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Original Article

Prevalence of Antibodies to PPD and Lipoarabinomannan of *Mycobacterium tuberculosis* among Patients with an Indication of Fine Needle Aspiration Biopsy

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Recent increase in the incidence of lung cancer often makes it difficult to differentiate between lung cancer and tuberculosis (TB), due to their radiologic similarities. Fine needle aspiration biopsy (FNAB) has been widely employed for the diagnosis of lung cancer and TB, but the diagnostic accuracy of TB is not high enough. As a rapid screening test for tuberculosis, we evaluated serological tests using *Mycobacterium tuberculosis* PPD and lipoarabinomannan (LAM) antigens. A total of 95 patients with indication of FNAB cytology from initial CT findings were enrolled. 25 patients had TB, 76 thoracic malignancy, and six (7.9%) of the lung cancer patients also had TB, indicating much higher prevalence of TB in thoracic tumor patients. Antibodies to PPD were elevated in 18 (72.0%) of 25 TB patients and in 22 (31.4%) of 70 patients with thoracic malignancy. In contrast, only 3 (4.7%) of 64 healthy controls aged 40 or above were seropositive to PPD antigen. The prevalence of anti-PPD antibodies in thoracic tumor patients was therefore significantly greater than that amongst the healthy controls ($p<0.001$, chi-square test). However, no significant difference in the prevalence of anti-LAM antibodies was found between study subjects and controls. This study demonstrates that thoracic tumor patients have significantly elevated antibodies to PPD; therefore, high anti-PPD seroreactivity in thoracic tumor patients should be cautiously interpreted. A longitudinal investigation on seropositive thoracic tumor patients is required to determine the role of the serological test for TB in lung cancer patients.

Key Words: Lung cancer, tuberculosis, fine needle aspiration biopsy, serodiagnosis, PPD

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INTRODUCTION

Tuberculosis (TB) is still a major public health problem worldwide with about 8 million new cases and 3 million deaths each year. The current laboratory diagnosis of TB relies on the microscopic identification of acid-fast bacilli and the culture of *Mycobacterium tuberculosis* from clinical samples of sputum and FNAB.[1] Although smear examination provides rapid detection, its sensitivity is in general very low. On the other hand, cultures provide greatest sensitivity and a definite diagnosis, but it takes about 3 - 8 weeks to get a final report, and there are numerous examples of TB cases in which sputum culture failed to grow *M. tuberculosis*.[2]

The immunodiagnosis of TB has long been a goal as an alternative. Although the tuberculin test has proven to be very useful for identifying persons infected with *M. tuberculosis* in areas of low prevalence, it has limited application in countries with a high prevalence, because the majority of the population are tuberculin positive due to either BCG vaccination or natural infection.[3] Numerous serological tests have been developed for the rapid, sensitive and cost effective diagnosis of pulmonary and extrapulmonary TB. In the literature, the sensitivity and specificity of serological tests have been reported to be 70 - 80% and 90 - 95%, respectively. Results tend to depend on the nature of antigens, testing formats, and the prevalence of TB among general

population in the study areas.[4] Due to the chronic nature of TB, however, it is difficult to decide whether the disease is current based on the presence of elevated antibodies to *M. tuberculosis* antigens.

Recent increases in the incidence of lung cancer, particularly in countries with a high prevalence of tuberculosis, often make it difficult to differentiate between lung cancer and TB. One reason is that pulmonary TB sometimes radiologically mimics lung cancer.[5] In addition, radiologic pictures of TB lesions become atypical in immunocompromised patients.[6] Fine needle aspiration biopsy (FNAB) has been widely employed for the diagnosis of malignant tumors, with a diagnostic accuracy reaching 90 - 95%.[7,8] However, the accuracy of FNAB cytology was found to be about 39-79% in non-malignant diseases, which is significantly less accurate than that for malignant lesions.[9,10] The lower diagnostic rate of FNAB for benign lesions is attributed to the need for larger tissue specimens and to the confusion caused by benign reaction surrounding malignancy.[9-11]

