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Detecting mycobacteraemia for diagnosing tuberculosis

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***Background & objectives*: In human immunodeficiency virus (HIV) infected persons with pulmonary tuberculosis (TB), sputum may not always show acid fast bacilli (AFB). Moreover, in most cases of suspected extrapulmonary TB (irrespective of HIV status) mycobacteria-containing material is not readily available for investigation. This study evaluated whether blood culture for *Mycobacterium tuberculosis* bacteraemia (mycobacteraemia) help in diagnosing TB in such cases.**

***Methods*: A total of 93 consecutive subjects with a clinical diagnosis of tuberculosis with or without laboratory confirmation, 42 with and 38 without coexisting HIV infection, and 13 patients with HIV infection without clinical evidence of TB were enrolled. Mycobacterial blood cultures were done using lysis centrifugation technique followed by subculturing onto the modified Lowenstein-Jenson medium (LJ-1) and Selective Kirchner's medium followed by subculturing onto the modified Lowenstein-Jenson medium (LJ-2, LJ-3).**

***Results*: Of the 15 (16.2%) subjects with evidence of mycobacteremia in 4 (26.7%) blood was the first/ only source of diagnosing TB. Among 80 patients with clinical diagnosis of TB whether supported by laboratory tests or not, 14 (17.5%) had mycobacteraemia. Among the 21 HIV infected patients with laboratory proven TB, 9 (43%) had mycobacteraemia.**

***Interpretation & conclusion*: Blood culture appears to be a useful additional test to diagnose TB in personss with HIV infection. In patients without HIV infection, but with clinical picture compatible with TB, blood culture for mycobacteraemia may occasionally help in the diagnosis. We recommend the use of the lysis centrifugation technique followed by direct smear of the sediment along with inoculation of the sediment into both modified Lowenstein-Jenson medium and the Selective Kirchner's medium with subsequent subculturing onto the modified Lowenstein-Jenson medium for mycobacterial blood culture for detecting mycobacteraemia.**

Key words Blood culture - HIV infection - mycobacteria - tuberculosis

Tuberculosis (TB) remains a leading cause of morbidity and mortality in developing countries with an estimated 14 million persons in India[1]. With the advent of the human immunodeficiency virus (HIV) pandemic, the problem of TB will get worse as has been seen already in developed countries[2]. The incidence of TB in patients with HIV infection/acquired immunodeficiency syndrome (AIDS) is nearly 500 times higher than in the general population[3]. Studies done at Vellore had shown that even in early years of the HIV epidemic in India, 52 to 65 per cent of symptomatic HIV infected persons had active TB[4,5]. Delay in the diagnosis of TB has adverse consequences for both the patients and their contacts[6,7]. If the patients remain untreated, the duration of illness is prolonged and there would be unnecessary cost of investigations and treatment for other suspected diseases. Therefore, early diagnosis of TB is essential.

In pulmonary TB, sputum offers a convenient sample for smear examination for acid fast bacilli (AFB) and/or culture. However, in HIV infected persons with pulmonary TB, a proportion of sputum samples do not

show AFB[3]. In HIV infected patients TB may frequently present in sites other than the lungs[4,5], lymphadenitis being the most common[2] but it may be in the bone, liver, or in almost any organ of the body. In most cases of suspected extrapulmonary TB (irrespective of HIV status) mycobacteria-containing material is not readily available for testing. In such cases blood culture for *Mycobacterium tuberculosis* bacteraemia (mycobacteraemia) could help in diagnosing TB.

Various studies have documented the presence of mycobacteraemia in patients with tuberculosis[8-17]. McDonald and colleagues[17] investigated 344 hospitalized febrile patients in Thailand and Malawi and detected mycobacteraemia in 34 (10%) patients. We conducted an open study to assess the frequency of mycobacteraemia in patients with or without confirmed TB. Many of them had HIV infection. A preliminary report of this study was published earlier[18]. In this study we describe the clinical and laboratory features of the patients with and without mycobacteraemia. An attempt was also made to compare Selective Kirchner's liquid medium[19] with the modified Lowenstein-Jenson (LJ)[20] slants for the detection of mycobacteraemia.

