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Original Article

Utility of bone marrow examination (BME) in the diagnosis of pyrexia of unknown origin (PUO)

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Abstract

Introduction: Bone marrow examination (BME) is a useful tool in the diagnosis of haematological and non-haematological diseases. It plays an important role in early diagnosis of the underlying cause of pyrexia of unknown origin (PUO) and can influence the management of patients. Bone marrow aspiration (BMA) plays a very important role in establishing a definitive diagnosis in cases of PUO. The aim of this study was to review the indications and usefulness of bone marrow aspirates sent for microbiological evaluation as a diagnostic tool with histopathological correlation.

Methodology: A prospective study was conducted from 1 January 2017 to 30 September 2019 in the Department of Microbiology and Pathology on the bone marrow aspirates of patients of all groups.

Results: A total of 148 bone marrow aspirates were included. The cases were categorized as classical PUO (n = 81/148, 54.7%), nosocomial PUO (n = 4 /148, 2.7%), neutropenic PUO (n = 18/148, 12.1%), and immunocompromised PUO (n = 45/148, 30.4%), among which were systemic lupus erythematosus cases n = 8/45 (22.2%), human immunodeficiency virus positive cases n = 10/45 (17.7%), and renal transplant cases n = 27/45 (60%). A total of 28 BMAs were positive for microorganisms, out of which bacterial pathogens were n = 12 (42.8%), mycobacterial n = 12, 42.8%, fungal (n = 3, 10.7 %), and viruses (n = 1, 3.5%).

Conclusions: This study helped in highlighting the role of bone marrow examination as an important diagnostic method in the diagnosis of infectious diseases.

Key words: pyrexia; granuloma; immunocompromised; bacterial; mycobacterial.

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Introduction

Bone marrow examination (BME) is a diagnostic tool for haematological and non-haematological diseases and uses two types of methods: bone marrow aspiration (BMA) and bone marrow biopsy (BMB). It plays an important role in the early diagnosis of the underlying cause of pyrexia of unknown origin (PUO) as the pathogens may be present within the marrow [1]. PUO refers to cases with prolonged fever, the cause of which cannot be ascertained despite all diagnostic investigations. PUO often presents a diagnostic challenge in clinical practice. The differential diagnosis is extensive, spanning all specialties of medicine, including infectious disease, rheumatology, oncology, haematology, endocrinology, and psychiatry.

The causes of PUO can be of four types: infective, inflammatory, neoplastic and miscellaneous. The four categories of potential etiology of PUO are classic, nosocomial, immune deficient, and human immunodeficiency virus (HIV)–related. Classic PUO is defined as fever of more than 38 °C for more than 3 weeks duration and following evaluation for at least 3 outpatient visits. The most common causes of classic PUO are infections, malignancy or collagen vascular diseases. Nosocomial PUO is diagnosed when the patient does not have incubating fever upon admission but develops fever after 24 hours of admission and the fever continues for more than 3 days. The most likely causes of nosocomial fever are *Clostridium difficile enterocolitis*, drug-induced, pulmonary embolism, septic thrombophlebitis, and sinusitis. Immune deficient PUO is defined as fever of more than 3 days in neutropenic patients mostly due to opportunistic bacterial, fungal or viral causes whereas HIV associated

PUO is defined as fever of more than 4 weeks in outpatients or more than 3 days in inpatients in HIV-confirmed cases. The most common cause of HIV associated PUO are Cytomegalovirus, *Mycobacterium avium* intracellulare complex, *Pneumocystis carinii* pneumonia, drug-induced, Kaposi's sarcoma, and lymphoma [8]. Since infection is the major cause of PUO, the yield from bone marrow cultures remains high in developing countries like India [2].

BME is one of the common tests recommended in the diagnosis of PUO, collagen vascular disorders, post renal transplants, and HIV along with other diagnostic methods such as radiological, serological and microbiological tests. It is a relatively safe procedure which can be performed on outpatients [3].

