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The Role of Transbronchial Lung Biopsy in the Diagnosis of Solitary Pulmonary Nodule

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A B S T R A C T

Transbronchial lung biopsy (TBLB) is a well-recognized diagnostic technique in diffuse interstitial lung diseases, but it is not considered to be the first choice in investigation of solitary pulmonary nodules (SPN). The main idea of this study was to increase the sensitivity of bronchoscopy using multiple techniques, especially TBLB, thus to avoid more aggressive diagnostic procedures. The objective of this prospective study was to evaluate the efficacy and safety of TBLB in the diagnosis of SPN, in comparison with other bronchoscopic techniques. Fifty patients with chest x-ray finding consistent with SPN underwent bronchoscopy with bronchial washing, brushing, bronchoalveolar lavage (BAL) and TBLB were included in this study. Thirty-one patients suffered from malignant tumors, while 19 patients had nonmalignant lesions. TBLB achieved overall diagnostic sensitivity of 62%, BAL of 29%, bronchial brushing of 16% and washing of 6%. Combining all techniques together, bronchoscopy had overall sensitivity of 86%. Concerning malignant lesions, TBLB had a sensitivity of 65%, specificity of 100%, and accuracy of 82%. TBLB had a significantly better yield for lesions with a diameter ≥25 mm than for lesions of <25 mm (sensitivity of 82% and 53% respectively, $p<0.05$). Diagnostic yield improved significantly with the increasing number of specimens (less than 3 specimens: sensitivity 59%, 3 or more specimens: sensitivity 87%, $p<0.05$). Complications of TBLB occurred in 2 (4%) patients: 1 incomplete pneumothorax and 1 hemorrhage. According to the results, we conclude that TBLB is an accurate and safe technique for the diagnosis of pulmonary solitary nodule with a diameter equal or greater than 25 mm.

Key words: *transbronchial lung biopsy, bronchoscopy, pulmonary nodule, lung carcinoma*

Introduction

Solitary pulmonary nodule (SPN) is described as a circumscribed lesion surrounded by normally ventilated lung parenchyma. Etiologically, it includes pri-

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mary lung tumors, metastases of extrathoracic neoplasia, and various nonmalignant lesions (infections, vasculitides, some connective tissue diseases, amyloidosis, bronchial and vascular abnormalities, pulmonary infarction, etc.)[1–2]. It is important to note that patients with respectable primary peripheral lung carcinoma have better prognosis after surgical treatment than those with centrally localized carcinoma[3]. Early diagnosis of SPN is particularly important, but in some circumstances localization and size of the nodule tend to be so inconvenient that the diagnosis can only be established by open lung biopsy. Percutaneous needle – aspiration/biopsy is the most widely used technique in such case, although it may be associated with some complications[4]. Thoracoscopy and video assisted thoracoscopy (VATS) enable accurate lung biopsy in subpleural region but these techniques require complete surgical equipment[5]. Diagnostic yield of fiberoptic bronchoscopy for peripheral nodule is variable, ranging from 30% to 60%. Even if fiberoptic bronchoscopy is not the first choice to investigate a peripheral lesion, it may still be recommended to screen the airways, especially if there is a suspicion of malignancy[6]. Concerning safety and availability of bronchoscopy, there is a rational question: could we increase diagnostic sensitivity of bronchoscopy using a higher number of techniques (especially TBLB) and avoid other more aggressive diagnostic procedures?

Patients and Methods

Patients

Fifty patients were included in this prospective study. The inclusion criteria were:

1) solitary pulmonary nodule on chest x-ray;
2) unexplained diagnosis after cytologic and microbiologic examination of sputum (3 smears);
3) signed informed consent; and
4) normal bronchoscopic appearance (absence of any abnormality in the visible area of fiberoptic bronchoscope).