Material & Methods

This study was conducted during March 1994 to March 1995 in the departments of Medicine and Microbiology at the Christian Medical College Hospital, Vellore, Tamil Nadu. The 93 patients included 82 men and 11 women with a age range from 15 to 76 (mean±SD 35±16.0) yr. Among them, 59 had active TB, of whom 21 had and 38 did not have HIV infection. Another group of 21 patients with HIV infection had only clinical and radiological features suggestive of TB. The remaining 13 had HIV infection, but no sign/ symptom of TB. Thus 55 subjects were HIV-positive and 38 were HIV-negative. The study population of 93 consecutive patients had the following specific criteria, seen in the medical OPD, wards or the TB or HIV clinics: patients with confirmed active TB; those with clinical and radiological features of TB irrespective of HIV status; and, HIV infected and symptomatic patients without clinical features of TB. The study protocol was approved by the ethics committee of the hospital.

Active TB was diagnosed in a patient when sputum, gastric juice, lymph node, bone marrow or any other fluid/ tissue and positive for AFB by smear or for *M. tuberculosis* by culture or when lymph node biopsy showed granulomas with caseation necrosis and palisading epithelioid cells. Patients with history of prolonged fever, weight loss and/or cough, and radiological evidence suggestive of TB, were considered to have clinically diagnosed TB. HIV infection was detected by antibody testing using the ELISA technique. When reactive by the first ELISA (screening) Recombigen HIV EIA 1/2 (Cambridge Biotech, Maryland, USA), it was retested in duplicate using the same ELISA. If the sample was reactive in two wells it was tested on a second ELISA (supplementary) - ABBOTT HIV1/2 (Illinois, USA). The results were then confirmed by immunoblot–HIV Blot 2.2 (Genelabs Diagnostics, Singapore).

From each patient approximately 10 ml of venous blood was aseptically collected and transferred immediately into a 35ml centrifuge tube with 0.66 ml of an aqueous reagent containing 75 mg saponin and 6.3 mg sodium polyethanol sulphonate[21].

The tubes were centrifuged at 3000 *g* for 30 min and the supernatant was aseptically removed. Nearly half of the sediment was used to prepare a smear on a glass slide and stained with auramine O (SD Fine Chem, Mumbai) (direct smear) and examined under fluorescent microscope[20]. The remaining sediment was inoculated in two media, namely Selective Kirchner's medium (50 ml) and modified Lowenstein-Jenson medium (LJ-1) and incubated at 37ºC. The culture media were prepared in-house with requisite quality control, as described previously[19,20]. The Selective Kirchner's medium was sampled (after gentle agitation) at 2 and 4 wk. Each sample was used to prepare a smear and also to subculture onto modified Lowenstein-Jenson medium (referred to as LJ-2 and LJ-3, respectively). The smears were examined as stated above. After 5 wk of incubation a final smear was made from the Selective Kirchner's medium and if found negative, the culture was considered negative and discarded.

LJ-1, 2 and 3 were incubated for 8 wk and inspected every week for growth of colonies. If growth occurred, the presence of mycobacteria was confirmed by smear examination for acid fast bacilli using the Ziehl-Neelsen

staining and appropriate biochemical tests were used to distinguish between *M. tuberculosis* and atypical mycobacteria[20]. If after 8 wk there was no visible growth, they were considered negative and discarded.

Mycobacteraemia was defined as the presence of mycobacteria in the blood, detected in one or more of the test procedures, namely, (*i*) direct smear of the lysis-sediment showed mycobacteria; (*ii*) LJ-1 showed mycobacterial growth confirmed by Zeil-Neelsen staining and the standard biochemical test; (*iii*) Selective Kirchner's medium smear was positive for mycobacteria; and (*iv*) LJ-2 or LJ-3 showed evidence of mycobacterial growth confirmed by Zeil-Neelsen staining and the standard biochemical test.

Results

Overall 15 (16.2%) patients had mycobacteraemia (Table I). Their age ranged from 24 to 65 (mean ±SD 37.3±15.9 yr), with a male : female ratio of 14:1. The direct smear of sediment of the lysed and centrifuged blood was positive in 2 cases (13.3%). However, in only one of them the inoculated culture showed growth. The direct culture on LJ medium (LJ-1) was positive in 8 (53.3%) cases, whereas the Selective Kirchner's medium was positive in 11 (73.3%) cases (Table II). No atypical (non-tuberculous) mycobacteria were detected among the cultured organisms. The time taken to detect mycobacteraemia in LJ-1 was 15-26 (mean 22.3) days. In the group diagnosed by Selective Kirchner's medium the smear was auramine O positive in 5 cases (33.3%) with the detection time ranging from 20 to 51 (mean 33.4) days. In two cases this was the only evidence of mycobacteraemia as there was no growth on the LJ medium. In one of them there was fungal contamination and overgrowth making it impossible to detect bacterial growth. The subcultures LJ-2 and 3 showed *M. tuberculosis* in 9 (60%) cases. The detection time from the date of sub-culturing was 13 to 31 (mean 20.6) days for LJ-2 and 10 to 21 (mean 17) days for LJ-3. Thus, from the day the blood culture was drawn, the detection time for LJ-2 was a mean of 36.3 days and for LJ-3 a mean of 45 days. Using both direct culturing (LJ-1) and Selective Kirchner's medium followed by subculturing the mean detection time was 10 to 31 (mean 26.4) days.

