Mycobacteremia in Patients with Disseminated and Extrapulmonary Tuberculosis

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ABSTRACT

Introduction: Myobacteremia is being increasingly recognized in patients with disseminated tuberculosis, however its value in establishing the diagnosis is uncertain. A prospective study designed to study the occurrence of mycobacteremia in patients with extrapulmonary and disseminated tuberculosis and to correlate the occurrence of mycobacteremia with HIV status of individual.

Material and methods: Seventy one patients with extra-pulmonary or disseminated tuberculosis were enrolled and apart from routine clinical evaluation necessary for establishing the diagnosis of tuberculosis, mycobacterial blood cultures were also taken. Rapid culture technique MB/Bact was used to evaluate mycobacteremia. The positive cultures were confirmed by using DNA probe methods. The positive cultures were identified using PCR for mycobacterium and sub cultured in the Lowenstein-Jenson media.

Results: Out of 71 patients mycobacteremia was present in 15.5% (11/71) of patients. Mycobateremia was more common in patients with HIV infection (p-value 0.02), Disseminated TB (p-value 0.045). In HIV positive patients there was also an association between low CD4 count and Mycobacteremia (p-value 0.014) Mycobacteremia was also associated with Mantoux non reactivity (p-value 0.002)

Conclusion: Mycobacteremia does occur in, patients with tuberculosis particularly in patients with HIV infection and disseminated tuberculosis. Patients with lower CD4 are more likely to show mycobacteremia.

Keywords: mycobacteremia, MB/Bact®, Disseminate tuberculosis, HIV

INTRODUCTION

Tuberculosis (TB) is a very important cause of morbidity and mortality, especially in developing countries.[1] The scenario is much worse when the Human Immunodeficiency Virus (HIV) pandemic is considered, with TB associated with AIDS/ HIV being 500 times more common than in general population.[2] Indian statistics reveal that amongst the 1.96 million reported cases of TB in 2007, 5.3% were HIV-positive with a significant mortality rate of 2.5 per 100,000 population/ year.[1]

HIV infected patients tuberculosis have atypical presentation; involving extra-pulmonary sites.[3,4] Disseminated tuberculosis (DTB) is fairly prevalent in HIV infected patients. DTB involves two or more non contagious organs, which may include cervical lymphadenopathy, blood, liver or bone marrow infected by tuberculosis. Diagnosis relies on one culture positive specimen, or histological / radiological evidence or strong clinical evidence consistent with active TB.[5-7] Immunosuppression puts the HIV population at risk for TB.[8] We can say that Disseminated tuberculosis is under-reported as extra-pulmonary sites are not routinely examined for TB. The data regarding exact incidence of disseminated tuberculosis is lacking. Disseminated tuberculosis and extrapulmonary tuberculosis like cervical lymphadenopathy is caused by hematogenous and / or lymphatic dissemination of *Mycobacterium tuberculosis*.[9] Granuloma formation in lung is not efficient in controlling the infection, especially in immunocompromised hosts and mycobacterium in these macrophages often undergo haematogenous and lymphatic dissemination.[10,11] Therefore, it is feasible to detect the mycobacteria in blood using more sensitive and faster diagnostic tools, such as automated culture methods.[12-22]

Prompt diagnosis is of paramount importance in cases of Tuberculosis as early treatment may decrease morbidity and mortality associated with it.[23,24] In pulmonary tuberculosis, sputum offers a convenient sample for smear examination for AFB and/or culture. However, in most cases of suspected disseminated or extrapulmonary tuberculosis, mycobacteria containing material is note easily obtainable for clinical testing. More invasive procedures like fine needle aspiration cytology (FNAC) or biopsy of the suspected site have to be performed for arriving at the diagnosis. In such cases blood culture for *Mycobacterium tuberculosis* bacteremia (mycobacteremia) may prove to be an easy way of diagnosing tuberculosis as well as looking for drug sensitivity. BACTEC system, MGlT (Mycobacteria growth indicator tube) and Septi-Chek are useful for rapid detection of bacterial growth. MB/Bact is the colorimetric method for the detection of bacterial growth.

