Bone Marrow Culture Vs Blood Culture in FUO

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ABSTRACT

Introduction: Bone marrow culture is considered superior to blood culture in evaluation of FUO. The aim of this study was to compare the usefulness of these two cultures.

Methods: A one year prospective cross sectional study was conducted to find out the usefulness of bone marrow culture and blood culture in the diagnosis of FUO. Marrow aspirates in each case were sent for bacterial, myocbacterial and fungal culture. Simultaneously venous blood was sent for bacterial culture. The results of BMCs and BCs were compared.

Results: Total 57 cases of FUO were included in the study. Male female ratio was 1.22:1. Age range was five to 83 years (median 30). Duration of fever was 21 to 365 days. Bacterial growth was seen in nine cases (15.78%) of BMCs and in three cases (5.26%) of corresponding BCs. Fungal or myocbacterial growth was not seen. Salmonella typhi was the commonest organism isolated in BMCs (three cases) followed by Staphylococcus aureus (two cases), Escherichia coli, Non fermenting Gram negative bacilli, Enterococcus species and Salmonella paratyphi–A (one case each). Two cases of Salmonella typhi and one case of Salmonella paratyphi–A were isolated in BCs.

Conclusions: BMCs are more useful than BCs in evaluation of patients with FUO, especially in cases of salmonella infection and are particularly important when the patient has already taken antibiotics. In immuno-competent patients presenting with FUO, BMCs for mycobacteria or fungi is unlikely to yield any growth.

Key Words: *blood culture, bone marrow culture, fever of unknown origin*

INTRODUCTION

Fever of unknown origin (FUO) is a common clinical problem and an enormous number of conditions, either uncommon diseases or unusual presentations of common diseases are implicated as cause.[1] Diagnostic spectrum is changing over time because of advent of sophisticated tests; however, it still poses diagnostic challenge to the physicians. The three major categories of diseases giving rise to FUO are infections, tumors, and connective tissue diseases.[2] Bone marrow cultures (BMCs) are performed in the evaluation of FUO, usually in conjunction with blood cultures (BCs), cultures of body fluids and tissues.[3] BMCs are often positive when BCs are negative, especially in cases of enteric fever.[4] In cases of salmonella infection, BMCs increase the diagnostic yield by about one-third when compared with BCs.[5] In the present study we compared the usefulness of BMCs with BCs in an attempt to detect systemic infection in patient with FUO.

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METHODS

This was a one year prospective cross sectional study. All the cases of FUO referred to department of pathology of Manipal Teaching Hospital, were included in the study. FUO was defined by the criteria of Petersdorf and Beeson: temperature of 38.3°C (101°F) or above persisting or recurring during a period of two weeks and seven days investigation in hospital, or if three out patient visits fail to result in a diagnosis.[6] Patients not fulfilling the above criteria were excluded from the study.

In all the cases clinical findings were recorded and Patients were informed about the procedure. Venous blood is drawn for bacterial culture. Bone marrow aspirations were performed under local anesthesia from posterior superior iliac crest using Salah needle attached to 20 cc syringe, after aseptic precaution. About 10 ml of marrow was aspirated in each case for bacterial, myocbacterial and fungal cultures. For bacterial culture aspirate were inoculated into biphasic brain heart infusion medium and biphasic MacConkey medium and incubated at 37°C for seven days with regular subculture on third and sixth days till the growth was observed. Subcultures were done and incubated at 37°C for 18-24 hours. The growths in the slant were Gram stained and the isolates were identified by biochemical and serological tests. For Mycobacteria, aspirates were inoculated into Lowenstain Jensen medium and incubated at 37° C till the appearance of the growth, maximum for eight weeks. For fungi aspirates were inoculated into Sabourad dextrose agar medium and incubated at room temperature till the appearance of the growth, maximum for 4 weeks.

The obtained data were collated and results were tabulated. The data were analyzed by measures of central tendency.

RESULTS

Total numbers of patients with fever, sent for BMCs were 74, but only 57 patients were included in the study. 17 cases were excluded from the study. HIV test was negative in all the cases. 30 cases were male and 27 were female. Male to female ratio was 1.22:1. Youngest patient was of five year and oldest patient was 83 year old. Median age was 30 years. Six cases (10.5%) were children (<15 years) and 10 cases (17.5%) were elderly (>65 years). Table 1 shows the age distribution of 57 patients. Shortest duration of fever was 21 days and longest was 365 days with mean of 30 days (Table 2).

BMCs in nine (15.78%) out of 57 patients exhibited bacterial growth and in three cases (5.26%) corresponding BCs also exhibited bacterial growth (Table 3 and 4). None of the BMCs showed mycobacterial or fungal growth. Frequencies of various bacteria isolated in BMCs are shown in table 4; the commonest was Salmonella typhi (33.5%). In two cases bacterial growth in BMCs and BCs were comparable (Table 3).

