

Significance of bronchoscopic lung biopsy in clinical practice

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Received 10.03.2008
Accepted 17.04.2008
Advances in Medical Sciences
Vol. 53(1) · 2008 · pp 11-16
DOI: 10.2478/v10039-008-0011-2
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ABSTRACT

Purpose: At present bronchoscopic lung biopsy (BLB) is widely used to diagnose various lung diseases. However placing of BLB in the diagnostic sequence of various clinical situations is not so clear. The purpose of the study was to evaluate the diagnostic value of BLB in a daily clinical practice.

Material and methods: The data obtained from the case records of all 304 patients who had undergone BLB since January 1996 to December 2007 at the Centre of Pulmonology and Allergology of Vilnius University Hospital Santariškių klinikos (Vilnius, Lithuania) were examined.

Results: Most of indications for BLB were a peripheral lung nodule (40% of all the cases), dissemination in the lung (24% of all BLBs) and non-resolving pulmonary infiltrates (16.3% of all biopsies). Adequate lung tissue for histological examination was obtained in 85% of the cases. Based on the pathological diagnosis and findings of other diagnostic methods the final clinical diagnosis was verified for most of the patients. However, at least in 8% of the cases, the final clinical diagnosis was yet syndromic. Of all the BLBs, serious complications occurred in 8 (2.6%) patients.

Clinically significant pneumothorax requiring chest tube treatment occurred in 5 (1.6%) of 304 patients. Severe bleeding occurred in 3 (1%) out of all BLBs.

Conclusion: BLB is a relatively effective and safe method for diagnosing lung diseases. In most cases of the lung infiltrate, nodule, dissemination and diffuse changes, BLB is suitable to choose method for lung biopsy.

Key words: bronchoscopy, bronchoscopic lung biopsy, carcinoma of lung, interstitial lung diseases, tuberculosis

INTRODUCTION

The ability to obtain lung tissue without subjecting a patient to an open lung biopsy is a major advance in diagnostic bronchoscopy. Bronchoscopic lung biopsy (BLB) was first performed in 1963 using the rigid bronchoscope, and in 1965 the results of 13 patients were reported. In 1974 first results of the BLB via the flexible bronchoscope were published [1]. BLB is utilised to sample alveolar parenchyma beginning at the bronchiolar (noncartilaginous segment of the airway) [2].

At the present time, BLB is widely used to diagnose various lung diseases. Indications for bronchoscopic lung biopsy are diffuse or solitary pulmonary infiltrates, nodules,

interstitial changes and other unless the diagnosis was not confirmed by less invasive techniques [3,4]. For most patients, BLB is helpful for specific diagnosis and treatment. However, the placing of the BLB in the diagnostic sequence of various clinical situations is not so clear. There are some alternative invasive methods: computed tomography (CT), fluoroscopy or sonoscopy guided percutaneous transthoracic needle biopsy for the solitary lung nodules or mass, thoracoscopic or surgical lung biopsy for suspected interstitial lung disease, mediastinoscopy for mediastinal, or hilar lymphadenopathy.

The aim of the study was to evaluate the diagnostic value of the bronchoscopic lung biopsy in a daily clinical practice.

MATERIAL AND METHODS

The data obtained from the case records of all 304 patients who had undergone the bronchoscopic lung biopsy since January 1996 to December 2007 at the Centre of Pulmonology and Allergology of Vilnius University Hospital *Santariškių klinikos* (Vilnius, Lithuania) were examined. The population of the study consisted of 118 (39%) female and 186 (61%) male patients, with a mean age of 54 years (age range, 17 to 83 years) at the time of biopsy. The local institutional Committee for Biomedical Ethics does not require the approval or a signed patient's information consent form for the retrospective study of case records. Indications for the BLB are shown in *Tab. 1*.

The bronchoscopic lung biopsies were performed applying local anesthesia under the fluoroscopic control. Procedures were performed by two experienced bronchoscopists. Performance of BLB was described earlier in detail [5,6].