With the epidemic of the AIDS and increased use of immunosuppressant drugs and availability of rapid culture techniques, mycobacteremia has now been documented more frequently and has become a useful tool for detection of disseminated *Mycobacterium avium-intracellulare complex* (MAC).[25-27] Bacteremia with *Mycobacterium tuberculosis* is also being increasingly reported, although less frequently than MAC, as a marker of disseminated mycobacterial infection in patients with AIDS.[28]

The present work was planned to study the occurrence of mycobacteremia in patients with disseminated tuberculosis with or without HIV infection using the rapid culture technique MB/Bact and to study the clinical correlates of mycobacteremia if any.

MATERIAL AND METHODS

This was a prospective study designed to study the occurrence

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of mycobacteremia in patients with extrapulmonary and disseminated tuberculosis and to correlate the occurrence of mycobacteremia with HIV status of individual. This pilot study included Seventy one consecutive patients of proven extrapulmonary and disseminated tuberculosis at Department of Medicine, All India Institute of Medical Sciences, New Delhi from July 2007 to May 2009.

Inclusion Criteria

- Patients with clinical / microbiological diagnosis of extrapulmonary and disseminated tuberculosis (as per the WHO criteria).[7]
- Patients who were more than 12 years of age.
- Patients who gave consent for study

Exclusion Criteria

- Patients who had received anti tubercular treatment (ATT) for 15 days or more

Case Definition

A. Extrapulmonary Tuberculosis (EPTB) refers to tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.[5-7]
Diagnosis was based on

1. one culture positive specimen, or
2. Histological and/or radiological evidence or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of ATT and therapeutic response to it.

B. Disseminated Tuberculosis refers to[5-7]
Involvement of two or more non contiguous organs. or
Involvement of bone marrow or blood or liver by tuberculosis.
Involvement by tuberculosis means either one culture positive specimen, or
histological / radiological evidence or strong clinical evidence consistent with active TB, followed by a decision by a clinician to treat with a full course of ATT and therapeutic response to it.

Patient Evaluation

Detailed history was taken. A complete general physical and systemic examination was performed. Complete hemogram, serum biochemistry, PPD intra dermal test, HIV serology and chest x ray was done for all the patients. CD4 count of all patients seropositive for HIV was done. Other imaging procedures such as USG abdomen, CECT chest, abdomen and head or MRI spine or brain etc were performed as per the clinical profile of the patients. Specimen such as sputum, gastric lavage, bronchoalveolar lavage, fine needle aspirate cytology/ biopsy specimen (Node, Liver, Spleen, Bone marrow, etc) and fluids (pleural, pericardial, ascitic) were examined as per the individual needs of the patients.

Sample Collection

From each patient, 10 ml of venous blood was collected under aseptic precautions. The sample was collected in tubes containing acid citrate dextrose. The samples were immediately transported to the laboratory where it was inoculated into the BACT/ALERT MB culture bottle which contains the growth supplements (figure-1).
BACT/ALERT MB culture bottles with addition of enrichment fluid and mycobacterial detection system is a non selective culture medium for the qualitative and recovery of the mycobacteria from blood. The system employs a colorimetric sensor, growth of microorganism produces carbon dioxide which changes the color of the gas permeable sensor at the bottom of the each culture bottle from blue-green to yellow. The lighter color results in an increase in reflectance units as monitored by the system. Bottle reflectance is monitored and recorded by the instrument every 10 minutes (figure-2).
The positive cultures were confirmed by using DNA probe methods. These bottles are kept in the system, which monitors the bottles every 1 hour. The positive cultures were identified using PCR for mycobacterium and sub cultured in the Lowenstein-Jenson medium for the identification of the species and the morphology. The cultures were incubated for 42 days until considered negative.

Data Collection

All the relevant clinical and laboratory data was recorded in the predetermined Proforma and transferred to Microsoft excel® worksheets. Patients were classified into subgroups according to their HIV seropositivity status and other clinical parameters.

STATISTICAL ANALYSIS

Figure-1: Photograph showing a fresh Bact/Alert MB® (MB/Bact®) culture bottle (Blue arrow) having blue base and other inoculated bottle that has flashed positive (yellow arrow) showing the change in the color of indicator to yellow.

