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Computed tomography thorax abnormalities in immunocompetent patients with tuberculous meningitis: An observational study

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ABSTRACT

Objective: Computed tomography (CT) of the thorax is the imaging modality of choice to detect or demonstrate lesions suggestive of active pulmonary tuberculosis. We aimed to evaluate the imaging abnormalities detected on CT of the thorax in patients with tuberculous meningitis (TBM).

Methods: In this prospective study, we enrolled consecutive newly-diagnosed patients with TBM. Patients were subjected to detailed clinical evaluation and laboratory investigations including MRI of brain and thoracic CT. Patients were administered WHO recommended treatment and followed-up for 6 months. At 6 months, disability assessment was done.

Results: We included 81 patients. Fifty-six patients (69.1%) had abnormalities in CT of thorax. Miliary tuberculosis was seen in 10 (18%) patients. Centrilobular nodules were the commonest parenchymal abnormality seen in 23 (41%) patients. Pleural abnormalities and mediastinal lymphadenopathy were seen in 8 (14%) and 47 (84%) patients, respectively.

On multivariate analysis, meningeal enhancement (OR = 3.5, 95%CI 1.2–9.8, P = 0.017) and CBNAAT positivity (OR = 8.7, 95%CI 1.0–73.0, P = 0.045) were independently associated with an abnormal CT of thorax. The sensitivity and specificity of CT thorax in identifying definite cases (CB-NAAT positive) of TBM were found to be 93.33% and 36.36%, respectively. Positive predictive value and negative predictive value of abnormal CT thorax in predicting definite TBM were 25% and 96%, respectively.

Conclusion: CT thorax abnormalities were noted in approximately two-thirds of TBM patients, and were more frequent in definite TBM cases. CT thorax abnormalities helped in upgrading the diagnostic certainty level, in many patients with tuberculous meningitis, from possible to probable.

1. Introduction

Tuberculous meningitis (TBM) comprises around 1% of all tuberculosis cases [1]. In addition, approximately half of the TBM patients either die or become severely disabled [2]. It should be noted that TBM is definitely diagnosed only in a small proportion of cases. This is because the yield of cerebrospinal fluid (CSF) microscopy, CSF culture and CSF cartridge-based nucleic acid amplification technology (CB-NAAT) is quite low. This uncertainty in diagnosis frequently leads to a delay in treatment [3,4].

Tuberculosis spreads via the inhalation of aerosolized droplet nuclei containing tubercle bacilli. After reaching the lungs, the bacilli spread to extra-pulmonary sites, including the brain, by hematogenous route [1,5]. The evidence of tuberculosis other than in the lungs support the diagnosis of TBM in a suspected case and leads to prompt initiation of antituberculosis treatment. The lung is the first organ affected by tuberculosis (clinically or sub-clinically) before the development of TBM [6–8]. In this study, we evaluated the lungs in TBM patients with computed tomography (CT) thorax.

2. Material and method

This prospective study was conducted in the Department of Neurology in collaboration with the Department of Radiology and Department of Microbiology, King George Medical University, Lucknow, a tertiary care facility in North India. The study was approved

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by the Institutional Ethics Committee (ethical approval number 1464/ethics/R-cell-16). Written informed consent was obtained from all participants before their inclusion in the study.

All consecutive newly-diagnosed patients with TBM were included. Patients were diagnosed on the basis of consensus TBM diagnostic criteria, described by Marais and co-workers. All included patients were categorized into definite, probable or possible groups [9]. Patients with human immunodeficiency virus (HIV) disease were excluded. Patients who had taken prior anti-tuberculous treatment and corticosteroids were also excluded.