BME is an important investigation in patients with infective fever of unknown origin with or without cytopenia, particularly in subjects with negative blood cultures. The yield is higher in bone marrow cultures than blood cultures as the concentration of organisms is 10 times higher in bone marrow than in blood and the count of viable organisms in the bone marrow are less affected by antibiotics [1].

BME may either confirm clinically suspected disease or may provide previously unsuspected diagnosis. Bone marrow granuloma (BMG) is not a frequent finding in a BMB. The incidence ranges from 0.3% to 2.2%. The etiologies of BMG are numerous, ranging from infections to inflammatory disorders, hematolymphoid neoplasms, and tuberculosis. Tuberculosis is the commonest etiology of BMG in India [1,2]. A variety of other morphological changes in the bone marrow have been described in various infectious and systemic diseases resulting in PUO. These changes may be features of acute inflammation (interstitial oedema, vascular congestion, haemorrhage, ischemic necrosis or suppurative necrosis) or chronic inflammation with granuloma formation, reactive lymphoid hyperplasia, plasmacytosis, histiocytosis or fibrosis. BMB is useful in the investigation of PUO as it leads to an etiological diagnosis in most cases [4]. BMA leads to a specific diagnosis, guides specific treatment, prevents potentially ineffective or harmful treatment, and provides important prognostic information [5]. BMB is a rapid test for clinical decision making in suspected cases of mycobacterial infection or hematological malignant diseases [2]. BME is considered positive if diagnostic findings are reported by histopathological evaluation (HPE) or if microbiological evaluation yield evidence of specific infection [2].

The old definition of PUO which was proposed by Petersdorf and Beeson nearly 6 decades ago to gain broad acceptance was “fever higher than 38.3 °C (100.9 °F) on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week’s investigation in hospital” [6]. With subsequent advancements in medical care, Durack and Street [10] proposed a revised definition in 1991 for classical PUO to include a provision for patients with an uncertain diagnosis despite 3 days in the hospital or 3 outpatient visits. They also outlined 3 additional groups of PUO: nosocomial (health care–associated), neutropenic (immune-deficient), and HIV related [7,8].

As the yield of BME in the diagnosis of infections has not been extensively studied, a prospective study was undertaken to find the utility of BME in the diagnosis of microbiological infections. The objectives of this study were to review the indications for microbiological evaluation of BMA; to assess the usefulness of BMA analysis as a diagnostic tool; and to correlate the microbiology results with the findings of BMB.

Methodology

This was a prospective study conducted from 1 January 2017 to 30 September 2019 (2 years and 9 months) in the Department of Microbiology and Pathology on bone marrow aspirates received from various clinical departments from patients of all age groups. The clinical details of these patients were collected as soon as the samples were received in the Microbiology laboratory from diagnosed cases of PUO. All the BMA received in the department with a diagnosis of PUO were included in the study. All the cases with insufficient samples were excluded from the study. All the samples received were reviewed, classified and analysed based on PeterDorfs criteria and modified according to Durack and Streets criteria [8]. The patients were classified as having classic, nosocomial, neutropenic or immunocompromised PUO based on the time course of disease and number of investigation days, presence of fever upon hospital admission, presence of neutropenia and associated comorbid conditions (HIV, Systemic Lupus Erythematosus, post-transplant).

All the isolates were diagnosed by standard methods. BME was considered positive if diagnostic findings were reported upon histopathological evaluation or microbiological evaluation yielded evidence of specific infection. The diagnostic yield of BME was the proportion of total bone marrow cultures

and biopsy samples showing specific diagnostic findings.

Microbiological and pathological workup

All the BMAs were stained by using special stains such as Geimsa stain for intracellular bacteria, Ziehl Neelsen stain for acid fast bacilli, auramine rhodamine stain for immunofluorescent bacilli of *Mycobacterium tuberculosis* and Grocotts Gomoris methenamine silver (GMS) stain for fungal elements. HPE on the BMB specimens was done in the Department of Pathology and was reviewed for granuloma formation.