Table 1. Age distribution of patients with FUO

Age group (years)	No. of cases	%
1-14	6	10.5
15-44	32	56
45-64	9	16
>65	10	17.5
Total	**57**	**100**

Table 2. Distribution of duration of fever in patients with FUO

Duration of fever (days)	No. of cases	%
21-30	43	75.44
31-60	5	8.77
61-90	6	10.5
91-180	1	1.75
181-365	2	3.5
Total	**57**	**100**

Table 3. Result of bone marrow culture

S.N.	Age (year)	Sex	Organisms isolated in BMCs	Organism isolated in corresponding BCs
1	37	F	*Escherichia coli*	No growth
2	27	F	*Staphylococcus aureus*	No growth
3	20	F	*Non fermenting Gram negative bacilli*	No growth
4	76	F	*Salmonella typhi*	No growth
5	15	M	*Staphylococcus aureus*	No growth
6	38	M	*Salmonella typhi*	No growth
7	12	F	*Enterococcus sps.*	*Salmonella typhi*
8	23	M	*Salmonella para typhi-A*	*Salmonella paratyphi -A*
9	5	F	*Salmonella typhi*	*Salmonella typhi*

Table 4. **Frequency of various organisms isolated in bone marrow culture**

Organisms	No. of cases	%
Salmonella typhi	3	33.5
Staphylococcus aureus	2	22.5
Escherichia coli	1	11
Salmonella paratyphi-A	1	11
Enterococcus sps	1	11
Non fermenting GNB	1	11
Total	**9**	**100**

Table 5. **Comparison of 5 studies evaluating detection of organism by bone marrow culture in patients with FUO**

Studies	No. of cultures	No. (%) of specimens with positive BMC
Volk et al[3]	215	1 (0.5)
Marsh et al[13]	124	4 (3.2)
Riley et al[14]	433	51 (11.8)
Nicholas et al[15]	342	59 (17.3)
Present study	57	9 (15.78)

DISCUSSION

Diagnosis of FUO requires multidisciplinary approach including clinical history. History of travel in recent past and drug history is of great importance. Bone marrow examination in FUO is an important diagnostic modality. In present study BMCs alone yielded accurate diagnosis in 15.78% of cases. 15.78% (nine cases) of BMCs and only 5.26% (three cases) of BCs showed bacterial growth (Table 3). BCs did not reveal bacterial growth in isolation without BMCs revealing bacterial growth. Except in one case out of nine cases, BMCs alone were sufficient for the diagnosis without any role of BCs. In that one case BC revealed growth of Salmonella typhi; BMC in this case revealed growth of Enterococcus species the clinical significance of which is doubtful as patient responded to treatment for salmonella infection, although Enterococcus species is known to cause septicemia and infective endocarditis, and the ubiquitous nature of this organism requires caution in establishing the clinical significance.[7] In one case BMC exhibited growth of non-fermenting gram negative bacilli which was not further classifiable. In this study salmonella was the commonest isolate in the BMCs, Salmonella typhi and Salmonella paratyphi-A together constituted 44.44 % of total positive bone marrow bacterial culture (Table 4). If one case of positive blood culture for Salmonella typhi is considered, enteric fever alone constituted 55.55% of total infections and 8.77% of cases of FUO. There was no mycobacterial and fungal growth in any of the cases.

In a study by Haq et al, infectious disease accounted for 63.21% of cases of FUO. Tuberculosis was the commonest accounting for 24.53%, followed by enteric fever (12.74%) and visceral leishmaniasis (9.43%).[8] In a study by Jung et al, commonest cause of FUO was infections (46.4%) and enteric fever was the commonest (29.6%) among that followed by malaria (9%), and tuberculosis (5.2%).[9] But these studies were not based only on BMCs and BCs, as in the present study. Nonetheless in this study enteric fever was the commonest cause of infection related FUO.[9]

In a study by Farooqui and colleague organism was isolated from the bone marrow in all the cases of salmonella infection and from blood in only 66% cases. In the same study further subtyping of the Salmonella species showed Salmonella typhi 83%, Salmonella paratyphi-A 11.8%, Salmonella paratyphi-B 4.1% and Salmonella paratyphi-C 0.9%.[4] In present study Salmonella typhi accounted for 80% and Salmonella paratyphi-A accounted for 20% of total salmonella infections (Table 3 and 4). Out of five cases of salmonella infection four cases (80%) showed positive BMCs while two cases (40%) showed growth in BCs as well. In one case (20%) growth was seen only in BC. Findings in this study are in accordance to study of Farooqui and colleague. BMCs could confirm a diagnosis of enteric fever in patients with negative BCs.[4] One of the reasons for BCs being negative and BMCs being positive in enteric fever may be antibiotic treatment before collection of blood for culture. An injudicious antibiotic regimen may diminish or eliminate the organism from blood, but salmonella being an intracellular organism, persists in the reticulo-endothelial system including bone marrow.[10] The intracellular location of bacteria protects them from conventional chemotherapeutic measures.[11,12] Enteric fever is the only bacterial infection in humans for which bone marrow examination is recommended.[5] In a study by John et al, the number of bacteria in blood but not bone marrow was correlated inversely with the duration of preceding fever.[5] Thus, with increasing duration of illness the ratio of bone marrow to blood bacterial concentrations increased; the median ratio was 4.8 during the first week compared with 158 during the third week. This study provided proof that the concentrations of Salmonella typhi in bone marrow are higher than in blood. Bone marrow contained over 10 times more bacteria than blood.[5] Effective antibiotic pre-treatment had greater effect in reducing blood counts of bacteria compared to bone marrow count.[5] How salmonella survives in the bone marrow despite the presence of high concentrations of bactericidal antibiotic which reaches high intracellular concentration is unclear.