All patients underwent detailed clinical evaluation. They were subjected to a battery of hematological and biochemical investigations including complete hemogram, liver function test, kidney function test, electrolytes, blood glucose and HIV enzyme-linked immunosorbent assay. CSF was examined for protein, glucose, cells, Gram staining, Ziehl-Neelsen staining, and India ink staining. All CSF specimens were assessed by Gene Xpert MTB/RIF system. All patients underwent cranial magnetic resonance imaging (MRI) with gadolinium enhancement. MRI was performed using a Signa Excite 1.5 T machine (General Electric Medical Systems, Milwaukee, WI, USA). Abnormalities in brain imaging, such as leptomeningeal enhancement, basal exudates, tuberculomas, hydrocephalus and infarcts, were recorded. Every enrolled patient was subjected to CT thorax (Phillips brilliance 64 slice CT scan machine). The thoracic imaging findings were divided into parenchymal, pleural and mediastinal lesions. Lesions measuring < 3 mm in diameter were termed as micronodules, 3 mm to 3 cm as nodules and > 3 cm as masses. Centrilobular nodules were defined as well-demarcated lesions in relation to a terminal or respiratory bronchiole in secondary lobule and are 2 mm away from the pleural surface or interlobar septa. The 'tree in-bud' appearance was defined as a linear structure with more than one adjoining branching sites. Miliary pattern was defined as the presence of widespread, randomly distributed micronodules in both lungs. Consolidation was defined as a homogeneous increase in pulmonary parenchymal attenuation obscuring the underlying broncho-vascular markings. Ground glass attenuation was defined as an area of parenchymal attenuation without obscuration of underlying bronchovesicular markings [10]. Lymphadenopathy was defined when the short axis diameter of lymph nodes was larger than 10 mm [11].

Severity of TBM was assessed by using British Medical Research Council stage criteria [12]. Patients, with a Glasgow coma scale (GCS) score of 15 with no focal neurological deficit, were included in Stage I. Patients with GCS score of 15 with focal neurological deficits and patients with GCS score of 11–14 were included in Stage II. Patients with GCS score ≤ 10 were included in Stage III. Functional assessment was done at baseline using the modified Barthel index (MBI) [13]. The MBI is a 20-point scoring system in which zero signifies death and higher points suggest better functional status.

Antituberculosis treatment was given to all patients as per the recommendation of World Health Organization [14]. In the intensive phase (initial two months), the patients received oral isoniazid (5 mg/kg/day; maximum dose 300 mg/day), rifampicin (10 mg/kg/day; maximum dose 600 mg/day), pyrazinamide (25 mg/kg; maximum dose 2 g/day), and intramuscular streptomycin (20 mg/kg/day; maximum 1 g/day). Oral isoniazid and rifampicin were further continued in the continuation phase for the next 7 months. For the initial 8 weeks, all patients also received dexamethasone. For the first 4 weeks, dexamethasone was given intravenously in a dosage of 0.4 mg/kg body weight per day. It was tapered by 0.1 mg/kg per week. For the next 4 weeks, oral dexamethasone was given, starting with 4 mg per day and tapered by 1 mg every week. Apart from this, patients also received anticonvulsants and cerebral edema-reducing measures as required. Patients were followed for 6 months. Outcome was assessed by using MBI at 6 months. Poor functional status was defined as MBI ≤ 12, and good functional status was defined as MBI > 12.

Sample size was calculated using Open EPI, version 3 (open source

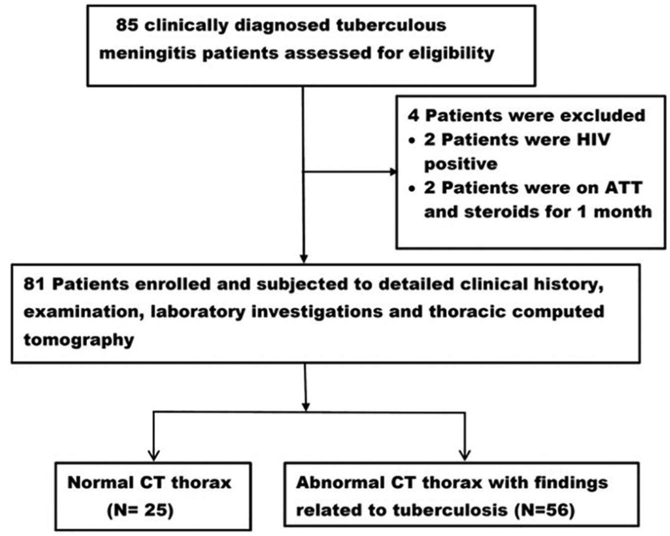

Fig. 1. Flow-chart of the study.
(ATT = Antituberculosis treatment; CT = Computed tomography; CSF = Cerebrospinal fluid, HIV = Human immunodeficiency virus)

calculator) [15]. By considering alpha error 5%, proportion of patients with abnormal CT thorax 50% and design effect 1%, the sample size was calculated to be 80. Data were analyzed using SPSS version 16 (Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation or median with range. Categorical variables were presented as percentage. The continuous variables were compared by independent *t*-test. Non-parametric tests (Kruskal–Wallis test or Mann–Whitney *U* test) were used wherever data were not normally distributed. The categorical variables were compared by chi-square test and Fisher's exact test. The differences were considered statistically significant if the two-tailed *p*-value was < 0.05. Multivariate analysis was done using binary logistic regression. Significance of change in proportions of possible to probable cases, after applying CT thorax findings, was assessed by Mc Nemar test.