Tuberculosis is the most common cause of benign disease as diagnosed by FNAB (59.3%), followed by aspergillosis (14.8%), benign tumors, including hamartoma and sclerosing hemangioma (14.8%) and bacterial infection (7.2%) over the last seven years at the Yonsei University Medical Center. The diagnostic rate of FNAB for pulmonary TB in 108 patients with negative sputum smears, involving combined hematoxylin-eosin and Ziel-Nielson stains, was only 36.1%. Moreover, 28.7% of patients were not diagnosed by FNAB, but tuberculosis was confirmed by histology or AFB culture. The remaining 35.2% were diagnosed as having TB by their improved response to anti-TB treatment (KO Choe, unpublished data). The diagnostic rate of FNAB was, therefore, too low, and for this reason one of purposes of study was to evaluate whether the serologic testing of patients who received FNAB can increase the diagnostic accuracy of pulmonary tuberculosis in the early phase.

Because the majority of the patients in Korea with indications by FNAB study have either lung cancer or pulmonary TB and the high incidence of TB among patients with lung cancer,[12,13] it would be of great value to verify the role of serologic testing to diagnose TB in the early stage, and to accurately diagnose coexisting TB in the patients with malignant tumors. Those with active pulmonary TB among the thoracic tumor patients have a higher risk of fatality from lung cancer or other malignancies, in spite of the very high mortality associated with tuberculosis per se. Conversely, chemotherapy and radiotherapy may induce extension of the tuberculosis. This is why rapid and accurate diagnosis of TB is so important for the proper management of TB and lung cancer patients. To date, however, little information is available about prevalence of antibodies to *M. tuberculosis* antigens among thoracic tumor patients. This study was thus initiated to determine whether serologic testing could help in the early diagnosis of TB, and whether it can detect combined malignancy and TB. The present study is the first to examine anti-TB seroreactivity among thoracic tumor patients. However, the false positivity of serologic test for TB was unexpectedly high in patients with thoracic malignancy, therefore, serologic testing cannot diagnose coexisting TB and malignancy, and the high titer of serologic test for TB in patients with thoracic tumor should be cautiously interpreted.

MATERIALS AND METHODS

Study patients and specimens

Fine needle aspiration biopsy (FNAB) samples of the lungs were obtained from 95 patients admitted to the Yonsei University Medical Center, in whom FNAB was indicated based on preliminary physical, chest X-ray and CT findings. Most of the patients had one or more mass-like lesions in the chest radiograph or on the CT scan and were suspected to have malignant lesion(s). FNAB specimens were submitted for cytology, Ziel-Nielson stain by microscope and mycobacterial culture examination of the aspirates. Multiple sputum samples were also obtained from study patients for microscopic and culture examination for *Mycobacterium tuberculosis*. In addition, serum samples were obtained from each patient for the detection of antibodies to the PPD and lipoarabinomman (LAM) antigens of *M.*

tuberculosis; and were kept at -20℃ until analysis. For controls, serum samples were obtained from 64 individuals with no sign of tuberculosis by chest X-ray, in a regular health check-up at the Yonsei University Medical Center, and who were aged 40 or above.

M. tuberculosis antigens

PPD antigen was purchased from the Statens Seruminstitut, Copenhagen, Denmark, and LAM antigen was provided through the NIH, NIAID Contract NO1-75320 at the Colorado State University, Fort Collins, CO, U.S.A.

Detection of antibodies to PPD and LAM

An enzyme-linked immunosorbent assay (ELISA) described by Voller et al.[14] was used with minor modification as reported previously.[15,16] Briefly, 100 μl of diluted PPD (1.0 μg/ml) and LAM (0.2 μg/ml) antigens in carbonate buffer, pH 9.6, were added to the wells of flat-bottom ELISA plates (Costar, Corning, Inc., Corning, NY, USA) and incubated overnight at 4℃ in a moist chamber. The wells were then washed with phosphate buffered saline (PBS) solution, pH 7.4, containing 0.05% Tween 20 (PBST) and blocked by adding 200 μl of PBST-0.05% normal goat serum (NGS) (Gibco BRL, Life Technologies, Inc., Grand Island, NY, USA) at 37℃ for 1 hour. After emptying the wells, 100 μl of serum diluted 1:300 in PBST-5% NGS was added to the wells, which were then incubated again at 37℃ for 90 min. The wells were then washed and 100 μl of affinity purified peroxidase-conjugated goat anti-human IgG (Calbiochem, Behring Diagnostics, San Diego, CA, USA) diluted 1:5,000 in PBST-5% NGS was added and incubation continued at 37℃ for 1 hour. After another washing, 100 μl of substrate solution, H_2O_2-O-phenylenediamine (Sigma Chemical Co., St. Louis, MO, USA) was added, and the wells were then re-incubated at room temperature for about 15 minutes. The reaction was then stopped with 100 μl of 2.5 N H_2SO_4 and the absorbance was read at 490 nm.

