Clinical Profile of Extrapulmonary Tuberculosis Among TB-HIV Patients in Cipto Mangunkusumo Hospital

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ABSTRACT

Background: *In view of increase in incidence of EPTB after the epidemic of human immunodeficiency (HIV) virus infection, the clinical profile of EPTB in patients with HIV infection was studied.*

Objective: *To obtain the profile and to assess the distribution of EPTB in TB-HIV patients.*

Methods: *We conducted a descriptive cross-sectional study by browsing through the medical records of TB-HIV patients who received treatment in HIV referral center (POKDISUS) Cipto Mangunkusumo Hospital between July 2008-December 2010. Ethical clearance was obtained from the ethical committee of Faculty Medicine, Universitas Indonesia and written on approval letter 135/PT02.FK/ETIK2010.*

Results: *EPTB prevalence was 32,95%. Overall, medical record of 522 HIV-positive TB patients were evaluated. The majority of the patients were males (84.3%), 18-40 years age group (91.9%), finished mid-level education (77.3%), and 31.4% belonged to Batavian ethnic group. Intravenous drug use were found to be the main transmission risk factor, representing 60.5% of the subjects. Prolonged fever (63.4%) was the most common clinical manifestation. Negative Acid Fast Baciili (AFB) smears were found in 34.9% of the subjects, while CD4+ counts of <50 cells/μL was found in 34.9% of the subjects. The most frequent site of extrapulmonary TB was peripheral lymph node (18,0%).*

Conclusion: *Our study therefore gives some perspective of EPTB and HIV coinfection in Indonesia thereby setting a platform for more studies. Furthermore, our findings might help reinforce the need for integrated management of HIV and TB in Indonesia, which is mandatory for the global fight against TB.*

Key words: *Extrapulmonary Tuberculosis, HIV*

ABSTRAK

Latar Belakang: Dikarenakan terjadinya peningkatan insidensi tuberkulosis ekstra paru pasca epidemi infeksi *human immunodeficiency virus* (HIV), diperlukan penelitian mengenai profil klinis tuberkulosis ekstra paru (EPTB) pada pasien dengan infeksi HIV.

Tujuan: Untuk memperoleh profil dan menilai distribusi tuberkulosis ekstra paru pasien TB-HIV.

Metode: Studi merupakan penelitian potong lintang deskriptif dengan mempelajari rekam medis pasien TB-HIV di pusat rujukan HIV (POKDISUS) Rumah Sakit Cipto Mangunkusumo antara Juli 2008-Desember 2010. Lolos kaji etik diperoleh dari komite etik Fakultas Kedokteran, Universitas Indonesia dengan surat persetujuan nomor 135/PT02.FK/ETIK2010.

Hasil: Prevalensi EPTB sebesar 32,95%. Mayoritas terdiri dari laki-laki (84,3%), usia 18-40 (91,9%), menyelesaikan pendidikan tingkat menengah (77,3%), dan 31,4% kelompok etnis Betawi. Penggunaan obat narkotika intravena menjadi faktor risiko transmisi utama (60,5%). Demam berkepanjangan (63,4%) menjadi manifestasi klinis yang paling sering ditemui. Apusan basil tahan asam (BTA) negatif ditemukan pada 34,9%, jumlah CD4 <50 sel/ul ditemukan pada 34,9% dari subyek. Lokasi terbanyak tuberkulosis ekstra paru adalah limfadenopati perifer (18,0%).

Kesimpulan: Penelitian in memberikan perspektif terhadap TB ekstra paru dan koinfeksi HIV di Indonesia, sehingga membuka peluang untuk penelitian lainnya. Selanjutnya, penelitian ini dapat membantu meningkatkan kebutuhan terhadap manajemen terintegrasi pada HIV dan TB di Indonesia, yang diperlukan untuk melawan TB secara global.

Kata kunci: Tuberkulosisi ekstra paru, HIV

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INTRODUCTION

Pulmonary Tuberculosis (PTB) is a common manifestation in adults with TB-HIV co-infection. However, as the immunity gets worse, HIV-infected individuals more often develop extrapulmonary and disseminated TB. The Incidence of extrapulmonary TB (EPTB) has increased after the epidemic of HIV infection. It is responsible for 10-50% of all TB case among HIV negative individuals, while in HIV positive group, it occurs in 38-80%.[1] Several studies found that up to 50% TB-HIV patients die during TB treatment.[2,3] In Thailand, verbal autopsies, laboratorium data, and medical records of TB-HIV patients who die during TB treatment state that TB is the cause of death in 27% of those patients, whereas more than a half of them were disseminated and Multi Drug Resistant TB (Complicated EPTB).[2]