3. Results

During the study period, 85 consecutive patients with clinically diagnosed tuberculous meningitis were assessed. Four patients were excluded. Reasons for exclusion have been provided in Fig. 1. A total of 81 patients were subjected to a detailed clinical evaluation, laboratory investigations and thoracic CT. Two patients were lost to follow-up, but their last evaluation findings were considered for final analysis. (Fig. 1)

Median age of all TBM patients was 30 years. Other clinical, neuroimaging and CSF parameters are presented in Table 1. Chest x ray was also performed in all cases. It was abnormal in 30 (37%) patients. In 8 cases, it showed miliary shadows, cavity in 2 cases, pleural effusion in 7 cases, fibro-consolidation in 4 cases and lymphadenopathy in 9 cases. Out of 81 patients who underwent CT thorax, 56 patients (69%) had CT thorax abnormalities. (Fig. 2) Parenchymal abnormalities were found in 79% patients. Pleural abnormalities were observed in 14% of patients. Mediastinal lymphadenopathy was seen in 84% of patients. Miliary tuberculosis was seen in 10 (18%) patients. Centrilobular nodules were the commonest parenchymal abnormality seen in 23 (41%) patients. (Table 2) On univariate analysis, meningeal enhancement (OR = 3.2, 95% CI 1.2–8.8, P = .017) and CBNAAT positivity (OR = 8.0, 95% CI 0.99–64.66, P = .03) were significantly associated with abnormal CT thorax. On logistic regression analysis, meningeal enhancement (OR = 3.5, 95%CI 1.2–9.8, P = .017) and CBNAAT positivity (OR = 8.7, 95%CI 1.0–73.0, p = .045) were independently associated with abnormal CT thorax. (Table 3).

Before CT thorax was performed, 15 cases were categorized as

Table 1
Clinical, radiological and laboratory characteristics of patients with tuberculous meningitis (*N* = 81).

Clinical variables	All TBM patients (n = 81)	TBM patients with CT Thorax showing tuberculosis related findings (n = 56)	TBM patients with normal CT Thorax (n = 25)	P value	Odds ratio	95%CI
Median age (range)	30 (18–81)	31 (18–81)	30 (18–65)	0.45		−9.86 to 4.74
Gender (male%)	63%	66.1%	56%	0.38	0.65	0.24 to 1.71
Median duration of illness in days (range)	25 (5–180)	27.5 (5–150)	21 (5–180)	0.94		−10.64 to 22.80
Fever	78 (96.3%)	55 (98.2%)	23 (92%)	0.22	4.78	0.41 to 55.38
Headache	79 (97.5%)	54 (96.4%)	25 (100%)	1.00	0.68	0.58 to 0.79
Seizure	20 (24.7%)	13 (23.2%)	7 (28%)	0.64	0.77	0.26 to 2.26
Altered sensorium	40 (49.4%)	31 (55.4%)	9 (36%)	0.10	2.20	0.83 to 5.82
Hemiparesis	5 (6.2%)	4 (7.1%)	1 (4%)	1.0	1.84	0.19 to 17.41
Paraparesis	1 (1.2%)	1 (1.8%)	0	1.0	0.68	0.59 to 0.79
Papilledema	36 (44.4%)	24 (42.9%)	12 (48%)	0.66	0.81	0.31 to 2.09
Optic atrophy	7 (8.6%)	5 (8.9%)	2 (8%)	1.0	1.12	0.20 to 6.24
Oculomotor palsies	33 (40.7%)	21 (37.5%)	12 (48%)	0.37	0.65	0.25 to 1.68
Baseline stage						
I	24 (29.6%)	13 (23.2%)	11 (44%)	0.14	NA	NA
II	44 (54.3%)	34 (60.7%)	10 (40%)		NA	NA
III	13 (16%)	9 (16.1%)	4 (16%)		NA	NA
Neuroimaging characteristics						
Hydrocephalous	20 (24.7%)	16 (28.6%)	4 (16%)	0.22	2.10	0.62 to 7.08
Basal exudates	28 (34.6%)	22 (39.3%)	6 (24%)	0.21	2.04	0.70 to 5.9
Infarcts	14 (17.3%)	11 (19.6%)	3 (12%)	0.53	1.79	0.45 to 7.08
Tuberculoma	31 (38.3%)	20 (35.7%)	11 (44%)	0.47	0.70	0.27 to 1.84
Meningeal enhancement	42 (51.9%)	34 (60.7%)	8 (32%)	**0.02**	**3.28**	**1.21 to 8.89**
CSF parameters						
Median CSF protein in mg/dl (range)	168 (31–3668)	169 (31–1027)	160 (48–3668)	0.94	NA	−42.32 to 387.22
Median CSF glucose in mg/dl (range)	36 (5–80)	36 (5–80)	38 (17–78)	0.94	NA	−4.85 to 13.78
Median total CSF cell count in cells/μL (range)	130 (10–1480)	152.5 (10–660)	120 (10–1480)	0.06	NA	−92.22 to 101.33
CB-NAAT positivity	15 (18.5%)	14 (25%)	1 (4%)	**0.03**	**8.0**	**0.99 to 64.66**
Rifampicin resistance	4 (4.9%)	4 (7.1%)	0	0.30	0.67	0.57 to 0.78
TBM Category (according to Marias et al)						
Definite	15 (18.5%)	14 (25%)	1 (4%)	0.03	NA	NA
Probable	20 (24.7%)	15 (26.8%)	5 (20%)			
Possible	46 (56.8%)	27 (48.2%)	19 (76%)			
Baseline severity						
MBI ≤ 12	42 (51.9%)	32 (57.1%)	10 (40%)	0.15	2.0	0.76 to 5.22
MBI > 12	39 (48.1%)	24 (42.9%)	15 (60%)	0.15	2.0	0.76 to 5.22
Good outcome (MBI > 12 at 6 months)	57 (70.4%)	39 (69.6%)	18 (72%)	0.83	1.12	0.39 to 3.17
Poor outcome (deaths + MBI ≤12 at 6 months)	24 (29.6%)	17 (30.4%)	7(28%)	0.83	1.12	0.39 to 3.17