Methods

All patients underwent local anesthesia with 2 ml of 2% Xylocaine solution applied directly to vocal cords, followed by 1 ml through bronchoscope to the trachea. We used Olympus T30 and T40 fiberoptic bronchoscope. Bronchial washing, brushing and TBLB were obtained in all patients, while bronchoalveolar lavage (BAL) was performed in 38 patients. Bronchial washings, brushings and BAL were cultured for *Mycobacterium tuberculosis*, nonspecific bacteria and fungi. Specimens obtained by TBLB were gently pressed to glass to make biopsy imprint, and then stored into 4% formalin. All samples (including biopsy imprint) were cytologically examined using May Grünwald Giemsa staining. Biopsy specimens were microscopically analyzed using various stains (HE, Prussian blue, Mallory, etc.).

Statistical analysis

Sensitivity was analyzed by a modified Bayes' theorem[7] using the following formula and expressed as %:

Sensitivity = [No of diagnostic findings / All patients] x 100.

We used a modified Bayes' theorem for malignant lesions in the following way:

Sensitivity = [No of findings positive for malignancy / No of all patients with malignancy] x 100.

Specificity = [No of findings negative for malignancy / No of patients without malignancy] x 100.

Accuracy = [true positive + true negative / true negative + true positive + false negative + false positive%% x 100.

The impact of various conditions (diameter of nodule and number of biopsy specimens) on the sensitivity of TBLB was expressed by Fischer's test of correlation for small samples.

Results

Fifty patients were included in the study: 42 male and 8 female, average age 59 years. Two patients had previously diagnosed malignant tumors (gastric cancer and breast cancer one each).

Nineteen patients (38%) had nonmalignant lesions: 12 patients had tuberculosis and 7 patients suffered from various diseases (vasculitides 3, pulmonary infarctions 2, fibronodular lesion 1, and nodular type of BOOP 1 patient). Bronchoscopy was diagnostic in 18 patients and nondiagnostic in one patient with fibronodular lesion, who finally underwent VATS. In case of SPN, nonmalignat bronchoscopic finding is usually uncertain and requires additional proof to be definitely confirmed. The diagnosis of nonmalignant lesions was verified as follows:

Tuberculosis was diagnosed on the basis of positive acid-fast bacilli and positive cultures for *Mycobacterium tuberculosis* in BAL fluid and/or histological finding of caseating granulomatous inflammation. All 12 patients with the diagnosis of lung tuberculosis were successfully treated with antituberculotic drugs and post-treatment follow up period was 1 year.

Histological findings of pulmonary infarction (3 patients) were compatible with positive perfusion/ventilation scans. These patients recovered upon anticoagulant treatment and nodular pulmonary infiltrates completely disappeared.

Patients with vasculitides (n=3) had ANCA positive sera. In one patient the diagnosis of vasculitis was additionally confirmed by biopsy of the skin and nasal mucosa. Two patients underwent renal biopsy, and histological findings were consistent with Wegener granulomatosis.

One patient with a histological finding of BOOP (nodular type) was treated with carbamazepine during the preceding 8 months, and had hematological and liver impairments consistent with drug adverse effect. According to histological finding of TBLB we presumed that the nodular type of BOOP may have been induced by carbamazepine. Nodular pulmonary lesion completely disappeared on chest x-ray 8 weeks after drug discontinuation. The patient remained well during the 1-year follow up period.

Thirty-one (62%) patients suffered from malignant tumors as following: squamous cell carcinoma – 13, adenocarcinoma – 5, small-cell carcinoma – 3, nodular type of bronchoalveolar carcinoma – 2, large-cell carcinoma – 1, neuroendocrine carcinoma – 1, nondifferentiated carcinoma – 4 patients, and 2 patients had metastases of extrathoracic malignant tumors. Bronchoscopy was diagnostic in 25 of these patients. In the remaining 6 patients diagnosis was made as follows: percutaneous needle biopsy – 4 patients, VATS – 1 patient, and open lung biopsy – 1 patient.