In many part of the world, many studies had mentioned susceptibility of HIV patients to develop extrapulmonary TB.[4-6,8] Additionally, in the recent guideline to improve diagnosis and treatment of extrapulmonary TB, World Health Organization (WHO) states EPTB in HIV-infected person has become a new clinical problem especially in remote area where

advance modality supporting diagnosis and treatment are unavalaible. Although pulmonary TB is the most common presentation of TB disease, it can involve any organ in the body. Extrapulmonary Tuberculosis is defined as the isolated occurrence of TB in any part of the body other than lungs such as lymph nodes, abdomen, genitourinary system, musculoskeletal and meninges. Mycobacteria may spread to any organ of the body through lymphatic or haematogenous dissemination and lie dormant for years at a particular site before causing disease. Manifestations may relate to the system involved, or simply as prolonged fever and non specific systemic symptoms. Tuberculosis is a worldwide disease and one of the major health problems of Indonesia. Extrapulmonary tuberculosis is increasing all over the world. However, only limited data is available about the situation of EPTB in developing countries including Indonesia, hence diagnosis may be elusive and is usually delayed.[1,3] This study reviews the general spectrum of cases diagnosed with EPTB at a large HIV referral center (POKDISUS) and presents their key demographics, dominant infection sites and the laboratory findings.

METHODS

This was a descriptive cross-sectional study by browsing medical records of TB-HIV patients conducted between July 2008-December 2010 at HIV Refferal Center of Cipto Mangunkusumo General Hospital that served as referral and treatment centers for HIV and TB in Indonesia. We included all patients with extrapulmonary TB, with single or multiple organ involvement and also MDR-TB patients. TB case with multiple organ involvement was classified based on the site representing the most severe form of disease. We excluded patients with both pulmonary and extrapulmonary tuberculosis, as per WHO guidelines they were defined as pulmonary. We explored sosio-demographic characteristic, clinical and laboratorium findings among patients co-infected with HIV and tuberculosis. Diagnosis of HIV infection was confirmed in all cases.Ethical clearance was obtained from the ethical committee of Faculty Medicine, Universitas Indonesia and written on approval letter 135/PT02. FK/ETIK2010. Patient confidentiality was assured for all the information provided.

RESULTS

Among 522 HIV-positive patients with TB, 172 subjects were extrapulmonary TB (32.95%). One hundred seventy two medical records of EPTB patients, and its distribution based on characteristic mentioned above were enrolled. Our subjects were mostly males (84.3%); the majority of the patients belonged to the 18-40 years age group (91.9%). The educational status and ethnicity of patients showed that 77.3% finished mid-level education, and 31.4% of the subjects belonged to Batavian ethnic group. Intravenous drug use were found to be the main transmission risk factor, representing 60.5% of the subjects, as seen in table 1. Prolonged fever (63.4%) was the most common clinical manifestation followed by chronic cough (60.5%). Negative Acid Fast Baciili (AFB) smears were found in 34.9% of the subjects, while CD4+ counts of <50 cells/μL was found in 34.9% of the subjects. The most frequent extrapulmonary site was peripheral lymph node (54.6%), followed by meningitis TB (12.7%) (Table 2)

Table 1. Demographic Profile

Characteristc	n	%
Sex		
Male	145	84,3
Female	27	15,7
Age (Years Old)		
<18	1	0,6
18 - 40	158	91,9
41 - 60	12	7,0
> 60	0	0,0
Ethnic		
Batavian	54	31,4
Java	38	22,1
Sundanese	22	12,8
Batak	17	9,9
Padang	11	6,4
Palembang	1	0,6
Bugis	2	1,2
Tionghoa	12	7,0
Educatonal Level		
Low level educaton	14	8,1
Mid level educaton	133	77,3
High level educaton	24	14,0
HIV transmission route		
Sexual	44	25,6
IVDU	104	60,5
Sexual and IVDU	19	11,0
Sexual and Transfusion	3	1,7
Sexual and Blood exposure	1	0,6
Sexual, IVDU, and Tranfusion	1	0,6