** Five patients showed presence of *Mycobacteria tuberculosis* in CSF Ziehl-Neelsen staining, all these patients were CB-NAAT positive as well. AFB was seen in sputum of two patients. These two patients also had CB-NAAT positivity in CSF. Statistically significant values are depicted in bold font.
AFB = Acid-fast bacilli; CB NAAT = Cartridge based nucleic acid amplification test; CSF = Cerebrospinal fluid; CT = Computed tomography; MBI = Modified Barthel index; NA = Not applicable; TBM = Tuberculous meningitis.

definite, 20 cases as probable and 46 cases as possible. After CT thorax, in 23 additional cases the diagnostic category was upgraded from possible to probable (p value < .001). (Table 4).

At 6 months, 24 patients had poor outcome (MBI ≤ 12). On univariate analysis, poor outcome was significantly associated with altered sensorium (OR = 6.3, 95%CI 2.0–19.5, P = 0.001), baseline MBI ≤12 (OR = 11.7, 95%CI 3.1–44.0, P < 0.001), stage III of TBM (OR = 24.1, 95%CI 4.7–122.1, P < 0.001), seizures (OR = 3.5, 95%CI 1.2–10.0, P = 0.017), hemiparesis (OR = 11.6, 95%CI 1.2–110, P = 0.023), papilledema (OR = 3.6, 95% CI 1.3–9.8, P = 0.01), oculomotor palsy (OR = 2.7, 95% CI 1.0–7.2, P = 0.04), and basal exudates (OR = 4.5, 95%CI 1.6–12.3, P = 0.003). None of the variables was independently associated with poor outcome. Abnormal CT thorax was not associated with poor outcome.

The sensitivity and specificity of CT thorax in identifying definite cases (CB-NAAT positive) of TBM were found to be 93.33% and 36.36%, respectively. Positive predictive value and negative predictive value of abnormal CT thorax in predicting definite TBM were 25% and 96%, respectively.

4. Discussion

We noted CT abnormalities in 69% of TBM patients. In the literature, X-ray detected abnormalities in 50% of TBM patients [6]. Similar to X-ray-based study, we noted that mediastinal lymphadenopathy is the commonest thoracic abnormalities in TBM [7]. Among the parenchymal lesions, the most common abnormality was centrilobular nodules. These findings are in accordance with other CT thorax-based studies in pulmonary tuberculosis [11]. In our study, miliary pattern was found in 10 patients, and we did not find any association between pulmonary involvement and poor outcome.