BMA and blood cultures were inoculated into BacT/ALERT bottles (bioMérieux, Marcy L'Etoile, France) and loaded into the BACT/ALERT system (bioMérieux, Marcy L'Etoile, France) for isolation of bacterial pathogens. The cultures that were flagged positive were inoculated onto 5% sheep blood agar and chrome agar medium and incubated at 37 °C for 48 hours until growth was observed. Blind subcultures of all the blood culture bottles were done on 5% sheep blood agar after the 5th day for the isolation of *Salmonella* spp and *Cryptococcus* spp, and also for slow and fastidious organisms like *Brucella* spp. All the plates were incubated under a CO_2 pouch for a maximum for a duration of 21 days.

In order to isolate mycobacteria, BMA was inoculated into distilled water (DW) and then into Lowenstein Jensens medium (LJ) and BacT/ALERT bottle and incubated at 37 °C until growth was observed or for a maximum duration of 8 weeks before being designated as negative. Fungal pathogens were isolated by inoculating BMA into Sabourauds dextrose agar (SDA) medium with chloramphenicol, with and without cycloheximide and was incubated at 25 °C and 37 °C for the isolation of dimorphic fungi for a duration of 4 weeks.

We considered any collection of epithelioid histiocytes as granuloma or well-formed granuloma with caseation necrosis.

Results

A total of 148 bone marrow aspirates were included in the study. Clinical indications were categorized as classical PUO (n = 81/148, 54.7%), nosocomial PUO (n = 4/148, 2.7%), neutropenic PUO (n = 18/148, 12.1%), and immunocompromised PUO (n = 45/148, 30.4%), among which SLE cases were n = 8/45 (17.7%), HIV were n = 10/45 (22.2%), and renal transplant cases were n = 27/45 (60%) (Table 1).

Males were predominant (88, 59.4%) than females (60, 40.5%) with age ranging from 16 to 80 years. Majority of the patients (74%) were in the age group of 16-49 years. All the patients had a history of prolonged fever with the mean duration of fever before hospitalization of 26 ± 4 days. Duration of fever ranged from 21-365 days (Table 2). In majority of the cases, fever ranged between 21-90 days. There was history of weight loss in majority of the cases and history of diarrhoea, hepatosplenomegaly, lymphadenopathy and anemia were observed in few cases of PUO.

A total of 28 BMAs were positive out of which 12 (n = 12, 42.8%) were bacterial pathogens (Table 3). Among them, 11/12 (39.28%) were positive based on BMA and 1/12 (3.5%) were positive based on serology (+BMB). Out of 12 (n = 12, 42.8%) mycobacterial samples, 6/12 were positive based on BMA and 6/12 were positive based on BMB and computed tomography (CT) imaging. There were 3 (n = 3, 10.7%) fungal samples and 1 (n = 1, 3.5%) virus samples. BMB findings of BMAs were correlated with serological and imaging findings wherever available.

BMAs in 8/12 (66.66%) cases showed bacterial growth and the corresponding blood cultures also had bacterial growth. In 3/12 (25%) cases there was growth only in BMAs and no growth in blood cultures, thus highlighting the importance of bone marrow cultures in cases where alternate diagnostic methods have not identified a reason for PUO. 1/12 (8.3%) case had no growth in bone marrow culture and only blood cultures had growth of methicillin sensitive *Staphylococcus aureus* (MSSA) (Table 3).

Table 1. Distribution of cases based on types of PUO (n = 148).

Types of PUO	n (%)
Classical	81 (54.7)
Nosocomial	4 (2.7)
Neutropenic	18 (12.2)
Immunocompromised	45 (30.4)
SLE with PUO	10 (22.2)
Renal Transplant/Pancytopenia with PUO	27 (18.2)
RVD with PUO	8 (17.7)

PUO: pyrexia of unknown origin; SLE: systemic lupus erythematosus; RVD: retro viral disease.

Table 2. Duration of fever in cases of PUO (n = 148).