Each test was performed in duplicate, and the mean absorbance of wells without antigen was subtracted from those of wells with PPD or LAM before analysis. Those carrying out the serological tests did not know the results of any clinical investigation or the ultimate diagnosis.

RESULTS

Cytologic findings of the fine needle aspiration biopsy (FNAB)

A total of 95 FNAB samples were examined for cytologically. Twenty-five patients were confirmed with pulmonary TB and 76 patients were diagnosed as having thoracic malignancy. The histologic type of the thoracic malignancy was proved to be primary lung cancer in 57 cases (squamous cell type in 25, adenocarcinoma in 23, small cell carcinoma in 5, non-small cell carcinoma in 4), lung metastasis from the extrathoracic primary tumor were present in 5 and other malignancies in 8 (carcinoid 1, chloroma 1, sclerosing hemangioma 1, thymic tumor 3, germinoma 1, mesothelioma 1). All tumors were confirmed by sputum cytology, FNAB cytology and/or surgical histology findings. Of the 25 TB patients, 12 (48%) were confirmed by cytology or histology (FNAB 11, bronchoscopic biopsy 1) and among these 4 culture positive results were obtained (Table 1). In comparison, there were 12 TB patients with sputum culture positive, 4 with sputum smear positive, 5 with NAB culture positive, and 3 with NAB smear positive. Overall, 18 (72%) of the 25 TB patients were bacteriologically positive either in FNAB or sputum samples, six (24%) were diagnosed by clinical findings, and one by sputum PCR.

Seroreactivity to PPD and lipoarabinomannan (LAM)

Serum samples were obtained from study subjects and were examined for the presence of antibodies to the PPD and LAM antigens of *M. tuberculosis* by enzyme-linked immunosorbent assay (ELISA). A scattergram of the IgG seroreactivity of individual patients and healthy controls to the PPD antigen is shown in Fig. 1. As seen in the figure, the majority of TB patients showed strong seroreactivity to the PPD antigen, although several had few antibodies to the antigen despite

Table 1. Clinical, Radiological and Laboratory Findings of TB Patients

ID No	Sex	Age	CT impression	NAB Cytology	NAB ZN	NAB culture	Sputum smear	Sputum Culture	Confirmed Diagnosis
1	F	53	TB	Inflammatory Cells	P	P	P	N	TB
2	M	46	TB	N	N	N	N	P	TB
3	M	61	-	N	N	N	N	N	TB
4	M	69	Lung ca.	Atypical cells	N	N	N	P	TB
5	M	59	-	N	N	N	P	P	TB
6	M	60	Lung ca.	TB compatible	N	N	N	N	TB
7	M	57	TB	N	N	N	P	N	TB
8	F	31	SPN*	N	P	P	N	P	TB
9	M	56	TB	TB compatible	P	P	N	N	TB
10	M	53	TB	Inflammatory Cells	N	N	-	P	TB
11	M	54	-	N	N	P	N	P	TB
12	M	45	TB	N	N	N	N	P	TB
13	M	50	Lung ca.	N	N	N	N	N	TB
14	M	57	TB	N	N	N	N	N	Clinical TB
15	M	21	TB	N	N	N	N	N	Clinical TB
16	M	47	SPN	Inflammatory Cells	N	N	N	N	Clinical TB
17	M	50	Lung ca.	Inflammatory Cells	N	N	N	N	Clinical TB
18	F	59	Lung ca.	N	N	N	N	N	Clinical TB
19	F	58	-	Inflammatory Cells	N	N	N	N	Clinical TB
20	M	20	Mediastinal mass	Germinoma	N	N	N	P	Germinoma & TB
21	M	76	Lung ca.	Squamous cell ca[4]	N	N	N	P	Sq cell ca & TB
22	M	80	Lung ca./TB	Squamous cell ca	N	P	N	P	Sq cell ca & TB
23	M	56	Lung ca.	Squamous cell ca	N	N	N	P	Sq cell ca & TB
24	F	90	Lung ca./TB	Adenocarcinoma[5]	N	N	N	P	Adenoca. & TB
25	F	32	Lung ca.	Adenocarcinoma	N	N	P	N	Adenoca. & TB