The salient clinical features of the 15 patients with mycobacteraemia are summarized (Table III). Among the 3 HIV negative patients with active TB and mycobacteraemia, one each had TB lymphadenitis, abdominal and pulmonary TB, and bilateral pulmonary TB. None of them had any other underlying chronic disease detected. They were older (mean age 57 yr) as compared to the HIV positive TB patients (mean 39.6 yr). Among the 9 mycobacteraemic patients with HIV infection and laboratory evidence of TB, 4 had pulmonary TB (sputum or gastric juice AFB positive), 3 had TB lymphadenitis (biopsy proven) and one each had pancreatic TB (pancreatic abscess aspirate showed AFB) and disseminated TB (bone marrow aspirate showed AFB). Among the 21 HIV positive patients with clinically suspected TB and radiological features suggestive of TB only 2 (9.9%) had mycobacteraemia. One had right paratracheal thickening suggestive of lymphadenopathy while the other had dilatation of bronchi in the right lower lobe (suggestive of bronchieactasis) on chest X-ray. One

Table I. Mycobacteraemia in different groups of patients

Clinical profile (N)	No. (%) with mycobacteraemia
Patients with active TB and no evidence of HIV infection (38)	3 (7.8)
Patients with HIV infection and active tuberculosis (21)	9 (42.9)
Patients with HIV infection with clinico-radiological features of tuberculosis (21)	2 (9.5)
Patients with HIV infection and no signs or symptoms of tuberculosis (13)	1 (7.7)
Total (93)	15 (16.2)

Table II. Comparison of direct inoculation in Lowenstein-Jenson medium (LJ-1) with inoculation in Selective Kirchner's medium and subsequent detection by subculture on LJ medium

	Kirchner's medium positive	Kirchner's medium negative	Total
LJ-1 Culture positive	5	3	8
LJ-1 Culture negative	6	79*	85
Total	11	82	93

*One sample was direct smear positive, negative in culture

Table III. Clinical features of the 15 patients with mycobacteraemia

Sl. no.	Age (yr)	Sex	HIV status	Fever at the time of blood culture	Site of evidence of TB	Clinical features	Chest X-ray
1.	41	M	–	Absent	Lymph node	Relapse of TB following 18 months of anti TB therapy	Normal
2.	69	F	–	Absent	Abdominal, pulmonary	Abdominal and pulmonary TB	Normal
3.	76	M	–	Absent	Pulmonary	Pulmonary TB	Bilateral, extensive,infiltrative
4.	41	M	+	Present	Pulmonary	AIDS, Pulmonary TB, suspected LN TB	Bilateral, infiltrative
5.	25	M	+	Present	Pancreatic fluid	AIDS, pancreatic abscess, para-aortic lymph node, ?TB spine	Pleural effusion-unilateral, Right midzone patch
6.	36	M	+	Present	Bone marrow	AIDS, cerebellar dysfunction	Normal
7.	27	M	+	Present	Pulmonary	AIDS, pulmonary TB	Military pattern
8.	33	M	+	Absent	Pulmonary	AIDS, Pulmonary TB, TB meningitis	Bilateral nodular shadows, conglomerate opacities with upper lobe sparing
9.	24	M	+	Absent	Lymph node	AIDS, LN TB, ? TB spleen	Normal
10.	47	M	+	Absent	Lymph node	AIDS, Hepatic encephalopathy, ?Carcinoma pancreas, suspected disseminated tuberculosis	Not available
11.	27	M	+	Absent	Pulmonary	AIDS, Pulmonary TB	Bilateral, parenechymal infiltrates with paratracheal LNs
12.	27	M	+	Absent	Lymph node	AIDS, LN TB	Not available
13.	26	M	+	Present	None	Klebsiella pneumonia and suspected disseminated TB	Right Paratracheal thickening
14.	37	M	+	Absent	None	Interstitial lung disease	Right lower-lobe bronchiectasis
15.	26	M	+	Present	None	AIDS wasting syndrome	Normal

All except patients no. 3 had a history of fever.
LN, lymph node; AIDS, acquired immunodeficiency syndrome; TB, tuberculosis; M, male; F, female

patient with HIV infection and mycobacteraemia had the wasting syndrome, but no clinical or radiological evidence of TB. Even though all 15 patients with mycobacteraemia had documented or historical evidence of fever, only 6 were febrile at the time of blood culture. Evaluation of their chest X-rays revealed 5 were normal, 1 had miliary mottling pattern, and 5 had other features that could be associated with TB. None had fibrocavitory TB that is usually seen in immunocompetent patients.