This study emphasizes the assumption that TBM is a manifestation of disseminated tuberculosis and occurs secondary to pulmonary tuberculosis. Simultaneous involvement of central nervous system and lungs depends on host- and pathogen-related factors. In the patients with compromised immune status, the chances of both site involvement

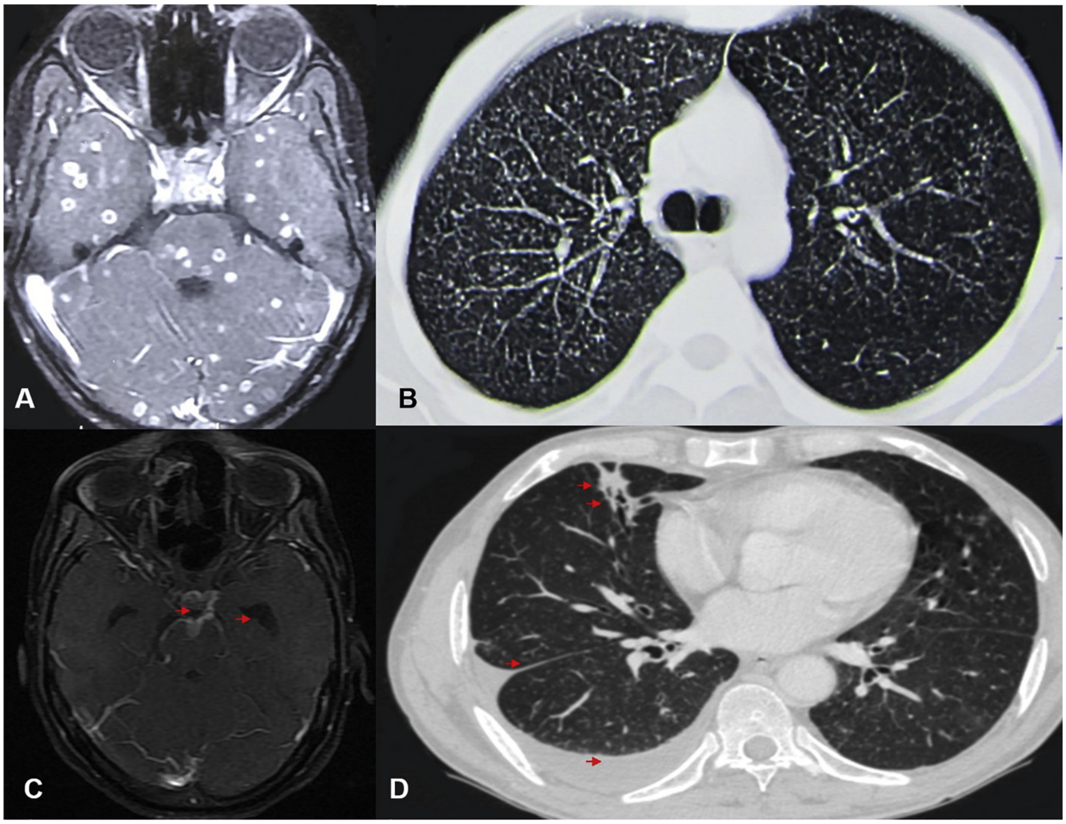

Fig. 2. Imaging of one patient showing multiple ring-enhancing lesions suggestive of tuberculoma in gadolinium-enhanced cranial magnetic resonance imaging (A) and miliary pattern in thoracic computed tomography (B). Another patient's gadolinium-enhanced cranial magnetic resonance imaging (C) showing basal meningeal enhancement and dilated temporal horns; and thoracic computed tomography (D) showing right-sided pleural effusion, fissural effusion and right middle lobe fibrosis.

Table 2
Tuberculosis related Computed tomography thorax findings in tuberculous meningitis patients.

Computed tomography thorax findings	Number of patients (n = 56)
Right lung field involved	23 (41.1%)
Left lung field involved	13 (23.2%)
Both sides involved	12 (21.4%)
Parenchymal abnormalities	44 (78.6%)
Centrilobular nodules	23 (41.1%)
Miliary pattern	10 (17.9%)
Fibro-consolidation	12 (21.4%)
Tree in bud appearance	4 (7.1%)
Cavity	4 (7.1%)
Collapse	4 (7.1%)
Fibro-bronchiectasis	3 (5.4%)
Calcified nodules	3 (5.4%)
Pleural abnormalities	8 (14.3%)
Pleural effusion	8 (14.3%)
Pleural calcification	1 (1.8%)
Fissural effusion	1 (1.8%)
Pleural enhancement	1 (1.8%)
Mediastinal lymphadenopathy	47 (83.9%)

Table 3
Multivariate logistic regression analysis of factors predicting abnormal CT thorax.