NAB, needle aspiration biopsy; ZN, Ziel-Nielsen stain; P, positive; N, negative; SPN : solitary pulmonary nodule; TB, tuberculosis; ca, carcinoma.

being diagnosed as having TB. Interestingly, a substantial portion of patients with lung cancer had elevated antibodies to the PPD antigen, and was comparable to TB patients in this respect. In contrast, seroreactivity to PPD was very low in general among the healthy controls age 40 or above. The mean and standard deviation of the O.D. readings to the PPD antigen were 0.57 ± 0.48 for TB patients, 0.24 ± 0.34 for patients having thoracic malignancy without tuberculosis, and 0.05 ± 0.05 for healthy controls (Table 2). Anti-PPD seroreactivity in patients with thoracic malignancy was, therefore, significantly greater than that in healthy controls ($p < 0.05$, Student t-test) (Table 2).

Antibodies to the LAM antigen were more

abundant in sera from all patient study groups and in the healthy controls than antibodies to the PPD antigen (Fig. 2). The mean and standard deviation of O.D. readings to the LAM antigen was 0.86 ± 0.65 for TB patients, 0.49 ± 0.44 for patients having thoracic malignancy without tuberculosis, and 0.39 ± 0.38 for healthy controls (Table 2). However, there was still a tendency towards higher seroreactivity to the LAM antigen among the TB patients, but no significant difference was noted between the lung cancer patients and the healthy controls.

Seroprevalence to PPD and LAM

In order to compare the prevalence of antibodies to PPD in the study patient groups, a cut-off value was determined by adding three times of the s.d. to the mean O.D. of the healthy controls, accordingly, a threshold vlue 0.21 or above was set for the PPD antigen. As shown in Table 2, 18 (72%) of 25 TB patients were seroposi-

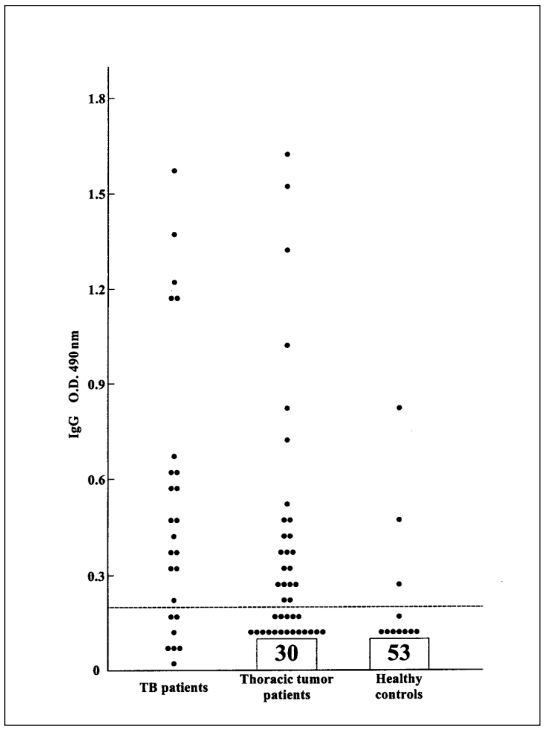

Fig. 1. Scattergram of IgG seroreactivity to PPD in sera from patients and controls. Each dot represents an individual, and all points above the dashed line were considered seropositive.

