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Short Communication

Factors influencing histoplasmosis incidence in multidrug-resistant pulmonary tuberculosis patients: A cross-sectional study in Indonesia

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Abstract

Histoplasmosis is an infectious disease caused by the dimorphic fungus *Histoplasma capsulatum*, which in chronic conditions, is generally difficult to distinguish from pulmonary tuberculosis (TB) based on its clinical appearance; therefore, diagnostic errors could occur. Meanwhile, the prevalence of multidrug-resistant pulmonary TB (MDR-TB) in Indonesia remains high. Study determining the incidence of histoplasmosis in MDR-TB is unavailable worldwide. The aim of this study was to determine the risk factors of histoplasmosis incidence in MDR-TB patients in Indonesia. A cross-sectional was conducted at H. Adam Malik General Hospital, Medan, Indonesia and the ELISA platform (semi-quantitative) was used to detect histoplasma antibodies. Factors associated with histoplasmosis incidence among MDR-TB were determined using a Chi-squared test. A total of 50 MDR-TB patients were included this study of which 14 of them (28%) had histoplasmosis. The majority of histoplasmosis occurred in males, in MDR-TB patients with a history of TB treatment and among who had chest x-rays with far-advanced lesions. However, statistical analyses indicated none of those factors (sex, TB treatment history, status of the lung) as well as age group, acid-fast bacillus result, *Mycobacterium tuberculosis* culture result, having pet, living in damp house, working in the field or plantation, having HIV infection and smoking status were associated with histoplasmosis incidence. This study highlights that the incidence of histoplasmosis is relatively high and therefore further studies are important to be conducted in Indonesia that has a high MDR-TB cases.

Keywords: Tuberculosis, resistant TB, MDR-TB, histoplasmosis, histoplasma

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Introduction

Histoplasmosis is a recognized disease caused by *Histoplasma capsulatum*, with soil serving as an environmental reservoir [1,2]. Mapping of histoplasmosis in Southeast Asia reported a total of 407 cases which is from Thailand (233 cases), Malaysia (75 cases), Indonesia (48 cases), and

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Singapore (21 cases) [2]. A study reported 13.61% cases of *H. capsulatum* in Medan, North Sumatra, Indonesia based on histoplasmin skin test [3]. The most common precipitating factors of positive histoplasmin test results are associated with pets, caves and forests [4]. Studies using the intradermal reaction test (IDR) with histoplasmin demonstrated a high prevalence of Histoplasma exposure in Americas general population and parts of Asia and Africa [5-8]. Autopsy studies in Brazil and Peru identified 7–28% of deaths related to tuberculosis (TB) and 12%–21% of deaths related to histoplasmosis [9,10].

According to The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC), the gold standard criterion for histoplasmosis diagnosis is positive culture or histopathology or direct histoplasmic microscopy of clinical specimens (bone marrow, blood, biopsied tissue, sterile fluid, or respiratory specimens) [11]. However, EORTC/MSGERC also states that a diagnosis can be made with evidence of environmental exposure, compatible clinical disease and the presence of histoplasmic antigens in body fluids [12]. Culture has low sensitivity in acute and subacute cases while PCR showed a sensitivity of 98%, a specificity of 99%, and a positive and negative predictive value of 82% and 99%, respectively [13].

Several environmental conditions have been documented to support the presence of *H. capsulatum* in an area including high temperature, high humidity and soil pH above 10 and below 5 [14]. The areas with a high number of reported cases of histoplasmosis and significant skin reactivity to histoplasmin had soil types (pH ≥7) that overlapped [14]. The cities of Benin (15%) and Calabar (6%) which reported the highest rates were both in humid rainforest zone [14]. Individuals with a home or workplace adjacent to the garden had higher levels of skin reactivity than those without fruit trees [14]. The skin test survey showed a significantly higher positivity rate among people working/living around the forest, most of whom were from rural areas, a finding consistent with a previous report reporting 8.8% histoplasmin reactivity in patients visiting rural clinics [14].

Histoplasmosis has been considered a co-infective disease with acquired immunodeficiency syndrome (AIDS). A previous study found that the majority of histoplasmosis patients were men with a mean age of 35 years old and immunodeficiency status was found in the majority of patients [15]. Another study found that among histoplasmosis patients, 58% had human immunodeficiency virus (HIV) infection, 28% of patients had other immune deficiencies, and only 14% had no immune deficiencies [16]. Other than HIV infection, histoplasmosis is associated with environmental and toxin exposures, autoimmune diseases, malignancies and their treatment, chronic lung disease, immunosuppressive therapy, pancytopenia, T-cell deficiency, and malnutrition [17]. A study demonstrated that variables associated with decreased incidence of histoplasmosis were antiretroviral treatment for more than 6 months, fluconazole treatment, and pneumocystosis among HIV-positive patients [18]. A study found that the mortality was 13.5% at 1 month, 17.5% at 3 months, and 22.5% at 6 months after the diagnosis of histoplasmosis [18].