In a study by Volk et al only 0.5% of BMCs and corresponding BCs in the patients with FUO showed clinically significant growth in an immunocompromised patient and the organism isolated was Mycobacterium avium intracellularae.[3] In contrast present study showed 15.78% of growth in BMCs. A summary of diagnostic yield of BMCs in five studies is shown in table 5. A population characteristic of Volk et al was non-restricted while a population characteristic of Marsh et al, Riley et al and Nicholas et al was HIV patients.[3, 13-15] In present study the isolates were bacteria but in other four studies the isolate was Mycobacterium avium intracellularae.

Yield of BMCs in present study was 32 times better (15.78% versus 0.5%) than the other study (Volk et al). In absence of hematological justification for bone marrow evaluation, BMCs and BCs in a work up of patient significantly increase the cost. It is difficult to justify performing BMCs on all patients with FUO. Neither BMCs nor the BCs will detect the causes of all systemic infections; an algorithm that conserves resources should be followed in which BMCs are performed if the BCs and other easily obtained tissues have been cultured, and the results are repeatedly inconclusive.

CONCLUSIONS

A bone marrow examination including BMCs is important part of investigation of FUO, but this alone is insufficient to trace specific etiology in all the cases. A good clinical history, radiological and hematological evaluation including bone marrow coupled with BMC and serology would yield diagnosis in a high proportion of cases. Yield of BMCs is more than BCs especially in cases of suspected salmonella infection and in patients treated with antibiotics as was the case in present study; however, its role is insignificant in isolating mycobacteria or fungi in immuno-competent patients.

REFERENCES

1. Arnow PM, Flaherty J P. Fever of Unknown Origin. The Lancet. 1997;350:575-80.
2. Knockaert Daniel C, Vanneste LJ, Bobbaers HJ. Recurrent or Episodic Fever of Unknown origin. Review of 45 cases and Survey of the Literature. Medicine. 1993;72:184-96.
3. Volk EE, Miller ML, Kirkley BA, Washington JA. The diagnostic usefulness of bone marrow cultures in patients with Fever of Unknown Origin. Am J clin Pathol. 1998;110:150-3.
4. Farooqui BJ, Khursid M, Ashfaq MK, Khan MA. Comparative yield of Salmonella typhi from blood and bone marrow cultures in patients with Fever of Unknown origin. J Clin Pathol. 1991;44:258-9.
5. Wain J, Bay PVB, Vinh H, et al. Quantization of bacteria in bone marrow from patients with typhoid fever: Relationship between counts and clinical features. J Clin Microbiology. 2001;39:1571-6.
6. Petersdorf RG, Beeson PB. Fever of Unknown origin: report on 100 cases. Medicine. 1961;40:1-30.
7. Facklam RR, Teixeira LM. Enterococcus. In: Balows A, Duerden BI. editors. Systemic Microbiology. Vol 2. In: Leslie C, Albert B, Max S. Topley & Wilson's Microbiology and Microbial infections. 9th ed. London: Arnold publication; 1998. P. 669-82.
8. Haq SA, Alam MN, Hossain SM, et al. A study of prolonged pyrexia in Dhaka. Bangladesh Med Res Counc Bull. 1996;22:33-42.
9. Jung A, Singh MM, Jajoo U. Unexplained fever-analysis of 233 cases in a referral hospital. Indian J Med Sci. 1999;53:535-44.
10. Suter E. Interaction between phagocytes and pathogenic microorganisms. Bacteriol Rev. 1956;20:94-132.
11. Mandell GL. Interaction of intraleukocytic bacteria and antibiotics. J Clin Invest. 1973;52:673-9.
12. Holmes B, Quie PG, Windhorst DP, Pollara B, Good RA. Protection of phagocytozed bacteria from killing action of antibiotics. Nature. 1966;210:1131-2.
13. Marsh RD, Paul M, Siddique T, et al. Bone marrow culture for diagnosis of mycobacterial and fungal infections in febrile patients. J Fla Med Assoc. 1991;78:357-60.
14. Riley UBG, Crawford S, Barrett SP, et al. Detection of myocbacterial in bone marrow biopsy specimens taken to investigate pyrexia of unknown origin. J Clin Pathol. 1995;48:706-9.
15. Nicholas L, Florentine B, Lewis W, et al. Bone marrow examination for the diagnosis of mycobacterial and fungal infections in the acquired immunodeficiency syndrome. Arch Pathol Lab med. 1991;115:1125-32.