Among 80 patients with clinical diagnosis of TB either supported by laboratory tests or not, 14 (17.5%) had mycobacteraemia. Among the 21 patients with laboratory proven TB and HIV coinfection 9 (43%) had mycobacteraemia. Of the 40 HIV infected persons with clinical AIDS, 25 per cent had mycobacteraemia. In 4 (26.7%) of the 15 patients with mycobacteraemia, blood was the first/only source of diagnosing TB. Extrapulmonary TB and atypical features on chest

Table IV. Comparison of patients with and without mycobacteraemia

General features Features	Mycobacteraemia present (n=15)	Mycobacteraemia absent (n=78)
Age (yr) Range (mean ±SD)	24-65 (37.27±15.9)	15-76 (35.04±16.0)
Sex ratio M/F	14	6.8
Temperature at culture	Febrile 6, Afebrile 9	Febrile 8, Afebrile 81
History of fever	15 (100%)	63 (80%)
With HIV infection	12	43
Site of TB (smear/culture/biopsy proven) or clinically diagnosed TB:		
Pulmonary (n=40)	5	35
Lymph node (n=13)	4	9
Pleural (n=1)	0	1
Bone Marrow (n=2)	1	1
Ascitic Fluid (n=1)	1	0
Pancreatic abscess fluid (n=1)	1	0
Clinically diagnosed (n=32)	3	29
Chest X-ray :		
Normal (n=30)	5	25
Suggestive of TB	0	49
- Fibrocavitory, apical-infiltrates, upper lobe consolidation (n=49)		
Miliary mottling (n=2)	2	0
Hilar adenopathy with parenchymal infiltrates (n=1)	1	0
Paratracheal thickening (n=1)	1	0
Bilateral infiltrates (n=2)	2	0
Pleural effusion (n=1)	1	0
Paratracheal lymphadeno-pathy with parenchymal infiltrates (n=1)	1	0
Non specific (n=4)	0	4

TB, Tuberculosis; HIV, human immunodeficiency virus; M, male; F, female. Chest X-ray of 2 patients was not available

X-ray were more common in patients with mycobacteraemia, than in those without (7/15 vs. 11/78 and 8/15 vs. 4/78 respectively). Patients with mycobacteraemia were also more likely to be HIV infected (80 vs. 20%), have lymphadenopathy (33 vs. 10%) and a history of fever (100 vs. 80%). Normal chest X-rays were seen in 5 (33.3%) and 25 (32.1%) among those with and without mycobacteraemia respectively (Table IV).

Four (40%) of 10 patients with HIV infection and sputum with AFB positivity and 3 (38%) of 8 HIV infected patients with TB lymphadenitis, had mycobacteraemia. Of 3 patients with bone marrow evidence of documented TB, one had HIV infection and had mycobacteraemia while the other 2 did not have HIV infection and mycobacteraemia.

Discussion

Mycobacterial blood culture appears to be a useful additional diagnostic tool in the early diagnosis of TB, particularly in the HIV infected and also in HIV-negative

patients. Among the 15 patients with mycobacteraemia in the present study, blood was the only source of *M. tuberculosis* in 4 (26.7%) subjects. Studies by other investigators have shown that blood was the only/first source of *M.tuberculosis* in 33 per cent of patients with mycobacteraemia[8,9]. In a recent study in India[22], only 4 patients with HIV and clinical TB had mycobacteraemia, 3 with *M. tuberculosis* and one with *M. phlei*.

Among our 80 subjects diagnosed with TB, 14 (17.5%) had mycobacteraemia. Among HIV-infected patients with laboratory proven TB 43 per cent had mycobacteraemia, while among 38 HIV negative patients with TB only 3 (7.0%) had mycobacteraemia. Among HIV-infected patients, older individuals had higher probability for mycobacteraemia especially if they had extrapulmonary TB. The frequency of mycobacteraemia in our study was similar to studies done in other developing countries. Bouza and colleagues[8] have shown that 14 per cent of TB patients had mycobacteraemia; among those with HIV co-infection 26-42 per cent had mycobacteraemia while 8 (19%) patients with mycobacteraemia were HIV negative. In a study done in Thailand and Malawi[17] for mycobacteraemia in 344 adult inpatients with fever, 10 per cent had mycobacteraemia. Patients who had HIV infection, oral thrush, lymphadenopathy, chronic cough of more than one month duration, fever, or weight loss were more likely to have mycobacteraemia. Our results were comparable to this study.