After the inspection of the tracheobronchial tree, a bronchoscope was inserted to subsegmental or smaller bronchus until the wedging position. Under fluoroscopic control, biopsy forceps (a crocodile type biopsy forceps was used) was pushed forward until mass or a nodule or a peripheral position in the case of diffuse changes. The position of biopsy forceps was controlled by two directions of chest fluoroscopy. Afterwards, the forceps were withdrawn about 2-3 cm, then opened and pushed forward. Usually this maneuver was repeated once or twice, then the forceps were closed and withdrawn. The bronchoscope was not removed from a wedge position unless there was an evidence of significant bleeding. In the case of diffuse lung changes, the BLB was performed after a patient's inhale. In the case of a solitary nodule or of an infiltrate, the BLB was performed independent of the breathing phase.

Two to twelve (average 7) biopsies were performed on the solitary nodules or mass and 2-18 (average 9) biopsies were performed in other cases. Most of the samples were of 1-3 mm in diameter.

The BLB samples were examined at the Lithuanian National Centre of Pathology (Vilnius, Lithuania). The Centre is accredited by the College of American Pathologists.

RESULTS

A sufficient amount of the lung tissue for pathological diagnosis establishment was obtained in 257 (85%) cases of the bronchoscopic lung biopsy. Pathological diagnosis is shown in *Tab. 2*. Efforts to perform the bronchoscopic lung biopsy were unsuccessful or the obtained material was insufficient for diagnosis in 47 cases (31 peripheral lung node or pulmonary infiltrate cases and 16 other radiological syndrome cases). High-grade bronchial deformations, pulmonary fibrosis (impossibility to insert forceps into the proper small bronchi), the absence of the connection between peripheral lung node and bronchi, scant x-ray visibility of the pathological formation (high-grade lung fibrosis, obesity) and insufficient

Table 1. Indications for bronchoscopic lung biopsy for 304 subjects.

Indication	N	%
Solitary lung nodule	122	40
Multiple small pulmonary nodules	72	24
Non-resolving pneumonia	50	16,3
Diffuse reticular lung changes	28	9
Multiple pulmonary infiltrates	18	6
Mediastinal or hilar lymphadenopathy	12	4
Diffuse ground glass opacity of the lung	2	0,7
Total	304	100

Some patients have got not only the main radiographical pattern but also other radiological symptoms (ex. mediastinal or hilar lymphadenopathy and some small pulmonary nodules, multiple pulmonary infiltrates and some ground glass opacities).

Table 2. Pathological diagnosis established after bronchoscopic lung biopsy.

Pathological diagnosis	N	%
Carcinoma of lung, metastasis of carcinoma	85	34
Pneumofibrosis	35	14
Granulomatous pneumonitis	34	13,6
Pneumonia, lung abscess	27	10,8
Organizing pneumonia, bronchiolitis obliterans organizing pneumonia	20	8
Tuberculosis	16	6,4
Pneumoconiosis	12	4,8
Respiratory bronchiolitis, bronchitis	10	4
Alveolitis, diffuse alveolar damage	7	2,8
Eosinophilic pneumonia	4	1,6
Silicosis	2	0,8
Pulmonary alveolar proteinosis	2	0,8
Wegener granulomatosis	1	0,4
Metastasis of Hodgkin lymphoma	1	0,4
Metastasis of sarcoma	1	0,4
Total	257	100

patient assistance were the main reasons of the failure.

The peripheral lung formations and focuses of infiltration were from 1 to 8 cm in diameter. Pathological diagnosis was defined in 141 (82%) cases of the peripheral lung formations or single infiltration, and pathological diagnosis was defined in 116 (88%) cases of lung dissemination, multiple infiltrations, diffuse changes of the lung x-ray diffuse ground glass picture and enlarged mediastinal lymph nodes.

All patients with the radiological enlarged mediastinal lymph nodes syndrome and confirmed pathological neoplasm diagnosis under the computed tomography had some additional small nodules in the lung parenchyma. The obtained biopsy material revealed that all the patients with the same radiological enlarged lymph node syndrome, but without nodules on CT scan, had signs of granulomatous inflammation.

Table 3. Final diagnosis based on pathological diagnosis and findings of other diagnostic methods respectively to the main radiographical pattern*.