The clinical presentation of acute pulmonary histoplasmosis is milder and often asymptomatic in immunocompetent patients. After an acute pulmonary histoplasmosis infection, chronic pulmonary histoplasmosis (CPH) may develop. CPH is generally difficult to distinguish from pulmonary TB based on its clinical appearance; therefore, diagnostic errors often occur [19]. Considering that Indonesia is a Second World country with the largest number of TB cases and the success rate of therapy is below the target, the possibility of multidrug-resistant pulmonary tuberculosis (MDR-TB) with histoplasmosis can occur. Pulmonary TB, especially MDR-TB, can coexist with CPH. A study at the Persahabatan Hospital showed fungal colonization in patients with former MDR-TB was 68.9% (42 out of 61 patients) [20].

The similarity of factors influencing the incidence between histoplasmosis and TB makes it highly likely that histoplasmosis may also be associated with MDR-TB. However, study assessing the association between MDR-TB and histoplasmosis is limited. Therefore, the aim of this study was to determine the risk factors of histoplasmosis incidence in MDR-TB patients in Indonesia.

Methods

Study setting and patients

A cross-sectional study was conducted at MDR-TB Polyclinic of H. Adam Malik General Hospital, Medan, Indonesia from December 2022 to April 2023, to determine factors associated with histoplasmosis incidence in MDR-TB patients. The sampling method employed was total sampling.

All MDR-TB patients who: (a) aged >18 years; (b) having confirmed diagnosis of MDR-TB based on molecular rapid tests; (c) willing to participate in the study by signing an informed consent form were considered eligible. All patients with MDR-TB with extensive resistance, having fungal infection, pregnancy, or having severe psychosis were excluded.

Data collection and study variables

Some potential associated factors were collected during the study through interviews, medical records and direct assessment. The interview asked the patients related to comorbid diseases, history of previous TB treatment, history of having pets, condition of the house, history of working in the field or plantations, and the patient's smoking history. Data regarding anti-TB therapy history, Mycobacterium Growth Indicator Tube (MGIT) culture results, and the extent of the lesion on the chest x-ray were also collected.

The dependent variable of the study was the incidence of histoplasmosis. Briefly, approximately 5 mL of venous blood was collected. Histoplasma IgG antibody analysis was then performed using an MVista Histoplasma Quantitative Enzyme Immunoassay (EIA) kit (MiraVista Diagnostics, Indianapolis, US). This semi-quantitative platform was able to detect the presence of IgG Histoplasma antibody in MDR-TB patients.

Statistical analysis

The data obtained was processed using the SPSS computer program version 26.0 (SPSS Inc., Chicago, USA). Chi-squared test or Fisher exact test was used to assess risk factors associated with histoplasmosis incidence in MDR-TB patients as appropriate. A *p*-value less than 0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 50 MDR-TB patients were included in this study and the characteristic data of the patients are presented in **Table 1**. The majority of the patients were male and aged between 46–60 years old age. Among the patients, most were non-smokers, 22% had a history of working in the field or plantations and 48% lived in damp houses. The most common comorbidity recorded was diabetes mellitus (DM) and 50% of them had no comorbid. There were 38% of patients that had far-advanced extensive lesions based on their chest x-rays.

Table 1. Demographic and clinical characteristics of MDR-TB patients included in the study (n=50)

Subject characteristics	Frequency	Percentage
Gender		
Male	36	72
Female	14	28
Age (years old)		
16–30	7	14
3–45	16	32
46–60	21	42
>60	6	12
Comorbidity		
Diabetes mellitus	22	44
HIV	2	4
Hypertension	3	6
Asthma	1	2
Cancer	1	2

Subject characteristics	Frequency	Percentage
No comorbidities	25	50
Tuberculosis treatment history		
No	18	36
Yes	32	64
Acid-fast bacillus result		
Positive	11	22
Negative	39	78
Mycobacterium tuberculosis culture		
Positive	34	68
Negative	16	32
Pets		
Yes	15	30
No	35	70
Damp house		
Yes	24	48
No	26	52
History of working in the field or plantation		
Yes	11	22
No	39	78
History of smoking		
Smoker	0	0
Ex-smoker	15	30
Non smoker	35	70
Extent of the lesion on chest X-ray		
Minimal advanced	15	30
Moderately advanced	16	32
Far-advanced	19	38
Histoplasmosis		
Negative	36	72
Positive	14	28

Factors associated with histoplasmosis incidence

Out of the total MDR-TB patients, 14 (28%) patients tested positive for histoplasmosis. Our univariate analysis indicated that sex (p=1.000), age group (p=0.116), TB treatment history (p=0.744), acid-fast bacillus result (p=0.148), *Mycobacterium tuberculosis* culture result (p=0.330), having pet (p=1.000), living in damp house (p=0.352), working in the field or plantation (p=1.000), having HIV infection (p=1.000), smoking status (p=1.000), and the status of the lung lesion (p=0.069) were not associated significantly with the incidence of histoplasmosis (**Table 2**).