Figure-2: Photograph showing the automated incubater used for MB/ Bact culture bottles with indicators showing culture bottles which have flashed positive (arrow)

The occurrence of Mycobacteremia was compared within subgroups using the Fischer's exact test for qualitative data in cases were numbers in any column were less than 5 and for rest χ^2 test was used and for quantitative data the Mann-Whitney Test for variables with large variance like TLC, platelet counts, ESR, creatinine, SGOT, SGPT, SAP for rest t-test was used.

RESULTS

Out of seventy one patients enrolled for study, mycobacterial blood culture using the MB/Bact method was found to be positive in 11 (15.5%) patients. Mycobacteremia was found to be significantly more common in HIV positive patients, being present in 28.5% (8/28) HIV positive patients as compared to 6.9% (3/43) in HIV negative patients (Table-1). The risk ratio with this association was found to be 4.1.

As shown in Table-2, the mean CD4 count in HIV positive patients with mycobacteremia was 69.6 ± 33.8 which was found to be significantly lower than the mean CD4 count in patients who did not have mycobacteremia.

On comparison of patients with CD4 counts ≤ 200 with patients having CD4 > 200 it was found that CD4 counts ≤ 200 was significantly associated with mycobacteremia with a P-value of 0.041. The risk ratio for this association was found to be 7.3. All 8 HIV positive patients with mycobacteremia had CD4 counts ≤ 200.

Mycobacteremia and Type of Tuberculosis

Out of total 46 patients who had disseminated tuberculosis mycobacteremia was present in 10 patients (21.7%) while out of 25 extrapulmonary tuberculosis patients only 1 had mycobacteremia (4%). This difference was statistically significant with P-value of 0.045 as shown in table-3.

Mycobacteremia and PPD Reactivity

PPD reactivity (Mantoux test positivity) was present in 85% (51 out of 60) of patients who did not have mycobacteremia as compared to only in 36.4% (4 out of 11) of patients who had mycobacteremia which was significantly lower (P-value 0.002). The mean diameter of induration was also significantly lower in patients with mycobacteremia (12.6mm vs. 6.9mm).

Mycobacteremia and Organ Involvement

Table-4 shows the association of involvement of different organs with the occurrence of mycobacteremia. Abdominal involvement was found to be significantly more common in patients having mycobacteremia as compared to patients without mycobacteremia (81% and 35% respectively) with P-value of 0.006. Peripheral lymphadenopathy was also more common in patients with mycobacteremia but the difference was not statistically significant.

DISCUSSION

With the epidemic of AIDS, mycobacteremia has been documented and has become a useful tool for detection of disseminated *Mycobacterium avium-intracellulare* complex MAC,[25-27]

Mycobacterium tuberculosis bacteremia (mycobacteremia) is also been increasingly reported, although less frequently than MAC, as a marker of disseminated mycobacterial infection in patients with AIDS.[28-39] Mycobacteremia has also been shown to occur in HIV negative individuals with tuberculosis especially disseminated tuberculosis.[35-39]

MB/Bact®	HIV -ve	HIV +ve	Total	P-value
Negative	40	20	60	0.020
Positive	3	8	11	
Total	43	28	71	Risk ratio = 4.1

Table-1: Mycobacteremia in HIV positive versus HIV negative patients

MB/Bact®	N	Mean	Std. Deviation	P-value
Negative	20	172.7	105.7	0.014
Positive	8	69.6	33.8	
Total	28	143.2	102.0	

Table-2: Comparison of CD4 counts in patients with or without mycobacteremia

MB/Bact®	EPTB	DTB	Total	P-value
Negative	24	36	60	0.045
Positive	1	10	11	
Total	25	46	71	Risk ratio = 5.4

Table-3: Mycobacteremia in DTB versus EPTB patients

Organ Involved	Mycobacteremia absent (n=60)	Mycobacteremia present (n=11)	P-Value
Lungs	25	7	0.204
Pleura	13	2	0.577
Mediastinum	19	6	0.133
Abdomen	21	9	0.006
Peripheral LN	20	7	0.090
CNS	9	0	0.337
Osteomyelitis	5	0	1.000
CVS	2	0	0.712
Bone Marrow	2	1	0.401
Miliary	7	3	0.180