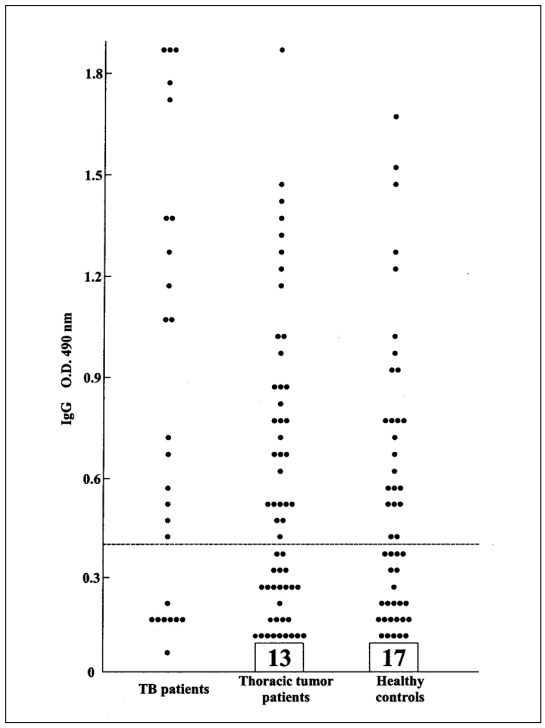

Fig. 2. Scattergram of IgG seroreactivity to LAM in sera from patients and controls. Each dot represents an individual, and all points above the dashed line indicate a significant level of anti-LAM antibodies.

Table 2. Prevalence of Antibodies to PPD and LAM among Study Patients and Controls

Subjects	PPD		LAM	
	O.D. 490 nm	No.	O.D. 490 nm	No.
Tuberculosis only (n=25)	0.57 ± 0.48*	18	0.86 ± 0.65	17
Tuberculosis with malignancy (n=6)	0.59 ± 0.53	5	0.56 ± 0.53	3
Malignancy only (n=70)	0.24 ± 0.34†	22‡	0.49 ± 0.44	32
Healthy controls (n=64)	0.05 ± 0.05	3	0.39 ± 0.38	24

*Mean ± SD.
†$p < 0.05$, Student t-test against healthy controls.
‡$p < 0.001$, Chi-square test against healthy controls.

tive to the PPD antigen. Of 70 patients with lung malignancies, 22 (31.4%) had elevated antibodies to PPD. In contrast, only 3 (4.7%) of 64 healthy controls had anti-PPD antibodies over the cut-off value despite the fact that over 60 % of these aged persons tested positively for tuberculosis in general tuberculosis survey in Korea.[17] The seroprevalence of anti-PPD antibodies among patients with lung malignancies was significantly greater than among the healthy controls ($p<0.001$, chi-square test). Seroreactivity to the PPD antigen was analyzed according to the histologic type of the thoracic malignancy. As shown in Fig. 3, IgG seroreactivity to PPD was in general greater in patients with well-differentiated lung cancer than in those with the poorly differentiated type. The anti-PPD seroreactivity of patients with the well-differentiated cell type of primary lung cancer was 0.35 ± 0.43 (n=28), which was significantly greater than the 0.09 ± 0.08 (n=11) of the undifferentiated type ($p<0.01$, Student t-test). Likewise, the anti-PPD seropositive rate among thoracic tumor patients with squamous cell type was significantly higher than that of the other types, and this was particularly true in the case of the unclassified and small cell type ($p<0.01$, Student t-test) (Table 3). However, no statistical significance could be attached to the correlation between the stage of cell differentiation in the primary lung cancer group without coexisting TB (n=51) and anti-PPD seroreactivity (p=0.54 by ANOVA) (Table 4).