Table 2. Clinical, Distributon and Laboratorium Findings

	n	%
Symptoms		
Chronic cough	104	60,5
Loss of weight	94	54,7
Prolonged fever	109	63,4
Malaise	73	42,4
Night sweats	62	36,0
Neurological manifestaton	31	18,0
Haemoptysis	3	1,7
Oral ulcer	37	21,5
Nausea	50	29,1
Diarrhea	66	38,4
Site		
Panuviets	7	1,3
Pleural effusion	11	2,1
Central Nervous System (Meningits/ME TB)	22	4,2
Lymphadenopathy colli	94	18,0
Milliary Tuberculosis	0	0,0
Abdominal :		
- Peritoneum	8	1,5
- Colon	2	0,4
- Liver	3	0,6
Pericardits TB	0	0,0
Osteomielits TB	0	0,0
Acid Fast Bacilli smear		
Positve	13	7,6
Negatve	60	34,9
Unavailable	99	57,6
CD4 (sel/mm3)		
< 50	60	34,9
51 - < 100	47	27,3
101 - < 200	25	14,5
> 200	16	9,3
Unavailable	24	14,0

DISCUSSION

TB involves virtually all organ systems of the body. The most common presentation is pulmonary TB. It can also occur with involvement of other sites but is still called as pulmonary TB. When TB involves other sites without the involvement of lungs it is known as EPTB. The incidence of EPTB is increasing with the emergence of human immunodeficiency virus (HIV). In the era before HIV pandemic, EPTB constituted 10-20% of tuberculosis cases. Now, with the HIV pandemic it accounts for more than 50% of all TB cases.[9]

A prevalence of EPTB of 32.95 % in our study is quite high compared with a recent finding of EPTB of 17% in Yaoundé the capital city of Cameroon. Our finding is, however, similar to what was found in Nepal in 2008 and in India in 2006, which are settings with similar TB burden like ours. Relatively lower prevalence of 20-25% was found in Iran and in many areas of the United States, which are areas with lower TB burden[10]. In our study, out of 172 cases of EPTB, 145 (84.3%) cases were in males. The distribution of male gender in this study is consistent with several previous reports from Barthwal.[1] This finding is in accordance with other studies. However, several other studies have shown female reponderance. The causes of female preponderance in their studies were thought to be due to low socioeconomic status and male dominant society.[6,9,11-15]

Most of our study group patients (91,9%) belonged to the age group of 18-40 years, which is the sexually active age and is also the most productive in one's life. In India, a study reported 76% in the age group of 21-40 years and also the occupational profile of their patients revealed that a majority of them were farmers and laborers followed by transport drivers[16]. Mohanty et al[17] reported 36.8% patients working as manual laborers while Rajsekaran et al[18] found majority (55.6%) of patients working as farmer. Other authors have found sero-positivity rate was highest among those who were unemployed (40%) followed by the business professionals (35%)[19]. The percentage of the professions is thus seen to vary in different studies, largely due to the differences in the occupational patterns and the source from where the patients were selected. Some studies mentioned strong correlation of TB with sosio-economic factor,

whereas other studies correlates knowledge and educational level. Patients with a better knowledge has a better adherence. This influences treatment outcome, including the progresivity of TB.[20] However in our study, EPTB were mostly found among of them who finished mid-level education. No significant correlation between the time of dignosis of TB after HIV-positive diagnosis was established. Contrast to the study in Thailand evaluating cause of death in TB-HIV patients, found that delay of TB diagnosis were partially responsible for those incidence.[2] Delay of diagnosis also motivated the release of new algorithm for screening TB in HIV-infected individuals by New England Journal of Medicine in 2010.[3]

There are some factors which influence progresivity of TB. Among them is host immunity status. As the age gets older, immunity status is weakened. Data from recent study is consistent with epidemilogical finding in United States where 27% of extrapulmonary TB were found in those age >60 years old where the mean age for this case is 44 years old.[12] This is contrast to our study where EPTB were mostly found in group age < 35 years. Similar results were reported in Barthwal et al's.[1] In Germany, EPTB even were found in younger group where the mean age is below 15 years old.[6]

Extrapulmonary TB were mostly found among Batavian ethnic group. It can be explained since this study was conducted in Jakarta where majority of the population are batavians. Unfortunately, we did not explore the spesific characteristic of Batavian ethnic group that enable them to be more susceptible to develop EPTB.

Besides, chronic chough (60.5%), the most common reported symptoms were loss of weight (54.7%) and prolonged fever (63.4%). The clinical presentation of TB depended on the stage of HIV-1 infection and associated degree of immunodeficiency. In early HIV-1 infection, the features are characteristic for post primary TB and resemble those seen in the pre-HIV era. More advanced immunodeficiency is usually associated with an increased frequency of disease resembling primary pulmonary TB and extra-pulmonary disease. Prolonged insidious symptoms found in majority of patients consisting of weight loss, prolonged low grade fever and nocturnal sweat may delay the diagnosis. The classical picture of pulmonary TB is seenmainly in less immuno-compromised patients
(CD4 counts > 200 cells/mm3)[21]. A BMI of <18 was found to be a significant predictor of a low CD4 count. Apart from suggesting severe immunosuppression, these results imply that nutritional support should form part of the comprehensive package of care of HIV-infected TB patients[22].

