



The Prevalence of Histoplasmic Skin Test in Lung Cancer Patients

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Abstract

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BACKGROUND: Histoplasmosis is a disease caused by fungus called *histoplasma capsulatum*. Several studies reported cases of histoplasmosis that resembled malignancy. It is a fact that the clinical syndrome of neoplastic disease is not limited to malignancy so that infectious diseases should be considered in the differential diagnosis.

METHODS: This is descriptive research with consecutive samples. The sample was the patients with lung cancer aged 25–75 years old. The researcher assessed histoplasmic skin test on interdermal administered with fungal protein. After being observed for allergic reaction in 48–72 h, induration >5 mm shows positive reaction.

RESULTS: This research included 25 samples consisting of 21 men and 4 women. The result showed one person (4%) with positive histoplasmic skin test result containing squamous cell carcinoma and radiological features of solitary pulmonary nodule. There is an insignificant relationship between cancer cell types and the histoplasmic skin test results ($p = 0.24$). There is an insignificant relationship between histoplasmic skin test result and radiological features ($p = 0.48$).

CONCLUSION: There is one person with positive histoplasmic skin test result with squamous cell carcinoma and radiological features of solitary pulmonary nodule.

Introduction

Lung cancer in broad definition is all malignancies occurred in the lungs, including the malignancies originating from the lungs themselves and outside the lungs (tumor metastasis in the lungs) [1]. A study to a series of 2,908 patients with suspected diagnosis of lung cancer who underwent a biopsy showed that fungal infections were the most common lung infections resembling cancer, reaching 46% of diagnosed infections. The clinical manifestations and radiographical findings of such an infection are indistinguishable from those of a lung neoplasm [2].

Classically considered endemic mycoses, dimorphic fungus *Histoplasma capsulatum* is reported to cause fungal infection known as histoplasmosis [3]. Non-invasive biomarkers of fungal exposure that indicate the possibility of benign disease rather than malignancy will help clinicians evaluate Incidental Pulmonary Nodule (IPN) arising from endemic areas. Therefore, for a group of nodules that are exposed to histoplasmosis, the clinician will take an alternative approach to differentiate them from malignant disease, thereby increasing the evaluation of the nodules compared to imaging alone [4].

The histoplasmic skin test method evaluates the reactivity of patients with histoplasmosis when administered on intradermal with fungal protein (HMIN) [5]. Several studies recommend this methodology to be applied on the primary diagnosed of symptomatic or asymptomatic infections caused by *H.capsulatum* in immunocompetent individuals.

Methods

Subject

The research subjects consisted of 25 people (21 men and four women). All subjects were taken from Haji Adam Malik Hospital, North Sumatra University Hospital, and Elizabeth Hospital from January – December 2020. The inclusive criteria in this sample were lung cancer patients who had been diagnosed based on cytology/histopathology and upright lung cancer types (Small Cell Lung Carcinoma/SCLC or Non-Small Cell Lung Carcinoma/NSCLC), aged 25–75 years old. Exclusive criteria in the sample were patients with pulmonary TB, patients with

COPD-Asthma, and patients with lung cancer who were or were undergoing treatment.

Smoking status is divided to never smoker, ex-smoker, and current smoker. Brinkman index uses the product of the average number of cigarettes smoked per day and the length of smoking per year. There are three categories: Mild Brinkman Index (0–199), Moderate Brinkman Index (200–599), and Severe Brinkman Index (600) [6]. Body mass index is calculated as weight in kilograms divided by the square of the height on meters (kg/m^2) and is categorized into four groups according to Asian-Pacific cutoff points, underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}22.9 \text{ kg}/\text{m}^2$), overweight ($23\text{--}24.9 \text{ kg}/\text{m}^2$), and obese ($\geq 25 \text{ kg}/\text{m}^2$) [7].

This research has been accepted by the Ethics Committee, Faculty of Medicine, University of North Sumatra, and prior informed consent has been given to the subject.

Histoplasmic skin test

Prepare 0.1 cc of Histoplasma antigen in a 1cc syringe. Clean the volar area of the forearm with an alcohol swab. Injection histoplasma antigen on interdermal (needle slope $5\text{--}15^\circ$) from the distal forearm (injection is successful if the wheal $\pm 6 \text{ mm}$). Observe for allergic reactions that occur at the injection site in the form of induration (erythema is not measured) at 48–72 h after injection. Draw a line toward induration with a pen. Measure the diameter of induration and record the results. Induration $>5 \text{ mm}$ indicates a positive reaction.