Final diagnosis	Nodule (n=92)	Multiple small nodules (n=61)	Infiltrate (n=59)	Diffuse reticular lung changes (n=27)	Multiple infiltrates (n=16)	Mediastinal or hilar lymphadenopathy (n=12)	Diffuse ground glass opacity (n=2)
Lung cancer, metastasis	64	27	12			17	
Pneumofibrosis	10	15	18	63			
Pneumonia, lung abscess	16	2	34				
Sarcoidosis		23			19	83	
OP, BOOB			22		49		50
Tuberculosis	4	10	9				
Bronchiolitis, bronchitis	3	2		15			
Alveolitis		3		15			50
Pneumoconiosis	1	5	2	7			
Granulomatous pneumonitis		10					
Eosinophilic pneumonia			3		13		
Silicosis		3					
PAP					13		
Wegener granulomatosis					6		
Metastasis of lymphoma	1						
Metastasis of sarcoma	1						

*Data are shown in percents from all patients with appropriate radiological syndrome (based on chest x-ray or CT) and defined pathological diagnosis after bronchoscopic lung biopsy. BOOP – bronchiolitis obliterans organizing pneumonia. OP – organizing pneumonia. PAP – pulmonary alveolar proteinosis.

After the histological investigation, there were diagnosed neoplasm, tuberculosis, and silicosis. Unfortunately, in most of the cases, pathological findings were insufficiently specific for the precise disease diagnosis, as shown in *Tab. 2*. For example, granulomatous pneumonitis was diagnosed in the cases with tuberculosis, sarcoidosis and hypersensitivity pneumonitis. It should be mentioned that epithelioid granulomas without necrosis were found in 3 cases of lung adenocarcinoma, tuberculosis, in one case of lymphoma and one case with myeloma. Six of twenty patients with organizing pneumonia had hematological diseases, 1 – lung cancer, 1 – hepatitis. Infectious or unknown etiology of organizing pneumonia was defined in the remaining cases under trial. Final clinical diagnosis was established according to the data of histological examination data; if needed, it was conducted together with the data of another investigation methods. Clinical diagnoses of the patients with different radiological syndromes, determined after the bronchoscopic lung biopsy, are shown in *Tab. 3*.

As indicated in the *Tab. 3*, even after the pathological diagnosis was established and the data of other examinations (e.g. CT, bronchoalveolar lavage, analysis of the lung function) and tests became available, and sometimes a clinical diagnosis remained only syndromic. For at least 21 (8%) patients, the final clinical diagnoses were granulomatous pneumonitis, alveolitis and similar disorders. Usually, these were the patients who arrived in our Centre from other hospitals, and they were empirically treated with specific medication. Mostly,

these were the cases when patients with suspected tuberculosis were treated applying antituberculous drugs and the cases when patients with suspected sarcoidosis were treated with corticosteroids.

Of all the BLBs, serious complications occurred in 8 (2.6%) patients. Clinically significant pneumothorax requiring chest tube treatment occurred in 5 (1.6%) of 304 patients. Four of them had severe pneumofibrosis, and one of them had lymphangitis carcinomatosa. Non-significant pneumothorax not requiring the chest tube treatment occurred in other 2 (0.7%) patients with bacterial pneumonia.

Severe bleeding occurred in 3 (1%) out of all BLBs. In all the cases, the bleeding was stopped during the same procedure, after the bronchoscope tip in bronchus was occluded for several minutes. There were 2 patients with thrombocytopenia, and there was one with pneumoconiosis and severe pulmonary hypertension. There was no death case related to BLB.

DISCUSSION

The data of 304 bronchoscopic lung biopsies were evaluated retrospectively. The major findings were as follows:

- 1) Most of indications for BLB were a peripheral lung nodule, dissemination in the lung, non-resolving pulmonary infiltrate.
- 2) Adequate lung tissue for histological examination was

obtained in 85% of the cases.

- 3) Carcinoma of the lung, metastasis, pneumofibrosis, granulomatous pneumonitis and pneumonia were the most common pathological diagnosis.
- 4) Based on the pathological diagnosis and findings of other diagnostic methods, the final clinical diagnosis was verified for most of the patients.
- 5) Respectively, related to the main radiographical pattern, the most common diagnosed disorders were as follows: neoplasm in the case of peripheral nodule, lymphangitis carcinomatosa and sarcoidosis in the case of dissemination, pneumonia and organising pneumonia in the case of infiltration, idiopathic pulmonary fibrosis and non-specific interstitial pneumonia in the case of diffuse reticular interstitial lung changes, organising pneumonia in the case of multiple infiltrates, and sarcoidosis in the case of mediastinal or hilar lymphadenopathy.
- 6) Even after the pathological diagnosis was established and the data of other examinations and tests became available, at least in 8% of the cases, the final clinical diagnosis was yet syndromic.
- 7) BLB has rarely caused severe complications.