Type of PUO	Duration of fever (days)
Classical	28-60
Nosocomial	4-21
Neutropenic	3-60
Immunocompromised	
SLE	30-60
RVD	30-60
Renal transplant/Pancytopenia	28-60

PUO: pyrexia of unknown origin; SLE: systemic lupus erythematosus; RVD: retro viral disease.

Table 3. Bacterial pathogens isolated from bone marrow aspirates (BMA) (n = 11).

S. no	Diagnosis	Organism from BMA	Organism from blood cultures
1	Post Renal Tx	*K. pneumoniae MDR*	*K. pneumoniae MDR*
2	PUO	*B. cepaciae*	*No growth*
3	PUO	*E. cloacae*	*No growth*
4	FN with PUO	*E. cloacae MDR*	*E. cloacae MDR*
5	FN with PUO	*A. baumannii HRI*	*A. baumannii HRI*
6	PUO	*E. faecalis*	*E. faecalis*
7	PUO	*No growth*	*MSSA*
8	PUO	*Pandorea spp*	*Pandorea spp*
9	Tx failure	*P. aeruginosa MDR*	*P. aeruginosa MDR*
10	PUO	*E. coli MDR*	*No growth*
11	PUO	*E. coli ESBL*	*E. coli ESBL*
12	PUO	*K. peumoniae*	*K. pneumoniae*

Tx: transplant; *K. pneumoniae: Klebsiella pneumoniae;* MDR: multi drug resistant; PUO: pyrexia of unknown origin; *B. cepaciae: Burkholderia cepaciae; E. cloacae: Enterobacter cloacae;* FN: febrile neutropenia; *A. baumannii: Acinetobacter baumannii; HRI: highly resistant isolate; E. faecalis: Enterococcus faecalis;* MSSA: methicillin sensitive *Staphylococcus aureus; E. coli: Escherichia coli;* ESBL: extended spectrum beta lactamases.

Table 4. Culture positive cases of *Mycobacterium tuberculosis* from BMA (n = 6).

S. no	Diagnosis	Auramine Rhodamine	TB culture by LJ (weeks)	By 3D liquid medium (weeks)	BMA findings	HPE /BMB findings	Final diagnosis
1	RVD	negative	4	4	*M. tb*	Granuloma	Tuberculosis
2	Post Renal Tx	positive	5	2	*M. tb*	Granuloma	Tuberculosis
3	Pancytopenia in Tx	negative	3	3	*M. tb*	Granuloma	Tuberculosis
4	SLE	negative	5	4	*M. tb*	Granuloma	Tuberculosis
5	Post Renal Tx	negative	5	5	*M. tb*	Granuloma	Tuberculosis
6	Post Renal Tx	negative	6	5	*M. tb*	Granuloma	Tuberculosis

RVD: retro viral disease; Tx: transplant; TB culture: tuberculosis culture; LJ medium: Lowenstein Jenson medium; *M. tb: Mycobacterium tuberculosis,* BMA: bone marrow aspirate; HPE: histopathological examination; BMB: bone marrow biopsy.

Table 5. *Mycobacterium tuberculosis* cases through BMB and CT imaging findings (n = 6).

S. no	Diagnosis (n = 6)	BMB findings	CT imaging
1	RVD with Kochs (1)	Granulomatous inflammation	TB etiology
2	Post Renal Tx (2)	Granuloma	TB etiology
3	SLE (2)	Granuloma	TB etiology
4	PUO (1)	Granuloma	TB etiology

BMB: bone marrow biopsy; CT: computerized tomography; RVD: retro viral disease; Tx: transplant; SLE: systemic lupus erythematosus; PUO: pyrexia of unkown origin; TB: tuberculosis.

Table 6. Fungal pathogens isolated from BMA (n = 3).