Clinical variables	P value	Odds ratio	95%CI
Meningeal enhancement	0.017	3.50	1.24 to 9.84
CB-NAAT positivity	0.045	8.74	1.04 to 73.07

CB NAAT = Cartridge based nucleic acid amplification test; CT = Computed tomography.

are high. Pulmonary tuberculosis (on chest X-ray) was reported as high as 85% in HIV-infected children [8]. Our ability to detect pulmonary lesions depends on the sensitivity of the screening tool used. In this study, we noted that almost two-third of immunocompetent TBM patients had lesions consistent with pulmonary tuberculosis.

High-resolution computed tomography of chest is imaging method of choice to evaluate lesions of pulmonary tuberculosis. Characteristic lesions suggestive of active pulmonary tuberculosis include centrilobular nodules, poorly defined nodules, tree-in-bud lesions, consolidation and parenchymal cavities. Miliary tuberculosis is characterized by multiple small nodules diffusely distributed in both the lungs. CT thorax reveals miliary lesions even before it becomes apparent on X-ray. These nodules may coalesce and form a focal area of bronchopneumonia. CT helps in accurately diagnosing even small lesions of 1–3 mm in size. Centrilobular nodules are visualized as ill-defined fluffy nodular opacities. These nodules result from bronchogenic spread of *Mycobacterium tuberculosis*. The "tree-in-bud" tuberculous lesions, on CT thorax, are characterized by multiple areas of centrilobular nodules with a branching pattern resubliming a budding tree. Pleural effusion may be the sole imaging manifestation of pulmonary tuberculosis [16–19]. Enlarged paratracheal or hilar lymph nodes are commonly involved in tuberculosis and help in differentiating primary from post-primary tuberculosis. Hilar, right paratracheal, subcarinal, and aorto-pulmonary lymphadenopathy are common in tuberculosis. Enlarged lymph nodes indicate reactivation of latent tuberculous infection, active pulmonary tuberculosis and as a part of miliary dissemination. Pleural effusion suggests active tuberculous disease while pleural thickening and pleural calcification indicates healed tuberculosis [18]. Lee and co-workers reported that out of 146 patients suspected of tuberculosis, 133 (91%) could be correctly diagnosed of pulmonary tuberculosis. Pulmonary tuberculosis could be rightly excluded in 76% of 42 patients

Table 4
Impact of CT thorax on categorization of TBM patients.

	Before CT thorax	After CT thorax
Definite cases	15	15
Probable cases*	20*	43*
Possible cases	46	23

CT = Computed tomography; TBM = Tuberculous meningitis.
* Rise in proportion of probable cases after CT thorax is statistically significant (Mc Nemar test, p value < 0.001).

without tuberculosis. Lee and co-workers found that the diagnostic sensitivity of CT thorax was comparable to that of sputum culture [20].

The currently available diagnostic methods can provide microbiological confirmation in approximately 50% of tuberculous meningitis cases. In Indonesia, CSF samples of 1180 adult meningitis suspects were examined, tuberculous meningitis was bacteriologically confirmed in 501 (42%) patients only. Sensitivity of CB NAAT was 46%. Patients with severe disease showed higher yields for tuberculosis confirmatory tests [21]. In our study, the negative predictive value of CT thorax in predicting definite case of TBM was 96%. CT chest finding, if present, help in establishing the diagnosis of tuberculous meningitis with greater confidence, even if bacteriological confirmatory tests are unrewarding.

A major limitation of our study was that we did not perform tests to establish microbiological confirmation of lung lesions. Bronchoscopy-guided bronchoalveolar lavage in such patients could help in confirming tuberculosis in a greater number of patients. We were not able to reliably exclude other alternative diagnoses that share the same subacute course and have clinical features similar to that of tuberculous meningitis, like, partially treated bacterial meningitis, fungal meningitis or toxoplasma meningitis. In our study, number of definite (bacteriologically confirmed) tuberculous meningitis cases was low, probably due to the limited bacteriological examinations. We did not perform CSF culture for *Mycobacterium tuberculosis*. Our findings need to be interpreted with caution.

In conclusion, CT thorax abnormalities were noted in more than two-thirds of adult patients with TBM. Demonstration of CT thorax abnormalities, consistent with tuberculosis, helped in upgrading diagnostic certainty level, in many patients of tuberculous meningitis, from possible to probable.

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