Another study[11] showed a higher incidence of mycobacteremia in patients with fever above 39.5ºC. Fourteen of 15 patients with mycobacteraemia in our study had a history of fever. However, 9 of these 15 were afebrile at the time of the blood culture. Thus mycobacteraemia occurred in the absence of fever, although the yield might have been higher if we had taken the blood cultures when the patients were febrile.

Of the 34 patients with mycobacteraemia in the study done in Thailand and Malawi[17] 5 had received antituberculosis treatment prior to blood culture. Thirteen had either abnormal chest radiographs or AFB in sputum smears on or before admission. The remaining 16 (55%) patients had unrecognized mycobacteraemia. Of these, 13 (81%) had cough; three had normal chest radiographs and none had been subjected to sputum examination.

Another study revealed that raised lactate dehydrogenase (LDH) levels and military pattern on chest X-ray were predictors of mycobacteraemia[11]. In our patients with mycobacteraemia, 30 per cent had normal chest X-rays. Thus chest X-ray features may not predict the presence of mycobacteraemia. We did not measure LDH levels in our patients. A higher incidence of mycobacteraemia has been shown in women[10]. It had also been shown that most HIV-negative TB patients with mycobacteraemia had other underlying diseases[8]. However, in the present study none of the HIV-negative patients with mycobacteraemia had any other immunocompromizing illness. Thus, in immunocompetent subjects with fever also mycobacterial blood cultures could prove a useful diagnostic test. There are reports of the diagnosis of splenic TB by ultrasound and mycobacterial blood cultures[13]. One of the HIV patients in the present study with TB lymphadenitis and mycobacteraemia also had abdominal TB with multiple hypoechoeic areas in the spleen as seen in the ultrasound. In summary, varied clinical and laboratory features are seen in patients with mycobacteraemia[12].

We used the lysis centrifugation method followed by inoculation into modified LJ medium as its sensitivity was comparable to that of the BACTEC system provided lysis centrifugation method was used[21,22-25]. In a study in which BACTEC system was used without lysis centrifugation, the sensitivity of detecting mycobacteraemia was low[22]. The comparison of direct culture onto LJ medium versus the use of the Selective Kirchner's medium reveals a positivity of 53.3 and 73.3 per cent respectively – if only either of the two had been done 46.6 or 26.6 per cent of the cases would have been missed. Thus both methods should be used together to get the best results. For sputum samples the modified LJ medium is recommended, while the Selective Kirchner's medium is suitable for samples other than sputum[19].

The time taken to detect mycobacteria on direct inoculation (22.3 days) was similar to data from earlier studies where the detection times ranged from 26 to 42 days (mean 29 days)[8] and 28 days[14]. Direct smear of the sediment was positive only in 2 of 15 cases (13.3%), findings similar to Stone and colleagues[15] who found 4 per cent direct smear positivity. The smear from

the Selective Kirchner's medium was positive in 33.3 per cent of cases and in two was the only evidence of mycobacteraemia, the *M. tuberculosis* not growing on the LJ medium. In one case this was probably due to fungal contamination.

Clark and colleagues[12] in a study on HIV patients with pyrexia of unknown origin showed that 6 of 8 patients with mycobacterial infections had mycobacteraemia. Among these, 8 patients had bone marrow evidence and 6 had liver biopsy evidence of mycobacterial infection. Of the 3 patients with bone marrow evidence of TB in the present study, only 1 had mycobacteraemia. Bone marrow biopsies may not therefore be a substitute for mycobacterial blood cultures in our setting.

Studies in Africa have shown that *M. tuberculosis* bacteraemia was more common than that of *Mycobacterium avium intracelulare* (MAI)[16]. The same appears to be true for India, as MAI or other atypical mycobacteria were not detected in the present study. This could be because AIDS patients in India die of diseases such as due to *M. tuberculosis* before they can develop MAI disease.

In conclusion, mycobacterial blood culture is a useful additional diagnostic test to diagnose TB in persons with HIV infection. In patients without HIV infection, but with clinical picture compatible with TB, blood culture for mycobacteraemia may occasionally help in the diagnosis. We recommend the use of the lysis centrifugation technique followed by both direct smear of the sediment along with inoculation of the sediment into both modified LJ medium and the Selective Kirchner's medium with subsequent subculturing onto the modified LJ medium for detecting mycobacteraemia.

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