S. no	Diagnosis	Organism from BMA	Organism from blood cultures	Final diagnosis
1	RVD	*C.neoformans*	*C.neoformans* (positive by HPE)	Cryptococcosis
2	Febrile neutropenia	*C.tropicalis*	*C.tropicalis*	Candidiasis
3	SLE	*C.guillermondi*	*C.guillermondii*	Candidiasis

BMA: bone marrow aspirate; RVD: retro viral disease; SLE: systemic lupus erythematosus; HPE: histo pathological examination; *C. neoformans: Cryptococcus neoformans*; *C. tropicalis: Candida tropicalis*; *C. guillermondi: Candida guillermondi.*

Table 7. Correlation of serological test results with BMB findings (n = 2).

S. no	Diagnostic test	Initial diagnosis	Positive by serology	BMB findings	Final diagnosis
2	Widal test	PUO	1	1 (Erythrophagocytosis) reactive marrow suggestive of typhoid	*Typhoid*
5	Parvovirus IgM positive	Post Renal Tx	1	1 (Erythroid hypoplasia with viral inclusions in erythroid precursors possibly parvovirus)	*Parvovirus*

BMB: bone marrow biopsy; PUO: pyrexia of unknown origin; Tx: transplant.

Out of 12 cases of *M. tuberculosis*, a total of 6 BMA cases that tested positive were also diagnosed by BMB (Table 4). Among these, 1/6 cases had both granuloma and acid-fast staining bacteria in the BMB specimens. In 3 cases, *Mycobacterium tuberculosis* bacilli was isolated from the liquid medium within 2 weeks, and in 2 cases MTB was isolated from solid medium within 5 weeks. In 6/12 cases, BMB showed tuberculous granulomas and were concordant with CT-imaging findings (Table 5).

Fungal cultures were diagnostic in 3/3 cases of BMA and BMB, and *Candida tropicalis*, *Candida guillermondi* and *Cryptococcus neoformans* were isolated (Table 6).

One (1/160) case showed diagnostic titres for *Salmonella* by Widal test where it correlated with BMB findings. One case of parvovirus diagnosed serologically was concordant with BMB findings (Table 7). A definitive diagnosis could be achieved in 28/148 (18.91%) cases who had infectious etiology (Table 8).

Discussion

BMA and BMB are used commonly in clinical practice to diagnose invasive tissue infections such as mycobacterial and fungal infections. BMA are helpful in diagnosing bacterial, fungal and tuberculous infections.

PUO was the most common (54.7%) presentation among our cases. In previous studies, infectious diseases accounted for 63.2% cases of PUO [3]. Kumar *et al*. showed 42 (76%) cases of adults and 13 (24%) of children and the mean age of presentation was 32.3 years (range, 1-72 years) [4]. The male to female ratio in their study was 2.2:1. The present study also showed male predominance. There were 88 males (59.4%) and 60 females (40.5 %) with age ranging from 16 to 80 years. Majority of the patients (74%) were in the age group of 16-49 years and there were no cases documented within the pediatric age group in the present study.

Datta *et al.* showed no yield of bone marrow cultures (aerobic, mycobacterial, and fungal) except for one patient with HIV infection who had positive bone marrow fungal culture (*Rhodotorula*) [2]. In our study we isolated 11 bacterial, 12 mycobacterial, and 3 fungal cases.

A study by Kumar *et al*. that included 55 cases, reported 35% infections caused by leishmaniasis, 29% by HIV and 15% by tuberculosis [4]. Other etiological agents included fungal infections (histoplasmosis and aspergillosis), enteric fever, scrub typhus, parvovirus, falciparum malaria and filariasis. In the present study a total of 28 BMAs were positive, out of which 11 (35.4%) were bacterial pathogens, 12 (38.7%) were mycobacterial pathogens, 3 (10.5%) were fungal pathogens, and 1 (3.5%) were viruses. There were no parasites detected from the BMA but fungal pathogens *Cryptococcus neoformans* (n = 1) and *Candida tropicalis* (n = 1) and *C. guillermondi* (n = 1) were detected.

In another study, the most common clinical presentation was fever (80%) and the most common clinical finding was splenomegaly (66%) which was similar to the present study with a median duration of 26 + 4 days in all the types of PUO diagnosed [4]. In the present study, the clinical presentation of all the classical cases with PUO had high grade fever.

