

Contribution of cell block obtained by endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of malignant diseases and sarcoidosis

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ABSTRACT

Aim: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe and minimally invasive procedure that can be performed in outpatient settings. Several studies have demonstrated the usefulness of EBUS-TBNA in the diagnosis of sarcoidosis and malignant diseases. This study focused on the role of cell block (CB) analysis in determining the diagnostic yield of EBUS-TBNA in malignant diseases and sarcoidosis. **Materials and Methods:** The study was conducted at a training and research hospital. Records of patients who underwent EBUS-TBNA between March 2011 and December 2014 for diagnosed sarcoidosis or malignancy were retrospectively analyzed. Results of all EBUS-TBNA smears and CB were separately evaluated to determine the diagnostic value of each. **Results:** There were 84 sarcoidosis and 179 malignancy patients. In the malignancy group, CB contributed to cancer diagnosis in 15 (8.3%) patients and subclassification in 19 (10.6%) patients. In the sarcoidosis group, for 45.2% of patients (38/84), smears were not diagnostic but CB showed granulomatous inflammation. **Conclusion:** CB significantly increases the diagnostic yield of EBUS-TBNA for sarcoidosis. In our study, in the malignancy group the diagnostic yield was low but it was helpful for subclassification, especially for adenocarcinoma.

Key words: Cell block (CB), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), malignant diseases, sarcoidosis

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a safe and minimally invasive procedure that allows the bronchoscopist to see beyond the airway and to evaluate mediastinal and hilar pathology. Current guidelines recommend EBUS-TBNA before mediastinoscopy for the mediastinal staging of lung cancer.^[1,2] EBUS-TBNA has also

been performed to diagnose enlarged mediastinal nodes detected by computed tomography (CT) and/or hypermetabolic lymph node(s) (LNs) detected by positron emission tomography/computed tomography (PET/CT).

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How to cite this article: Erer OF, Erol S, Anar C, Aydoğdu Z, Özkan SA. Contribution of cell block obtained by endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of malignant diseases and sarcoidosis. *Endosc Ultrasound* 2017;6:265-8.

Access this article online

Quick Response Code:



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DOI:

10.4103/2303-9027.180763

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Received: 2015-03-28; **Accepted:** 2015-05-08

The material obtained using EBUS-TBNA can also be processed as a cell block preparation (CB) for additional diagnostic procedures. Recent studies have shown that a combination of CB and smear preparation increases the diagnostic yield of EBUS-TBNA.^{13,41} CB preparations are, however, not yet widely used in EBUS-TBNA samples and there is little information about its contribution to the diagnostic process. Therefore, the aim of this study was to evaluate the contribution of CB in the diagnostic yield of EBUS-TBNA in sarcoidosis and malignancy.

MATERIALS AND METHODS

Study design

This is a retrospective study of prospectively followed-up cases in which the diagnostic value of CB prepared from cytological specimens of hilar and mediastinal lymphadenopathies was obtained by EBUS-TBNA.

Case selection and inclusion criteria

The medical database of our hospital was searched. Patients who were diagnosed with sarcoidosis or malignancy with EBUS-TBNA between March 2011 and March 2014 were included.

This study was approved by the local Ethical Committee.

EBUS-TBNA and evaluation of specimens

EBUS-TBNA was performed using an EBUS-guided TBNA bronchoscope (7.5 MHz, BF-UC160F; Olympus Optical Co., Tokyo, Japan) by the oral route under topical anesthesia and conscious sedation (midazolam). Mediastinal and hilar LNs were examined systematically. Mediastinal LNs with short axis ≥ 5 mm were aspirated. EBUS-TBNA was performed for diagnosing enlarged and/or hypermetabolic mediastinal or hilar LNs. Informed consent was obtained from every patient.

LNs were aspirated with dedicated 22-gauge needles (NA-201SX-4022-C; Olympus, Tokyo, Japan). At least three consecutive aspirates were obtained from each LN station. Some amount of the aspirate was smeared onto glass slides, air-dried, fixed immediately with 95% alcohol, and stained with hematoxylin and eosin (H&E). The rest of the aspirate was placed into a mixture of formalin and alcohol in order to obtain a CB for histological examination. Rapid onsite cytological examination (ROSE) was not available. CBs were embedded in paraffin, and 6- μ m thick sections

were obtained and stained as deemed necessary by the cytopathologist. Routine H&E staining was used on CB sections and immunohistochemical staining (IHCS) was applied for the identification or phenotyping of malignant cells in all of the patients. Somatic mutations of the genes coding the tyrosine kinase domain of epithelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) were not examined on CB samples in our pathology laboratory. All aspirates were also sent for acid-fast staining, mycobacterial cultures, and polymerase chain reaction (PCR).

Final diagnoses

Malignancy

Tissue obtained by EBUS-TBNA was considered malignant when the aspirated material contained malignant cells. Tumor-positive findings from EBUS-TBNA samples were not surgically validated, but tumor-negative findings were validated by mediastinoscopy, video-assisted thoracoscopic surgery (VATS), or thoracotomy. If a patient rejected these procedures, radiological follow-up was done. During the follow-up period, if LNs enlarged as a result of clinical radiological evaluation, it was accepted as “false negative.”

IHCS was performed for all patients to confirm diagnosis and determine the subtype of cancer.

Sarcoidosis

Sarcoidosis was diagnosed when all of the following criteria were fulfilled:

1. Demonstration of necrotizing or nonnecrotizing granulomas on EBUS with negative acid-fast bacilli,
2. No growth of mycobacteria on culture, and
3. Clinical and radiological presentation consistent with sarcoidosis.