Design study

This research is a descriptive study to the histoplasmic skin test on lung cancer patients. Statistical analysis used *statistical software* SPSS 17.0 with $p < 0.05$.

Results

The demographic characteristics of the subjects in this study based on age, gender, smoking status, Brinkman index, and body mass index are as shown in Table 1.

In this study, one person (4%) had a positive result on histoplasmic skin test with squamous cancer cell type and radiological features of solitary pulmonary nodules (Tables 2 and 3).

Table 1: Respondent's characteristic

Characteristics	n	(%)
Gender		
Male	21	84.0
Female	4	16.0
Age		
<40 years old	1	4.0
40–49 years old	3	12.0
50–59 years old	11	44.0
>60 years old	10	40.0
Cytology/histopathology		
Small cell ca	1	4.0
Adenocarcinoma	19	76.0
Squamous cell ca	5	20.0
Smoking status		
Ex-smoker	18	72.0
Never smoker	4	16.0
Current smoker	3	12.0
Index brinkman		
Mild	1	4.0
Moderate	4	16.0
Severe	15	60.0
Body mass index		
Overweight	1	4.0
Normoweight	12	48.0
Underweight	12	48.0

Discussion

In this study based on statistical analysis, the highest average was obtained at the age of 50–59 years old (36%) and >60 years old (36%). Reported in one study, older age is associated with cancer development due to biological factors including DNA damage over time and telomere shortenings. Thus, the median age of lung cancer diagnosis is 70 years old for both men and women [8].

The statistics in this study also indicate that the most types of lung cancer cells were adenocarcinoma (76%). Several studies in Indonesia and in Medan city similarly reported that the most common lung cancer is found in subtype of adenocarcinoma with advanced stag so that distant metastasis to several organs were found [9]. The study from Elisna *et al.* found that from the 1,874 subjects studied, 1,753 (94%) subjects were found with cytopathological type of adenocarcinoma [10].

It is found in this study the Severe Brinkman Index as the biggest category of smoking history at 60%. In the study of Soeroso *et al.*, it is found that smokers with Severe Brinkman Index are mostly clove cigarettes smokers [11]. Arumsari reported that almost half of lung cancer patients at Dr. Soetomo Hospital Surabaya are heavy smokers. The use of tobacco cigarettes is the biggest risk factor in the development of lung cancer, where up to 90% of lung cancers are caused by smoking [12].

From the statistics analysis of this study, the most body mass index category found are normoweight (48%) and underweight (48%). The report based on the results of a meta-analysis showed that obesity is a protective factor against lung cancer, especially on current smokers and ex-smokers [13]. Sankini also reported additional proves based on the results of his research that obesity is associated with a reduced risk of lung cancer [14].

It is found in this study the insignificant relationship between cancer cell types and histoplasmic skin test result. Bello reported from 294 patients diagnosed

Table 2: The relationship between cancer cell types and histoplasmic skin test results

	Skin test result		p value
	Positive (n)	Negative (n)	
Small cell carcinoma	0	1 (4.0%)	0.24
Adenocarcinoma	0	19 (76.0%)	
Squamous cell carcinoma	1 (4.0%)	4 (16.0%)	

with histoplasmosis, 15 showed lesions resembling primary neoplasia. The most common clinical symptoms include fever, cough, weight loss, and chest pain, while five patients were found asymptomatic. Clinically and radiologically, neoplastic diseases are not limited to malignancy; therefore, granulomatous infectious disease should be considered in the differential diagnosis [15].

Table 3: Radiological features and histoplasmic skin test result

Radiological features	Skin test result		p value
	Positive (n)	Negative (n)	
Solitary pulmonary nodule	1 (4.0%)	4 (16.0%)	0.48
Solitary pulmonary mass	0	19 (76.0%)	
Pleural effusion	0	1 (4.0%)	
Atelectasis	0	0	

Conclusion

Several studies reported histoplasmosis cases resembling malignancies. The histoplasmic skin test method evaluates the reactivity of patients with histoplasmosis when administered on interdermal with fungal protein (HMIN). In the study, there was one person (4%) with positive result in histoplasmosis skin test with squamous cell carcinoma. It is found in the study that there is an insignificant relationship between cancer cell with histoplasmic test results.

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