Mycobacterial bone marrow infection is the most common diagnosis established by BME performed for PUO. Transplant patients are immunosuppressed and are prone to develop infections like tuberculosis and the majority of these infections are a result of reactivation of dormant disease [4]. In the present study *Mycobacterium tuberculosis* was documented from 10 cases of transplant patients.

In a study of 69 patients, it was reported that 1 patient had infection due to *Mycobacterium tuberculosis* and 2 patients showed non-tuberculosis mycobacteria such as *Mycobacterium avium* or *Mycobacterium kansasii* which was high when compared with the present study and there was no case of non-tuberculous *Mycobacteria* documented in this study [9]. In another study, 9 patients were positive for HIV [10] and the present study showed 10 cases of HIV (17.7%). In the present study there were 12 (38.7%)

Table 8. Total infectious etiological agents (n = 28).

Types of infectious etiological agents	BMA culture/BMB /serology/CT imaging	Number	Percentage
Bacteria	BMA culture	11	39.28
M. tuberculosis	BMA culture	6	21.4
	BMB + CT imaging	6	21.4
Fungi	BMA culture	3	10.7
Parvovirus B19	Serology + BMB	1	3.5
Typhoid	Serology + BMB	1	3.5
Total		28	

BMA: bone marrow aspirate; BMB: bone marrow biopsy; CT: computerized tomography; *M. tuberculosis: Mycobacterium tuberculosis.*

cases of mycobacterial infection. All the BMA from which *M. tuberculosis* was isolated, also had associated finding of granulomas from 5 cases as observed previously [4]. In a study by Nirvana *et al*. BMB findings showed *M. tuberculosis* in 17 out of 77 patients [11].

Previous studies have noted absence of acid-fast bacilli in 64% of marrow biopsies [12]. In the present study, there was only 1 case positive by acid fast staining. This is similar to findings observed by Gupta *et al.* [13]. Two of these cases were on prior empirical therapy with anti-tuberculosis treatment (ATT) which showed a good prognosis

It has been reported that fungi are very rarely seen in BMA, except in immunocompromised patients such as HIV or following BMT or cancer chemotherapy [14]. In a study by Vechi *et al*. [15], *C. neoformans* was isolated from a HIV infected patient. We also isolated *C. neoformans* from a retro viral disease (RVD) case.

In previous studies, fungal infections accounted for 4 cases (7%) of which 3 were histoplasmosis on BMA [4]. Similar findings were also observed in another study where fungal infections accounted for 5 cases of which 3 were histoplasmosis and 2 were caused by *Cryptococcus neoformans* [16]. In the present study fungal infections accounted for 3 cases and BMA was positive in 3 patients who had clinical acquired immune deficiency syndrome (AIDS), with one case of cryptococcosis and 2 cases of candidiasis caused by *C. tropicalis* and *C. guillermondi* which were disseminated infections. A similar finding was also observed in an advanced HIV patient with disseminated cryptococcocal disease [17].

In a study by Sampath *et al*. no organism could be isolated from BMCs except in the case of one patient where *Brucella* was isolated [1]. In the present study, microorganisms were isolated from 3/12 BMCs and there was no growth in blood cultures. Prior treatment with antibiotics may have been the cause for elimination of bacteria from the blood.

Jha *et al.* showed that BMCs in 9 (15.78%) out of 57 patients exhibited bacterial growth and in three cases (5.26%) corresponding blood cultures also exhibited bacterial growth [18]. In the present study, 8/12 cases which were positive by BMC also showed growth in corresponding blood cultures probably implying dissemination of infections.

In 3/12 cases only BMA showed growth. In 1 case we observed that BMC was negative and blood culture was positive with growth of methicillin sensitive *Staphylococcus aureus* (MSSA) where the pathogen was isolated from one set of peripheral line and one set of central line which was concluded as a central associated blood stream infection (CLABSI).

BMCs can be positive when blood cultures are negative [18]. The viable organism counts in the bone marrow is less affected by antibiotic treatment than blood counts [19]. The present study showed only 3 cases which had positive BMC but negative blood cultures.