For the LAM antigen, it was difficult to set a cut-off value for seropositivity because a substantial portion of the healthy controls had elevated antibodies to the antigen. Therefore, an O.D. value of 0.40, which was close to the mean O.D. value of healthy controls, was chosen to compare the patients groups in this study. Of the 25 TB patients, 17 (68%) were over the cut-off value, and this was somewhat close to the seroprevalence of the PPD antigen in TB patients (Table 2). Unlike the anti-PPD antibodies, however, no significant difference in seroprevalence with respect to the LAM antigen was found between the patients with lung malignancies and the healthy controls,

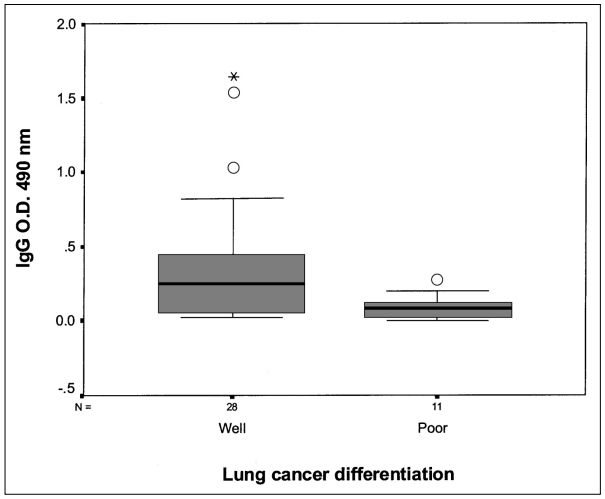

Fig. 3. Histogram of seroreactivity to the PPD antigen in sera from patients with primary lung cancer according to cell type. Summary plot based on the median, quartiles, and extreme values. The box represents the interquartile range, which contains 50% of all values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median. O: Cases with values between 1.5 & 3 box lengths from the upper or lower edge of the box. The box length is the interquatile range. * : Cases with values of more than 3 box lengths from the upper or lower edges of the box. The box length is defined as the interquartile range.

Table 3. Seroreactivity to PPD in Sera from Patients with Primary Lung Malignancy

Histologic type	O.D. 490 nm Mean ± SD	Serologic positive No.
Primary lung cancer* (n=57)		
Squamous cell carcinoma (n=25)	0.30 ± 0.34†	13
Adenocarcinoma (n=23)	0.28 ± 0.42	7
Unclassified or small cell carcinoma (n=9)	0.07 ± 0.08	0
Other malignancy‡ (n=13)	0.19 ± 0.13	2

*Primary lung cancer (n=57) excludes the cases with TB.
†Other malignancy; thoracic malignancy excluding primary lung cancer.
‡$p<0.01$, Student t-test the squamous vs. unclassified lung cancer.

Table 4. Correlation Between Seroreactivity to PPD and the Disease Stage of Primary Lung Cancer Patients without TB

Lung cancer stage	No.	O.D. 490 nm Mean ± SD
1	8	0.43 ± 0.52
2	4	0.15 ± 0.22
3	14	0.26 ± 0.31
4	17	0.22 ± 0.37
Total	43	

Anti-PPD seroreactivity; ANOVA, p=0.54.

with prevalences of 45.7% and 37.5%, respectively. Therefore, this study indicated that the LAM antigen is probably unsuitable for differentially diagnosing TB patients and healthy controls.

DISCUSSION

Serological tests have been widely explored for the rapid, simple and inexpensive diagnosis of tuberculosis. In this study, elevated antibodies to *M. tuberculosis* PPD antigen was found in 72% of the TB patients, and this sensitivity is comparable to other reports.[4] This may be acceptable considering its specificity of over 95% against healthy controls in Korea, where prevalence of TB was found to be 1.0% in a recent survey.[17] In contrast, the LAM antigen-based assay gave strong IgG responses even among healthy controls. The stronger reactivity to the LAM antigen can be explained on the basis of its potent immunogenicity or because of antibody stimulation by the molecule in other mycobacterial species, which resulted in the low specificity of the LAM-based serological test. Therefore, we believe that the PPD-based assay will be useful for detecting *M. tuberculosis*-specific antibodies.