Aggregate of established diagnoses was determined not only by the patients' population but also by diagnostic algorithms that are approved in our Department. In most cases, sarcoidosis, eosinophilic pneumonia, and tuberculosis were diagnosed based on typical BAL fluid cell changes. Only 2 patients with diffuse ground glass pattern on the CT scan underwent BLB. For the majority of patients with diffuse ground glass pattern, the final diagnosis (hypersensitivity pneumonitis, diffuse alveolar haemorrhage in the cases of collagen vascular disease, etc.) was confirmed by the typical clinical signs, the BAL fluid findings, the specific immune blood test and renal biopsy, when these were needed.

Safe and effective performance of the BLB begins with a proper selection and preparation of the patient for the procedure. The patient should understand the goals and risks of the procedure, and he or she should know how to communicate with the bronchoscopist during the procedure [1].

Contraindications and all potential risk factors should be evaluated carefully. The main contraindications of BLB are a patient's inability to cooperate, coagulopathy, thrombocytopenia, uremia, severe hypoxemia, severe pulmonary hypertension, superior *vena cava* syndrome, and mechanical ventilation [7]. However, clinically significant bleeding may occur, even with normal coagulation test results and without risk factors such as a history of bleeding and anticoagulant therapy [8]. Biopsy of localized disease should not be performed if the lesion is resected, regardless of the results of the biopsy [1].

The optimal quantity of biopsy samples is unknown. It is recommended to take 5 or 6 samples from a peripheral nodule or an infiltrate, and at least 3 samples should be taken from every lung lobe if changes are diffuse [5,6,9]. *Curley et al.* indicated that diagnostic biopsy specimen will likely be

obtained if the size of the specimen fills up the forceps, 2 to 4 biopsies are performed and toothed forceps are used [10].

We usually tried to take at least 4 to 6 samples from a peripheral nodule or mass if biopsy forceps was introduced into the center of lesion. Trying to take as many samples when sarcoidosis was suspected, we took the minimum of 6 to 8 samples when dissemination in the lungs was established. The attempt to take this number of biopsies was caused by the fact that other authors had indicated that, even when procedures were performed by experienced bronchoscopists, the BLB specimen alone was sufficient to establish the diagnosis only in 20 of 43 patients [10]; and, on the whole, no lung parenchyma was obtained [11] in 8% of all BLBs. Although BLB is performed under the fluoroscopic control, it is practically very difficult to identify the boundary between bronchi and alveoli. The biopsy forceps pinches off the lung tissue located between two branches of terminal bronchi. However, it is unclear if the biopsy forceps truly pierces the bronchus to obtain the lung tissue [1]. It should be noted that, even in the cases when no diagnostic abnormality is identified in the biopsy specimen, BLB might be clinically helpful because the results exclude specific processes suspected before the procedure [11].

The efficacy of the BLB for the localized nodule or mass depends on their size and the relation to bronchi. Diagnostic yield of the BPB is between 10% to near 100% for some diseases [1,3,4]. Retrospective analysis of patients with diffuse pulmonary diseases who underwent the fluoroscopy-guided BLB showed that bronchoscopic lung biopsy is a clinically useful test in 75% of the procedures. The reason for a failure in approximately one-third of patients was failure during the procedure to obtain an adequate quantity of lung parenchyma for a meaningful histological analysis [11].

Pathognomic findings in biopsy material usually are identifying in the cases of malignancy or tuberculosis. In most of other diseases, such findings are rarely found. Mostly pathological changes are representative for a group of disorders but not for a specific disease [2,12]. Our data indicated that it is easiest (minor number of biopsy is needed) to find organizing pneumonia and granulomas in biopsy material. However, organizing pneumonia (intraalveolar fibromyxoid nodular masses) may be associated with infection, neoplasm, connective tissue diseases, etc. Granulomas without necrosis can be caused by various diseases, such as sarcoidosis, tuberculosis, or sometimes as a paraneoplastic process in the case of carcinoma or lymphoma, etc. Therefore, further differential diagnosis is often essential. This is very important for countries with high prevalence of active and latent tuberculosis.