TBLB achieved overall diagnostic sensitivity of 62%, BAL of 29%, bronchial brushing of 16% and bronchial washing of 6%. Combining all techniques, bronchoscopy had an overall sensitivity of 86% (Table 1).

TBLB showed good results in the diagnosis of malignant lesions: sensitivity of 65%, specificity of 100% and accuracy of 82% (Table 2).

TBLB had a significantly better yield in lesions with a diameter ≥25 mm than for lesions <25 mm: sensitivity of 82% and 53%, respectively, $p<0.05$ (Table 3).

Diagnostic yield from TBLB was significantly improved with the increasing number of specimens: less than 3 speci-

mens – sensitivity of 59%, 3 or more specimens – sensitivity of 87%, $p<0.05$ (Table 3).

Complications of TBLB occurred in 2 (4%) patients: 1 hemorrhage and 1 pneumothorax. Complications were not life threatening and did not require surgical treatment. Both patients were treated by rest and cough-suppressants.

Discussion

TBLB is a widely used diagnostic technique for diffuse interstitial lung diseases; however, it has not yet been established as the first choice procedure for SPN. Results of previously published studies differ from author to author, the sensitivity ranging from 37% to 74% (Table 4). There are several reasons for that. Most of authors tend to avoid biopsy imprint for cytology, preserving the specimen exclusively for histopathological examination. However, according to literature data, better results were achieved using both cytological and histopathological analyses of biopsy specimens.

Another possible reason for variable results could be the ratio between malignant and nonmalignant lesions in various studies. Small biopsy samples are much more convenient for histopathological, and especially cytological analyses of malignant lesions, whereas the diagnosis of nonmalignant diseases (ex. vasculitides, chronic inflammation, pulmonary infarc-

TABLE 1
SENSITIVITY OF BRONCHOSCOPIC TECHNIQUES

Technique	No of diagnostic samples / No of patients	Sensitivity (%)
TBLB (overall results)	36/50	62
TBLB (histology)	29/50	58
TBLB (citology)	21/50	42
Brushing	8/50	16
Bronchial washing	3/50	6
BAL	11/38	29
Bronchoscopy (overall results)	43/50	86

TABLE 2
DIAGNOSTIC VALUE OF VARIOUS BRONCHOSCOPIC TECHNIQUES IN MALIGNANT LESIONS

Technique	False negative/true positive	Sensitivity (%)	Specificity (%)	Accuracy (%)
TBLB (overall results)	11/31	65	100	82
TBLB (histology)	14/31	55	100	78
TBLB (citology)	18/31	42	100	74
Brushing	24/31	23	100	68
Bronchial washing	29/31	6	100	63
BAL	17/23	26	100	69
Bronchoscopy (overall)	6/31	81	100	89

TABLE 3
ROLE OF NODULE SIZE AND NUMBER OF SPECIMENS

	Diagnostic biopsies	Non diagnostic biopsies	Total	Sensitivity (%)	p
Lesion diameter					
<25 mm	9	8	17	53	0.0358
≥25 mm	27	6	33	82	
No of specimens					
1–2	16	11	27	59	0.0298
3 or more	20	3	23	87	

TABLE 4
LITERATURE DATA ON TBLB SENSITIVITY IN DIAGNOSIS OF SOLITARY PULMONARY NODULES

Author	No of patients	TBLB sensitivity (%)	Bronchoscopy-overall sensitvity (%)
Shiner[14] (h+c)	51	65	75
Obara[15] (h+c)	226	74	Not available
Bilaceroglu[16] (h)	92	49	68
Milman[10] (h)	279	55	Not available
Debeljak[17] (h+c)	61	71	Not available
Katis[18] (h)	37	38	46
Gasparini[19] (h)	557	54	Not available
Mak[20](h)	63	37	55,6
Chechani[21] (h)	49	59	73
Ellis[8] (h+c)	78	68	Not available

h = histological examinations of specimens were exclusively performed;
h+c = both histology and cytology of biopsy imprint were performed

tion, etc.) commonly require bigger tissue samples than those obtained by TBLB. In Ellis' study, the sensitivity of TBLB for malignant and nonmalignant nodules was 69% and 10% respectively[8].