Table-4: Association of organ involvement with mycobacteremia

Present study was undertaken to evaluate the occurrence of mycobacteremia in patients with single site extrapulmonary and disseminated tuberculosis using a newer blood culture method, the Bact/ALERT MB® or the MB/BACT (BioMérieux). The MB/BACT Mycobacterial Detection System, a fully automated method, is claimed to be a faster and more sensitive method than the conventional L-J medium for the detection of mycobacteremia.[12-22] For evaluation of mycobacteremia we have used a single blood culture, as there are studies which have shown that single blood culture is as effective as multiple blood cultures for detection of mycobacteremia.[35,40]

In our study 71 patients were included, out of which 28 were HIV positive and 43 were HIV negative. In HIV positive patients 78.6% (22/28) of patients had

disseminated tuberculosis and 21.4% (6/28) had extrapulmonary tuberculosis, while in HIV negative patients 65.8% (24/43) had disseminated tuberculosis.

CD4 Counts were done in HIV positive patients only. Mean CD4 count of HIV positive patients with disseminated tuberculosis was found to be significantly lower (112.9 ± 74.6) as compared to EPTB patients (254.3 ± 118.3) with P-value of 0.013. This is due to the fact that patients with lower CD4 are more likely to have disseminated tuberculosis.[41,42]

Mycobacteremia

Out of seventy one patients enrolled for our study,

mycobacteremia was found to be present in 15.5% (11/71) of patients. Proportion of patients having mycobacteremia was higher in patients admitted in wards (22.2%; 8/36) as compared to patients following up in OPD (8.6%; 3/35) but the difference was not statistically significant.

In HIV positive patients the incidence of mycobacteremia was 28.6 % (8/28) and in HIV negative patients it was 7% (3/43). The occurrence of mycobacteremia in our study is similar to most of the studies done for the evaluation of mycobacteremia in patients with HIV infection, except for the studies done by Ramachandran et al (4%)[28] and Grinsztejn[35] et al (60%) as shown in Table-5. The presence of mycobacteremia in these studies ranged from 25.9% to 30.8%. However, mycobacteremia in the studies done on HIV negative patients, is more variable, ranging from 0% to 11.1% as shown in Table 5. However, most of these studies had small numbers of HIV negative patients thus making the results difficult to compare.

Grinsztejn et al found mycobacteremia to be present in 60% (30/50) of HIV positive patients.[32] Mycobacteremia in HIV positive patients in our study was present in a considerably lower proportion of patients (28.6%). This is due to the fact that our study population consisted HIV positive patients with or without DTB whereas their study population consisted entirely of HIV positive patients with DTB. In our study also in the sub-group analysis of HIV positive patients with DTB, excluding patients with single site EPTB, mycobacteremia was present in 36.4% (8/22) of HIV positive patients with DTB, which is similar to the results of Grinsztejn et al.[32]

Ramachandran et al found mycobacteremia to be present in HIV positive patients in only 4% (4/85). This is significantly lower than the occurrence of mycobacteremia in our study (28.6%).[28] May be because their study population consisted mostly of patients with isolated pulmonary tuberculosis (85%) and only 15% of patients had associated extrapulmonary tuberculosis. It is known that mycobacteremia is a very infrequent occurrence in patients with PTB as was shown in the study by Shafer et al in which mycobacteremia occurred in only 5% (2/40) of PTB patients as compared to 38.8% (7/18) of patients with extrapulmonary and/ or disseminated tuberculosis.[34]

Mycobacteremia was also found to be more common in patients with disseminated tuberculosis as compared to patients with extrapulmonary tuberculosis. In patients with DTB mycobacteremia was present in 21.7% (10/46) patients while mycobacteremia was present in only 4% (1/25) of patients with single site EPTB (P-value = 0.045). Patients with DTB are more immunocompromised, especially deficient in cell mediated immunity which predisposes them to mycobacteremia.[41] This is evident from the fact that mean diameter of induration in Mantoux test results was found to be lesser patients with disseminated tuberculosis as compared to single site extrapulmonary tuberculosis (10.02 ± 7.06 and 14.72 ± 7.45 respectively; P-value 0.008).