The frequency of EPTB cases by site was highest in lymph nodes (18.0%), followed by meningens (4.2%). Study done by Sreeramareddy et al in western Nepal also showed TB of the lymph nodes as the commonest location of EPTB (42.6%). Extrapulmonary tuberculosis at a regional hospital in Thailand also showed lymph nodes as a common location (29.6%).[1] Our result was comparable with that of the other studies. Some other studies have shown other sites as the commonest location of EPTB other than lymph nodes. Study done by Noertjojo et al in Hong Kong suggested pleura as the most common site of EPTB followed by lymph nodes. In USA, bone and joints were most common sites.[9] Meningitis tuberculosis was found to be second common sites of EPTB in our series. In another study, they also found a correlation between low CD4 counts and chance to have meningeal tuberculosis.[23] Since the carry a high risk of death, care for similar patients should include consideration of these form of EPTB. Lymph node enlargement are also associated with malignancy, hence evaluation for malignancy has to be conducted. Singh et al, reported lymphadenopathy in 21 (18.6%) subjects with supraclavicular lymphadenopathy being the most common findings in 14 (12.4%) subjects with mediastinal mass.[24]

Unavailability of laboratorium finding of some medical records of our subjects is an obstacle in this study. Moreover data regarding Acid Fast Bacilli status was unavailable in more than a half of our patients. In the remaining subject with acid fast bacilli status, less than a quarter of them were smear-positive. This was consistent with report from Toman's et al that HIV-related TB are usually smear-negative.[7] The most widely used TB diagnostic test, microscopic examination of sputum for acid-fast bacilli (AFB), is highly insensitive in HIV-infected patients, and modern broth-based culture methods are not routinely available in most developed countries[25]. Extrapulmonary TB occurs frequently and causes high mortality, but definitive diagnosis requires culture or pathological examination of specimens that may be difficult to obtain.[25] In World Health Organization (WHO) guidelines for TB diagnosis, mycobacterial

sputum culture must be performed in HIV-infected patients who are sputum smear negative and have a clinical suspicion of TB, reduced from three to two the number of sputum specimens that need to be examined before calling a TB suspect ‘‘smear negative,’’ and provided simplified guidelines for diagnosing common types of extrapulmonary TB. The WHO’s guidelines for diagnosing extrapulmonary TB recommend using symptoms or signs to guide testing of extrapulmonary sites. In multiple studies from high-burden TB countries, mycobacterial blood culture has been found to aid TB diagnosis in HIV-infected patients

with advanced immune suppression. Mycobacterial blood culture should probably be reserved for use in severely ill HIV-infected patients[25].

CD4 counts showed that extrapulmonary TB is more frequent in subject with CD4 counts of < 100 cell/

mm^3. This can be explained since CD4 level is one of the parameter to determine the stage of HIV infection that represent degree of immunity deficiency. It is estimated that more than 50% of HIV-infected patients will develop TB in their lifetime, and the annual risk of developing TB if HIV infected is 10%. Various studies have shown high mortality rates in HIV-infected TB patients in resource-limited settings. HIV infection increases the risk of acquiring TB, alters the clinical presentation of TB and reduces overall survival. High mortality rates in these patients have been attributed to severe immunosuppression as measured by CD4+ cell count, and to lack of antiretroviral therapy (ART)[22].

CONCLUSION

To conclude, extrapulmonary tuberculosis in HIV infected patients occurs during advanced immunosuppression with male and lymph node involvement being the commonest. The possibility of EPTB should be considered in this group of patients, and also TB screening must be conducted to all HIV patients. But, care notification is needed because the major case of extrapulmonary tuberculosis in HIV infected patients are usually smear-negative. Our study therefore gives some perspective of EPTB and HIV coinfection in Indonesia thereby setting a platform for more studies. Furthermore, our findings might help reinforce the need for integrated management of HIV and TB in Indonesia, which is mandatory for the global fight against TB. A comprehensive research plan is required to estimate the disease burden country-wide. Health care providers must remain cognizant of emerging issues such as increasing drug resistance and HIV prevalence in the country. A prospective cohort study can be conducted to asses risk factors/ predictors of EPTB in HIV population, thus a more optimal treatment can be established.

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