In the study by Jha *et al.*, 6 cases showed growth only by BMC and had negative blood cultures, 2 cases showed similar growth in BMC and BCs, whereas two different pathogens were observed from BMC (*S. paratyphi*-A) and blood cultures (*Enterococcus faecalis*) [16].

In the present study 3 cases showed growth only by BMC and negative by blood cultures and 8 cases showed similar growth in BMC and BC and in the present study two different pathogens were not isolated from BMC and BC.

Jha *et al*. showed that *Salmonella typhi* was the most common organism isolated from BMCs (n = 3), followed by *Staphylococcus aureus* (n = 2), *Escherichia coli* (n = 1), non-fermenting Gram-negative bacilli (n = 1), *Enterococcus* species (n = 1), *Salmonella paratyphi*–A (n = 1), and *Salmonella typhi* (n = 2) [18]. The present study identified *Pseudomonas aeruginosa* (n = 1), and *E. cloacae* (n = 2) where 1 isolate was multidrug resistant (MDR) and another isolate was susceptible, *Escherichia coli* (n = 2) where 1 isolate was extended spectrum beta-lactamase producer (ESBL) and other isolate was multidrug resistant, *K. pneumoniae* MDR (n = 2), *Acinetobacter baumannii* MDR (n = 1), *Pandorea* spp (n = 1), *Burkholderia cepaciae* (n = 1) and *Enterococcus faecalis* (n = 1) in BMCs.

Previous studies have shown that BMCs appear superior to modern blood culture methods and yield a higher rate of positive cultures in the identification of typhoidal *Salmonella*, chronic *Brucella* infections partially treated brucellosis than peripheral blood [19]. The present study did not identify *Brucella* and *Salmonella* cultures from BMA or BCs. However, in 5 cases *Brucella* serology was diagnosed with significant titres of 1 in 640 only by serology and 1 case showed diagnostic titres for *Salmonella,* 1 in 160 by serology and correlated with BMB finding where there was a good response to antibiotics doxycycline and ceftriaxone in these patients.

BMC in association with bone marrow morphology would be more useful in suspected infectious etiology [18]. In the present study we observed that BMA and

BMB were useful investigations in diagnosing patients with tuberculosis, fungal and bacterial infections.

In a previous study, a cryptococcosis patient was managed by intravenous administration of amphotericin B, 0.6 mg/kg/day, and followed by tab Fluconazole 400 mg/day in divided doses and tuberculosis cases were treated with ATT similar to the present study [20].

Pande *et al*. showed that among the diseases diagnosed by BME, 5 (62.5%) were of infectious origin and 3 (37.5%) were of hematologic/neoplastic origin [21]. Among the infectious cases, *Mycobacterium tuberculosis* was responsible in 3 cases (60%), and *Histoplasma capsulatum* in 2 cases (40%). In the present study 38.7% of cases were diagnosed as tuberculosis

Out of 26 cases where BMBs were done, culture results were positive for 15/26 cases. 11/26 Bone marrow trephine biopsy (BMTB) specimens were negative. The BMB findings led to definitive diagnosis of infection whereas GMS staining could not identify any pathogen. Presence of granulomas did not contribute to the identification of the cause of a systemic infection, although it is well known that there is a strong correlation between the presence of bone marrow granulomas and systemic infection.

Conclusions

Conventional bone marrow investigations have a good diagnostic yield in PUO. More than one method contributed in diagnosing the infectious diseases in our study. Good clinical evaluation combined with relevant investigations and judicious use of invasive procedures can lead to a definitive diagnosis in most of the cases. An important observation made in our study was the high probability of having a positive bone marrow diagnostic finding in patients with tuberculosis and bacterial infections. This study highlighted the role of BME as an important diagnostic step for the etiological diagnosis of infectious diseases along with BMB findings. BMB can provide early diagnosis and better management of such cases.

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Authors' contributions

All the authors contributed extensively to the study in reviewing and analysis of the data.

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