Mycobacteremia and Tuberculin Reactivity

Reactivity to Purified protein derivative (PPD or tuberculin) was evaluated by Mantoux test using 5TU of PPD. Patients with mycobacteremia were found to be more likely to be non reactive to PPD as compared to patients without mycobacteremia (P-value = 0.002). Mantoux test was negative in 63.6% (7 out of 11) of patients who had mycobacteremia while it was negative only in 15% (9 out of 60) of patients who did not have mycobacteremia. The mean diameter of induration was also significantly lower in patients with mycobacteremia (12.6 mm vs. 6.9 mm).

Mycobacteremia and HIV

Mycobacteremia was found to be significantly more common in HIV positive patients, being present in 28.5% (8/28) HIV positive patients as compared to 6.9% (3/43) in HIV negative patients. The risk ratio of this association was found to be 4.1. Previous studies have also clearly shown HIV to be a strong predisposing factor for mycobacteremia. Shafer et al also found mycobacteremia to be present in 25.9% (7/27) of HIV positive patients while out of 17 HIV negative patients none had mycobacteremia. In a recent study done at AIIMS, New Delhi

Authors	Study Design	Culture Method	Patient Population	Mycobacteremia		
				DTB	HIV +VE	HIV -VE
Present study	Prospective	MB/BacT	All forms of TB	21.7% (10/46)	28.6 % (8/28)	7% (3/43)
Shafer et al[34]	Prospective	BACTEC 13A	Hospitalized, All forms of TB	83% (5/6)	25.9% (7/27)	0% (0/17)
David et al[38]	Prospective	L-J and Kirchner's medium	All forms of TB	-	26.1% (12/42)	7.8% (3/38)
Gopinath et al[39]	Prospective	MB/BacT	All forms of TB	-	30.8% (16/52)	11.1% (3/27)
Grinsztejn et al[35]	Prospective	Middlebrook 7H9 broth and L-J	Hospitalized, HIV +ve with DTB	60% (30/50)	60% (30/50)	-
Ramachandran et al[28]	Prospective	BACTEC	All forms of TB	-	4% (4/85)	0% (0/20)
Ruf et al[25]	Prospective	L-J medium	Hospitalized patients with AIDS	58.8% (20/34)	14.7% (20/136)	-
Bacha et al[33]	Prospective	MB/BacT and BACTEC	AIDS with persistent fever	-	30% (13/44)	-
Sungkanuparph et al[37]	Retrospective	MB/BacT	Patients with prolonged fever	-	29.2% (155/531)	6 % (7/117)

Table-5: Occurrence of mycobacteremia in various studies

by Gopinath et al found similar results with mycobacteremia being present in 30.8% (16/52) of HIV positive patients as while in only 11.1% (3/27) of HIV negative patients.[39]

Also the mean CD4 count in HIV positive patients with mycobacteremia was 69.6 ± 33.8, which was found to be significantly lower than the mean CD4 count in patients who did not have mycobacteremia (172.7 ± 105.7) with P-value of 0.014. The risk ratio for developing mycobacteremia in HIV positive patients with CD4 counts ≤ 200 was found to be 7.3 as compared to HIV positive patients with CD4 count > 200. These results are consistent with a previous study by Gopinath et al who found mean CD4 count in patients with mycobacteremia to be 173.63 ± 49.2, which was significantly lower than the CD4 count in patients not having mycobacteremia (274.1 ± 32.8) with a P-value of 0.043.[39] This association could be explained by the fact that lower CD4 counts are associated with an impairment of CMI due to decreased production of IFN-γ and other effector molecules.[10,11]

There are also certain limitations of the study. The small sample size may be inadequate to draw definite conclusions. No control population of patients without the diagnosis of tuberculosis was enrolled, so exact sensitivity of the test could not be calculated. However, it can reasonably be suggested that blood culture for mycobacteria may be used for diagnosis of tuberculosis in HIV positive patients who are likely to have a disseminated disease.

CONCLUSION

Mycobacteremia is not an infrequent occurrence in current clinical practice Mycobacteremia is common in HIV positive patients and can also be seen in HIV negative patients. It is strongly associated with HIV infection, low CD4 counts in HIV positive patients, negative Mantoux test and presence of disseminated tuberculosis. Detection of mycobacteremia provides with an additional armamentarium in the diagnostic tools for tuberculosis especially in the setting of disseminated TB or in patients with HIV-TB coinfection

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