It was of interest to note that 7.9% of thoracic malignancy patients (8.8% of primary lung cancer patients) also had active TB in this study. This supports previous studies, which reported that the TB incidence in cancer patients was nine to eleven times greater than in the general population.[12,13] This may reflect an impaired cellular immunity in cancer patients,[18,19] which has been closely associated with the pathogenesis of TB, and may also explain why much a high proportion of patients with thoracic malignancy are seropositive to PPD. In contrast, the incidence of reactivated pulmonary TB among primary lung cancer patients ranged from only 1.9% to 2.1% in Japan.[20,21] This difference might be due to the marked difference in prevalence of TB in Korea and Japan (Korea 1.0%[17] vs. Japan 0.4%[22]), because the incidence of TB is closely related with a history of prior exposure to *M. tuberculosis* among lung cancer patients.[23] Considering the high prevalence of TB in Korea, therefore, the TB incidence rate of 8.8% among patients with primary lung cancer in this study was not unreasonable and supported previous findings.[12,13] Although the efficacy of anti-TB chemotherapy in lung cancer patients is comparable what that in patients without lung cancer, shortened survival has been reported, and this has been mainly attributed to late diagnosis.[24] In such cases, surgical treatment of cancer may have to be postponed or even contraindicated.

Our study also demonstrates that a significant portion of patients with thoracic malignancy had elevated antibodies to the *M. tuberculosis* PPD antigen. The seropositive rate of 31.4% among patients with thoracic tumor was significantly higher than among healthy controls in comparable age groups. However, the main question still remains, and that is, how to should elevated antibodies to *M. tuberculosis* PPD antigen in patients with thoracic malignancy be interpreted. In pulmonary TB, the anti-PPD seropositive rate was significantly higher among the far advanced (93.8%) than the minimally affected (28.6%), by chest X-ray findings and among the sputum culture positive (82.3%) than the culture negative (21.6%) patients (SN Cho, unpublished data). This may indicate a positive correlation between anti-PPD antibodies and actively progressing *M. tuberculosis* infection. Positivity for anti-PPD antibodies one year before TB diagnosis was higher than that of the PPD skin test ($p<0.001$), therefore, antibody markers may predict TB reactivation in HIV-positive subjects, including those with a negative PPD skin test.[25] In turn, the presence of elevated anti-PPD antibodies in patients with lung cancer may be related with the future reactivation of pulmonary tuberculosis due to lower cell-mediated immunity, and anti-TB chemoprophylaxis may be indicated. However,

the reactivation rate of TB, according to the seropositivity, was not meaningful in our study cases because of their relatively short survival.

Seroreactivity or seroprevalence to the PPD antigen showed some relation with the degree of cell type or the degree of tumor differentiation in this study. The values were significantly higher in squamous cell type than others, particularly than in the unclassified or small cell type. Also well-differentiated cell type showed significantly higher titer than poorly differentiated type in primary lung cancer. It is a well-known fact that squamous cell type or well-differentiated type has a better prognosis and longer survival period. This suggests that seropositivity to PPD in patients with primary lung cancer may be related with the activity of antitumor antigenicity and prognosis. Tumors may over-express certain proteins, which may serve as target antigens for immunological attack. Several reports have suggested that some mutual antagonism between TB and cancer exists, and tuberculin sensitization has been related with tumor histology and stage.[26] The PPD reaction was also useful for understanding the pathologic state and prognosis of patients with progressive lung cancer undergoing immunotherapy.[27] All inoperable lung cancer patients under radiochemoimmunotherapy, who converted from negative to positive PPD skin test, showed regression or no progression of the tumor and better survival.[28]

Future study needs to address the significance of elevated antibodies among patients with malignancy by longitudinal follow-up to identify any change in antibody levels, and clinical and laboratory studies should be conducted to assess reactivation rates and the expectation of longer survival with respect to tumor immunity. The information gained will be valuable for physicians to determine whether anti-TB preventive therapy is needed or whether it has a role in the monitoring of tumor regression in those with lung cancer and *M. tuberculosis*-seropositivity.

In summary, the our results indicate that serologic testing using the PPD antigen for pulmonary tuberculosis (including response to anti-TB drugs) has a sensitivity of 72%, and a specificity of 95.3%. TB incidence was much higher in patients with thoracic malignancy (7.9%) than in the general population (1.0%), and over 30% of patients with lung cancer without coexisting tuberculosis at admission also had elevated antibodies to the *M. tuberculosis* PPD antigen. Further investigation is necessary to prove the role of serologic testing either as a means of providing warning of pulmonary tuberculosis reactivation or for determining prognosis.

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