kumar S, Rau AR, Naik R, Kinhi H, Mathai AM, Pai MR et al. Bonemarrow biopsy in Non Hodgkin's lymphoma: A morphological study.Ind J Pathol Microbiol. 2009; 52(3): 332-8. 2011.
5. Sipahi OR, Senol S, Arsu G et al. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990-2006. Med Scimonit 2007; 13: 318-22.
6. Kapoor OP. Value of bone marrow examination in patient having pyrexia of unknown origin. Website [http://www.bhj.org/journal/20024403.jul/cost 434.htm] Retrieved on 15th April 2011.
7. Baruch SB, Cannani J, Braunstein R, Perry C, Ben Ezra J, Polliack A, et al. Predictive

parameters for a diagnostic bone marrow biopsy specimen in the workup of fever of unknown origin. Mayo Clin Proc 2012; 87(2): 13642.

8. Hot A, Jaisson I, Girard C, French M, Durand DV, Rousset H, et al. Yield of bone marrow examination in diagnosing the source of fever of unknown origin. Arch Intern Med 2009 Nov 23; 169(21): 2018-23.

9. Diebold J, Molina T, Camilleri-Broet S, le Tourneau A, Audouin J. Bone marrow manifestations of infections and systemic diseases observed in bone marrow trephine biopsy. Histopathology 2000; 37: 199–211.

10. Arnow PM, Flaherty JP. Fever of unknown origin.Lancet 1997;350(9077): 575-580.

11. Root RK, Petersdorf RG. Fever of unknown origin. In:Root RK, Waldvogel F, Corey L, et al, eds. Clinicalinfectious diseases. A practical approach. New York:Oxford Medical Publications 1999:459-469.

12. McCarthy PL. Fever. Pediatrics 1999;11:49-55.

13. deKleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. Medicine (Baltimore) 1997;76(6):392-400.

14. 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.

15. 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):51-55.

16. Davidson S. Clinical picture of pernicious anaemia priorto the introduction of liver therapy in 1926 andEdinburg subsequent to 1944. Br Med J1957;1(5013):241-243.

17. Mckee LC. Fever in megaloblastic anemia. South Med J 1979;72(11):1423-1424.

18. Singanayagam A, Gange N, Singanayagam A, Jones H.Folate deficiency presenting as pyrexia: a case report. Cases journal 2008, 1:275.

19. Jones RV, Payne RW: The occurrence of fever in anemia. Practitioner.1960;184: 618-20.

20. Diebold J, Molina T, Camilleri-Broet S, Tourneau A le, Audouin J. Bone marrow manifestations of infections and systemic diseases observed in bone marrow trephine biopsy. Histopathology 2000;37:199-211.

21. Shirono K, Tsuda H. Parvovirus B19-associated hemophagocytic syndrome in healthy adults. British J. Haematol 1995;89:923-6.

22. McKenna RW, Risdall RJ, Brunning RD. Virus associated hemophagocytic syndrome. Hum Pathol 1981;12:395-9.

23. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infectionand Malignancy-Associated Hemophagocytic Syndromes. Hematology Oncology Clinics of North America 1998;12:435-44.

24. Mirdha BR, Smantray JC, Mishra B, Xess I. Bone marrow Examination for Identifying Malaria in Fever of Unknown Origin. J Assoc Physicians India. 1999;47:177-9.

25. Bain BJ, Clark DM, Lampert IA. Bone Marrow Pathology: Infection and Reactive Changes. 2nd ed. Blackwell Science: Oxford;1996. pp51-87.

26. Jha A, Sarda R, Gupta A, Talwar OP. Bone marrow culture Vs Blood Culture in FUO. J Nepal Med Assoc. 2009;48:135-8.

27. da Silva MR, Stewart JM, Costa CH. Sensitivity of bone marrow aspiration in diagnosis of visceral leishmaniasis. Am J Trop Med Hyg. 2005;72(6):811-814.