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Characteristics of Extraneural Tuberculosis in Patients with Tuberculous Meningitis Hospitalized at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia in 2017–2021

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Abstract

Background: Tuberculous (TB) meningitis is the most severe manifestation of extrapulmonary TB and contributes to a high mortality rate. The presence of extraneural TB may raise suspicion of TB meningitis (TBM). This study aimed to explore the characteristics of extraneural TB in TBM patients.

Methods: This was a cross-sectional descriptive study using secondary data from medical records of TBM patients admitted at Dr. Hasan Sadikin General Hospital Bandung, Indonesia from 2017 to 2021. Demographic and clinical data were collected, including HIV status. TBM cases were classified into grades I, II, and III using Medical Research Counsil (MRC) criteria that were based on Glasgow Coma Scale (GCS) score and the presence of focal neurological deficits. The clinical classification diagnosis of TBM was made based on the Marais diagnostic criteria which included several diagnostic items and corresponding scoring which further divided TBM into three classes. Extraneural TB was defined as the finding of TB outside the nervous system. Disseminated TB was diagnosed based on the finding of ≥2 infected locations.

Results: During the study period, 497 medical records were analyzed. Most TBM patients experienced Grade II (76.9%) and extraneural TB site was found in 65.4%, with pulmonary TB as the common site (77%). The highest mortality rate was in disseminated TB (50%). The finding of extraneural TB did not differ between HIV-negative and HIV-positive patients (67.8% vs. 67.9%; p=0.101).

Conclusions: The presence of extraneural TB is common in patients with TBM. Therefore, extraneural TB evaluation is important to ensure TBM diagnosis. Further studies are needed to explore factors related to TBM diagnosis to ensure TBM patient's wellbeing.

Keywords: Characteristics, extraneural tuberculosis, tuberculous meningitis

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Introduction

Tuberculosis (TB), an infection caused by Mycobacterium tuberculosis, primarily affects the lungs. WHO has reported in 2022 that Indonesia is the second country in the world with the highest incidence of TB. Extrapulmonary TB refers to an infection involving other organs other than the lungs which usually results from the dissemination of pulmonary TB. While extraneural TB occurs within other organs excluding the central nervous system (CNS) which also may have been initially caused by the pulmonary infection.[1,2] Tuberculous meningitis (TBM) is the most severe extrapulmonary manifestation of TB infection. Although it only accounts for 1% of the total TB cases, the mortality rate of TBM may reach up to 60%.[3–7] The highest incidence of TBM is in South East Asia.[5,7,8]

The diagnosis of TBM is usually made based on clinical history, neuroradiology, evidence of TB infection in other body parts (extraneural TB, outside of the nervous system) and assessment of cerebrospinal fluid (CSF).[5,8] In the most widely cited published diagnostic criteria for TBM, evidence of extraneural TB is included in the assessment and may raise suspicion of TBM. Approximately 33–60% of the TBM patients have abnormal lung imaging findings. However, abnormalities of organs other than the lungs are also common in TBM patients.[9] A study discovers that extraneural TB is evident in 38% of TBM patients, the majority of whom are pulmonary TB.[10] This is confirmed by another study, which discovers that the presence of extraneural TB is significantly higher among TBM patients compared to the control group, which includes patients who are diagnosed with meningitis caused by other infections but TB.[11]

The prevalence of extraneural TB among TBM patients in Indonesia has not been widely studied. Therefore, this study aimed to examine the prevalence of extraneural TB among TBM patients and its characteristics to compare the number of certain extraneural TB in TBM patients for future studies.

Methods

This study was a cross-sectional analytical study, involving adult TBM patients aged 18 years old and older, admitted at the neurology ward of Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia in 2017 to 2021. Secondary data from medical records were collected using the total sampling method, including age, gender, HIV status, TB history, MDR status, TBM diagnosis and grading, extraneural TB diagnoses, hospitalization duration, and in-hospital mortality. Ethical approval was obtained from the Research Ethics Committee of Universitas Padjadjaran Bandung Indonesia with letter number 605/UN6.KEP/EC/2022.