Good biopsies may be difficult to obtain in the case of an advanced fibrotic disease [1]. Generally, using BLB to diagnose idiopathic interstitial pneumonia is not recommended [13]. However, the recently published data proved that characteristic histological features of usual interstitial pneumonia (UIP) could be identified on TBB specimens more often than previously appreciated [14]. Thus, BLB may be

more useful in confirming UIP than previously recognized. We used ATS/ERS criteria [15] for the diagnosis of idiopathic interstitial pneumonia (IPF). The BLB findings were qualified as information for the differential diagnosis only.

Historically, histopathologic evaluation has been viewed as the golden standard for the diagnosis in diffuse lung disease. That perception is changing [16]. Hunninghake et al. had found that the lung HRCT scan might strongly predict a correct diagnosis of IPF [17]. Aziz et al. [18] evaluated the influence of the results of the thin-section CT on request for different diagnostic methods for interstitial lung disease. They showed that with the CT findings, pulmonologists changed their pre-CT responses regarding the use of bronchoalveolar lavage, transbronchial biopsy, and thoracoscopic biopsy in 24%, 28%, and 29% cases, respectively. The request rate for thoracoscopic biopsy, on patients with the diagnosed idiopathic fibrosis, decreased from 26.8% to 11.2% after the CT.

It is important to carefully analyze the cases when some features of pneumoconiosis in biopsy specimens are found. In biopsy samples of our 5 elderly patients, fibrosis and the accumulation of pigment dust ("pneumoconiosis") were found; although, they were non-smokers and their job was (as they thought) not harmful to their lungs. It might be that they did not precisely remember their previous operating conditions. They lived and were employed in the countryside, some of them stoked up coal. Therefore, it was not formally possible to diagnose pneumoconiosis. Previous authors [12] indicated that the unreliable diagnostic yield of BLB is found in fibrosing alveolitis due to occupational exposure or autoimmune disease.

In our opinion, efficacy and the risk ratio for the BLB is higher than alternative biopsy methods, such as transthoracic needle biopsy and surgical lung biopsy efficacy and risk ratio. Our results and the data of other authors showed that BLB is a relatively safe diagnostic method. The pneumothorax rate after BLB is 2–5% [19,20]. Bleeding after the BLB for carefully selected patients is rare and not intensive. Life-threatening haemoptysis occurred in 2–4% of the BLB [6,19]. Death happened mostly due to the massive bleeding or pneumothorax was rare, and it occurred in 0–0.2% of the cases. [3].

Surgical lung biopsy does not always provide a specific diagnosis and does not always change therapy [21]. The mortality rate after surgical biopsy is 4–17% of all the procedures [22–26]. Surgical biopsy is increasingly reserved for the cases in which clinical or HRCT information is inconclusive or discordant, and diagnosis was not confirmed using less invasive techniques [16,27].

The transthoracic needle biopsy (TNB) is an effective diagnostic method in experienced hands. However, the pneumothorax rate after the TNB is 10–38% (up to 15% cases requiring chest tube treatment), haemoptysis and/or parenchymal hemorrhage incidence of 10–21%, death of 0.5–1.0% cases [28,29].

In the present study, a potential limitation was its retrospective nature. We have not compared different biopsy

methods. The present authors have followed up most of these patients for at least several years; however, in some cases of organizing pneumonia, granulomatous pneumonitis and pneumofibrosis aetiology were not specified.

CONCLUSION

To summarize, bronchoscopic lung biopsy is a relatively effective and safe method to diagnose lung diseases. In most cases of the lung infiltrate, nodule, dissemination, and diffuse changes, the BLB is a suitable method for lung biopsy.

ACKNOWLEDGEMENTS

The authors are indebted to Ms Danguole Reikaite for her assistance in the preparation of the English version of the manuscript. The authors have no conflicts of interest to disclose.

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