Adding other bronchoscope techniques, especially BAL, the overall sensitivity raises to up to 86%, like in our study.

It is well known that nodule size has a significant impact on the diagnostic result. Lai found a sensitivity of 35% for nodules smaller than 2 cm and even 65% for those exceeding 2 cm[9].

It has been recognized that the higher number of biopsy specimens raises the sensitivity of TBLB in diffuse interstitial lung diseases as well as in SPN. We found no false negative result when more than 4 biopsy specimens were obtained. Milman found the biopsies with <4 and ≥4 specimens to produce a sensitivity of 52% and 70%, respectively[10].

The rate of complications recorded in the present study was consistent with literature data (pneumothorax 0.03%–3%, hemorrhage 0.01%–4%)[11]. In comparison with percutaneous needle biopsy, TBLB showed lower sensitivity but better safety. Based on literature data, the sensitivity of percutaneous needle biopsy ran-

ges from 76.4% to 84%, with the rate of pneumothorax from 3.7% to 26%[12,13].

Based on the study results, it is concluded that TBLB is an accurate and safe technique for the diagnosis of SPN with a diameter of ≥25 mm. Using fiberoptic bronchoscopy with TBLB and BAL as the first choice technique, the more aggressive diagnostic procedures that often require surgical equipment can be avoided.

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ZNAČENJE TRANSBRONHALNE BIOPSIJE U DIJAGNOSTICI SOLITARNIH PERIFERNIH PLUĆNIH LEZIJA

SAŽETAK

Transbronhalna biopsija pluća (TBBP) etablirana je tehnika u dijagnostici difuznih intersticijskih plućnih bolesti, ali se relativno rijetko koristi u dijagnostici solitarnih perifernih plućnih nodusa (SPN). Dijagnostička osjetljivost bronhoskopije može se povećati istodobnim korištenjem više bronhoskopskih tehnika, naročito transbronhalne biopsije pluća. Cilj ovog prospektivnog istraživanja bila je evaluacija učinkovitosti i sigurnosti transbronhalne biopsije pluća u dijagnostici SPN. U istraživanje je uključeno 50 bolesnika s nalazom SPN na rentgenskoj snimci pluća. Tijekom bronhoskopije korištene su sljedeće tehnike: aspirat bronha, bris četkicom, bronhoalveolarna lavaža (BAL) i TBBP. Kod 31 bolesnika dijagnosticiran je zloćudni tumor, a u 19 bolesnika

radilo se o dobroćudnim nodusima. Najviše dijagnostički značajnih uzoraka dobiveno je transbronhalnom biopsijom (osjetljivost 62%), potom BAL-om (29%) i brisom (16%), a najmanje bronhoaspiratom (6%). Kombinacijom svih bronhoskopskih metoda osjetljivost bronhoskopije u cjelini bila je 86%. Ako se posebno izdvoje samo tumorske lezije, osjetljivost TBBP je bila 65%, specifičnost 100%, a pouzdanost 82%. Osjetljivost TBBP za lezije <25 mm bila je 53%, a za lezije promjera ≥25mm i veće 82%, što je statistički značajna razlika na razini $p<0.05$. Broj bioptata je statistički značajno utjecao na osjetljivost TBBP (do tri bioptata: osjetljivost 59%, tri ili više bioptata: osjetljivost 87%, $p<0.05$). Kompikacije su se pojavile u dvoje (4%) bolesnika (jedan pneumotoraks i jedno krvarenje). Na temelju navedenih rezultata može se zaključiti da je TBBP pouzdana i relativno sigurna metoda u dijagnostici perifernih solitarnih plućnih lezija promjera ≥25.