The clinical diagnosis of TBM was classified based on the Marais criteria and was divided into definite, probable, and possible TBM.[9] The Marais criteria were calculated based on clinical criteria, CSF criteria, cranial imaging criteria, and evidence of TB elsewhere. Clinical entry criteria and positive acid fast bacilli (AFB) in CSF, positive MTB in CSF culture, or positive nucleic acid amplification testing (NAAT) in CSF concluded definite TBM or AFB seen in histological changes consistent with TB in the brain or spinal cord with suggestive

Table 1 Demographic of Patients Diagnosed with Tuberculosis Meningitis (n=497)*

Variable	Median (IQR)	n (%)*
Age in year	31 (24–40.5)	
Male gender		265 (53.5)
Diagnosis/treatment history of TB before hospitalization		195 (39.2)
On therapy		66 (33.8)
Lost to follow up		11 (5.6)
Relapse and therapy failure		8 (4.1)
No Description		110 (56.4)
HIV positive**		59 (15.4)
TBM grade		
Grade I		15 (3.0)
Grade II		382 (76.9)
Grade III		100 (20.1)
TBM classification		
Definite		61 (12.3)
Probable		290 (58.3)
Possible		146 (29.4)
Hospitalization duration in days	19 (8–22)	
Mortality during hospitalization		136 (27.4)
Time to death in days	5 (3–10)	
TB MDR		16 (3.2)
One or more extraneural TB found		325 (65.4)

Note: *=Data are presented in n(%) unless stated otherwise; **=HIV status was available for 383 subjects, IQR=interquartile range; TB=tuberculosis; MDR=multi drug resistant

signs or symptoms and CSF changes, or visible meningitis. Probable TBM was defined as a score of ≥10 (without cerebral imaging) or ≥12 (available cerebral imaging), while possible TBM was defined as a total score of 6–9 (without cerebral imaging) or 6–11 (available cerebral imaging).

The grading of TBM was based on the British Medical Research Council (BMRC) staging system that categorized patients into three grades based on their level of consciousness and neurological signs. Grade I was defined with GCS 15 and no focal neurological deficits. Grade II included GCS 10–14 with or without focal neurological deficits or GCS 15 with focal neurological deficits. Grade III was present with GCS <10 with focal neurological deficits.[9] Findings of positive TB examinations in organs outside the nervous system were defined as extraneural TB.

The collected data were then processed using descriptive and analytic methods with IBM SPSS Statistics version 27, including demographics and TBM diagnosis, extraneural TB diagnosis, and the correlation between numbers of extraneural TB and numbers of death during hospitalization.

Results

During the study period, 514 medical records of adult TBM patients were collected; however, due to incomplete data (n=18), only 497 medical records were analysed, with a median age of 31 years (IQR 24–40.5) and predominantly male (n=265; 53.5%). The median hospitalization duration was 19 days (IQR 8–22), whereas among non-survivors (n=136), the median time to death was 5 days (IQR 3–10) as depicted in Table 1.

TB diagnosis and/or treatment before admission was found in 195 subjects (39.2%), and 66 (33.8%) of them were still on TB treatment when hospitalized for TBM diagnosis. HIV status was available for only 383 subjects, in whom HIV prevalence was 15.4%. Moreover, 16 (3.2%) were multidrug-resistant (MDR). The majority of subjects (382 patients; 76.9%) were diagnosed with Grade II TBM. Clinical diagnoses according to the Marais criteria were 61 (12.3%) definite, 290 (58.3%) probable, and 146 (29.4%) possible TBM (Table 1).

Details of demographics and TBM diagnoses in this study showed that 65.4% of subjects had at least one extraneural TB (Table 1). Furthermore, the types of extraneural TB found in the study subjects were mostly pulmonary TB (n=308; 77.0%), followed by spondylitis TB (n=31; 7.8%), and gastrointestinal TB (25 subjects; 6.3%). The definite extraneural TB diagnosis was not documented in the medical records. Besides, the type of extraneural TB found was extraneural TB diagnosis, which was present in 325 (65.4%) subjects, with some subjects having more than one diagnosis of extraneural TB. This resulted in a total of 400 diagnoses of extraneural TB. From 325 subjects who had extraneural TB, HIV status was available in only 260 subjects (40 HIV-

Table 2 Diagnosis of Extraneural Tuberculosis (n=325)*

Type of Extraneural TB	Total (n=400)	HIV-infected** (n= 40)	HIV-negative** (n=220)
Pulmonary TB	308 (77.0)	36 (90.0)	212 (96.4)
Spondylitis TB	31 (7.8)	1 (2.5)	17 (7.7)
Gastrointestinal TB	25 (6.3)		
Abdominal/peritonitis TB	15 (3.8)	5 (12.5)	15 (6.8)
Hepar TB	7 (1.8)		
Intestinal TB	3 (0.8)		
Lymphadenitis TB	16 (4.0)	1 (2.5)	12 (5.5)
Pleuritis TB	5 (1.3)	0 (0)	4 (1.8)
Adrenal TB	4 (1.0)	0 (0)	2 (0.9)
Bone TB	3 (0.8)	0 (0)	3 (1.4)
Myocarditis TB	2 (0.5)	0 (0)	2 (0.9)
Renal TB	2 (0.5)	1 (2.5)	1 (0.5)
Joint TB	1 (0.3)	0 (0)	1 (0.5)
Cystitis TB	1 (0.3)	0 (0)	0 (0)
Pericarditis TB	1 (0.3)	0 (0)	1 (0.5)
Arachnoiditis TB	1 (0.3)	0 (0)	1 (0.5)