Table 2. Association between factors and histoplasmosis incidence in MDR-TB patients

Risk factor	Histoplasmosis				*p*-value
	Negative (n=36)		Positive (n=14)		
	n	%	n	%	
Gender					1.000
Male	26	72.2	10	71.4	
Female	10	27.8	4	28.6	
Age (years old)					0.116
16–30	7	19.4	0	0	
31–45	13	36.1	3	21.4	
46–60	13	36.1	8	57.1	
>60	3	8.4	3	21.4	
TB treatment history					0.744
No	14	38.9	4	28.6	
Yes	22	61.1	10	71.4	
Acid-fast bacillus result					0.148
Positive	10	27.8	1	7.1	
Negative	26	72.2	13	92.9	
Mycobacterium tuberculosis culture					0.330
Positive	10	27.8	6	42.9	
Negative	26	72.2	8	57.1	
Pet					1.000
Yes	11	30.6	4	28.6	
No	25	69.4	10	71.4	

Risk factor	Histoplasmosis				*p*-value
	Negative (n=36)		Positive (n=14)		
	n	%	n	%	
Damp house					0.352
Yes	17	47.2	9	64.3	
No	19	52.8	5	35.7	
History of working in the field or plantation					1.000
Yes	17	47.2	6	42.9	
No	19	52.8	8	57.1	
HIV infection					1.000
Yes	2	5.6	0	0	
No	34	94.4	14	100	
History of smoking					1.000
Yes	26	72.2	9	64.3	
No	10	27.8	5	35.7	
Extent of the lesion on chest X-ray					0.069
Far advanced	11	30.6	8	57.1	
Moderate advanced	11	30.6	5	35.7	
Minimal advanced	14	38.8	1	7.1	

Discussion

MDR-TB, defined as resistance to isoniazid and rifampicin, is a growing threat and a significant burden on healthcare systems worldwide. A meta-analysis study demonstrated that a history of previous TB disease, incomplete TB treatment, and failure of TB treatment were strongly associated with MDR-TB [24]. Our study found the majority of MDR-TB patients who tested positive for histoplasmosis were male and aged 46–60 years old. A study reported a male-female ratio of 1.2:1 among suspected pulmonary TB with histoplasmosis and the mean age at presentation was 39 ± 14 years. The study also reported that 35% of the patients were people living with HIV, compared to 44.1% who had been diagnosed with TB [17]. Our study only found two HIV-positive individuals among the MDR-TB patients. This implies that there is a lower prevalence of MDR-TB among HIV patients in comparison to those with pulmonary tuberculosis. Unfortunately, this study could not find any associations of sex, age group, TB treatment history, having HIV infection among MDR-TB patients with the incidence of histoplasmosis.

Indonesia's tropical climate, with its high humidity and warm temperatures, provides an ideal environment for the growth of *H. capsulatum*, where the primary reservoir is soil [4,21]. Our study found that 28% of the MDR-TB patients tested positive for histoplasmosis and 42.9% of them had a history of working in the field or plantation, indicating that they were from agricultural areas. However, a study in Jakarta, a city in Indonesia, reported histoplasmosis was present in 11% of adults and 2.7% of children [22]. These similarities suggest that the occurrence of histoplasmosis in Indonesia remains relatively high. Other fungal pulmonary infections, such as coccidioidomycosis and paracoccidioidomycosis, are not endemic to Indonesia. Consequently, the occurrence of these infections is possible only through international travel [23]. Moreover, in Latin America, the estimated histoplasmosis incidence is equivalent to that of TB in people living with HIV, and the highest overall prevalence of prior histoplasmosis exposure was observed in Guatemala, Mexico [25].

The true burden of HIV-associated histoplasmosis is not fully known or overlooked, mainly due to its non-reportable disease. Histoplasmosis is still widely mistaken for MDR-TB, leading to numerous preventable deaths [28]. The clinical presentation of histoplasmosis is also very similar to that of TB, including primary pulmonary involvement that is self-limited and a latent phase that can cause coin lesions on chest radiographs; chronic secondary progressive lung disease localized at the apex of the lung and causing fever, coughing, and night sweats; and then progressing with widespread involvement [27]. A study reported that 44 of 45 patients had cavitation in the upper lobe, more often occurring in the right apex (84%). The cavity often had thick walls with some thickening of the apical pleura. Although calcified pulmonary granulomas are common (77.8%), hilar lymphadenopathy is rare (2.2%) compared with acute lung disease [19,29]. A cavity on a chest x-ray with a lesion diameter of >4 cm is called a far-advanced lesion. The majority of patients having this far-advanced lesion suffer from histoplasmosis.

Conclusion

This study found that 28% of MDR-TB patients tested positive for histoplasmosis. Interestingly, all factors, including sex, age group, TB treatment history, acid-fast bacillus result, *Mycobacterium tuberculosis* culture result, having pet, living in damp house, working in the field or plantation, having HIV infection, smoking status, and the status of the lung lesion had no significant association with the incidence of histoplasmosis. Although multiple risk factors have been included, this study suggests that there could be other factors associated with the incidence that were missed from our study and warrant further study.

Ethics approval

The study was approved by H. Adam Malik General Hospital, Medan, Indonesia (LB.02.02/XV.III.2.2.2/802/2023).

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this research are available from the corresponding author on request.

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