Note: *=One subject may have more than one extraneural TB diagnosis; **=HIV data was available in only 260 subjects
TB=tuberculosis

positive and 220 HIV-negative). The most common extraneural TB in both groups was pulmonary TB. No statistical difference was found between groups of HIV-positive and HIV-negative subjects with extraneural TB (p=0.101) (Table 2).

The in-hospital mortality rate in subjects with extraneural TB was 28.9%. Pulmonary TB was found in 88 (27.1%) subjects who died and 220 (67.7%) subjects who survived. Among all subjects with ≥2 extraneural TB locations, 62 (95.4%) had pulmonary TB as one of the diagnoses. One (1.5%) out of 17 (26.2%) subjects who died with ≥2 extraneural TB locations did not have pulmonary TB.

Ninety-four subjects with extraneural TB died during hospitalization. There was no statistical difference between the groups of deceased subjects who had extraneural TB in 1 location (number of deaths 77/260), 2 locations (number of deaths 14/59), and disseminated TB (number of deaths 3/6) (p=0.340) (data not shown).

Discussion

This study found that the prevalence of extraneural TB was quite high with 13.1% of them diagnosed with >1 extraneural TB location; however, the proportion did not differ between subjects with or without HIV.

The median age of TBM subjects was 31 years and most were male. This is similar to previous studies where subjects were mostly male and in the age range of 21–44 years.[10–15] Before admission, 39.2% of subjects had a history of TB infection in this study, while in other studies, the number varied from 6.7 to 58%.[10–15]

The HIV prevalence was 15.4%. This figure is higher than previous studies in several countries, namely in Turkey, Madagascar, and India, which ranged from 0.6 to 7.3%, but somewhat similar to a previous study in Indonesia.[10–12,16] In other countries with higher HIV prevalence, such as South Africa and Uganda, TBM patients have higher HIV prevalence, namely 83.7% and 96%, respectively.[15,17] TBM with HIV-positive has a higher mortality rate of during hospitalization.[17,18] In this study, 27.4% of subjects died during hospitalization, similar to previous studies from Madagascar and Brazil, with 28% and 29% mortality rates, respectively.[12,14]

Subjects were mostly diagnosed with grade II TBM, and the majority were classified as probable TBM. The MRC grading found in this study is similar to other studies in Vietnam and Uganda.[17,19] Predominance of probable cases is also found in several studies in India, Vietnam, and South Africa, which is 47.9–78.2 %,[11,18,19] while a study from South Africa has found that most subjects are grade III and definite TBM.[15] The definite cases in this study are found to be lower compared to other studies whose definite cases exceeded 30%.[11,16–19] However, in a previous microbiological study in the same setting, the definite cases reached 50%.[20] This may reflect incomplete data in the medical records.

The proportion of extraneural TB in this study (65.4%) was higher compared to other TBM studies from India, Turkey, Brazil, and East China which was 29.1–51.3%, however the most common extraneural TB was similar, namely pulmonary TB.[10,11,13,14] In many studies, extraneural TB is more likely to be found in HIV-positive patients,[21] but in this study, extraneural TB was found in both HIV-positive and HIV-negative subjects. The number of extraneural TB cases was compared to mortality incidence and hospitalization duration, resulting the median hospitalization duration of these patients was similar; however, mortality incidence was quite the contrary. No correlation was found between the number of extraneural TB involvement and mortality status (p=0.414). In addition, this study showed that the percentage of mortality among subjects with disseminated TB was the highest. These findings might be influenced by the limited observation time, which was only during hospitalization.

This study has some limitations as variables were only partially collected in some subjects. The definitive diagnosis of TBM may not be well recorded in the medical records. Data on the definitive diagnosis of extraneural TB need to be included. Furthermore, the diagnosis of extraneural TB might be overlooked in some subjects.

In conclusion, the prevalence of extraneural TB in TBM patients in this study is high and predominated by pulmonary TB. The proportion of extraneural TB in HIV-positive subjects is similar to those without HIV. There is no correlation between the number of extraneural TB locations and mortality status. This study may help in discovering the prevalence of extraneural TB in TBM patients and its accompanying characteristics. Further studies may be needed to explore the pathomechanism of extraneural TB in TBM patients and the influencing factors to improve the wellbeing TBM patients.

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