Statistical analyses

All analyses were carried out using the SPSS statistical package (ver. 16.0). Descriptive statistics were expressed as mean \pm standard deviation for continuous variables and as frequency (percentage) for categorical variables.

Diagnostic value of CB

1. Cytological examination of smears was not diagnostic, but CB found granulomatous inflammation or malignancy, it was defined as “contribution to diagnosis by CB.”
2. Cytological examination of smears was reported as only malignancy, but CB or IHCS reported the subtype of cancer; it was defined as “contribution to subclassification by CB.”

RESULTS

Between March 2011 and December 2014, 514 patients underwent EBUS-TBNA. Sensitivity and negative predictive value of EBUS-TBNA in malignancy and sarcoidosis group were 81.3% and 87.7%, and 84.8% and 96.5%, respectively.

Eighty-four (24 male, 60 female) sarcoidosis and 179 malignancy (147 male, 32 female) patients diagnosed with EBUS-TBNA were included in the study. The mean ages of the patients were 44.8 ± 13.5 years for sarcoidosis and 61.3 ± 9.4 years for the malignancy group. In total, 580 LNs were sampled. The subcarinal LN (station 7) was most commonly sampled, followed by the right lower paratracheal LN (station 4R) [Table 1].

Malignancy group

In the malignancy group, 362 LNs were sampled in 179 patients. In 29 patients (16.2%), smear cytology was malign, but there was no malignancy in CB. Examination of CB was reported as benign in 12 (41.3%), anthracosis in 7 (24.1%), and insufficient tumor tissue in 10 (34.4 %) of these patients. Because IHCS were not performed in these patients. Malignancy was determined in the CB of 150 (83.7 %) patients, and IHCS was performed for all of the patients.

In the malignancy group, smears of 15 (8.3%) patients were nondiagnostic or benign, but examinations of CB were diagnostic. For 19 (10.6%) patients, both smear and CB were diagnostic but histologic subtype was determined with CB. One of these 19 patients was diagnosed as squamous cell carcinoma with cytomorphological examination. However, IHCS reported adenocarcinoma. As a result, CB contributed to the diagnosis of malignancy in 8.3% of patients and subtype in 10.6% of patients [Tables 2 and 3].

Somatic mutations of the genes coding the tyrosine kinase domain of EGFR and ALK were not examined on CB samples.

Sarcoidosis group

In 46 (54.7%) patients, both smears and CB examinations found granulomatous inflammation. In 38 (45.2%) patients, smears were nondiagnostic but the examination of CB reported granulomatous

Table 1. The characteristics of patients and frequency of LNs diagnosed by EBUS-TBNA

Characteristics	Malignancy (%)	Sarcoidosis (%)
Gender [N (%)]		
Male	147 (82.1)	24 (28.6)
Female	32 (17.9)	60 (71.4)
Age [mean (min-max)] in years	61.3±9.4 (39-83)	44.8±13.5 (26-69)
Station of LNs [n (%)]		
7	117 (65.4)	77 (91.7)
4R	94 (52.5)	60 (71.4)
4L	44 (24.6)	7 (8.3)
11L	37 (20.7)	48 (57.1)
11R	31 (17.3)	25 (29.8)
10L	15 (8.4)	0
2R	12 (6.7)	0
10R	10 (5.6)	1 (1.2)
2L	2 (1.7)	0

LN: Lymph node, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

Table 2. The frequency of smear and CB in patients with sarcoidosis and malignancy diagnosed by EBUS-TBNA

Diagnosis	N	Smear diagnostic CB		Smear nondiagnostic CB		Smear nondiagnostic CB	
		diagnostic		nondiagnostic		CB diagnostic	
		N	%	N	%	N	%
Sarcoidosis	84	46	54.7	0	0	38	45.2
Malignancy	179	135	75.4	29	16.2	15	8.3

CB: Cell block, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration

Table 3. The frequency of malignancy patients and contribution of CB diagnosed by EBUS-TBNA

Type of cancer	Number of patients N (%)	The contribution of CB to diagnosis N (%)	The contribution of CB to subtype of malignancy N (%)
Lung cancer	163 (91.6)	12 (8.3)	19 (10.6)
Adenocarcinoma	62 (34.6)	2 (1.1)	12 (6.7)
SqCLC	52 (29)	5 (2.7)	4 (2.2)
SCLC	37 (20.6)	2 (1.1)	3 (1.6)
NSCLC	12 (6.7)	3 (1.6)	0
EPM	14 (7.8)	3 (1.6)	0
Lymphoma	2 (1.1)	0	0

CB: Cell block, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration, SqCLC: Squamous cell lung carcinoma, SCLC: Small-cell lung cancer, NSCLC: Non-small cell -lung cancer, EPM: Extrapulmonary metastasis

inflammation. There was no patient for whom smear was diagnostic and CB was not [Table 2].

DISCUSSION

This study showed that CB improved the diagnostic yield of EBUS-TBNA for diagnosis of sarcoidosis. Von Bartheld *et al.* have emphasized the importance

of CB in fine-needle aspiration (FNA)-based diagnosis of sarcoidosis,^[5] as among 18 smear negative patients in their study, CB analysis detected the presence of a nonnecrotizing granuloma in 6 (33%). Similarly, Iwashita *et al.* found that the diagnosis of sarcoidosis increased from 77.8% to 94.4% when CBs were used.^[6] Navani *et al.* reported that in patients with sarcoidosis, the sensitivity of EBUS-TBNA in detecting noncaseating granulomas was 85%. They mostly used air-dried cytological smears, but noted that in some cases, formalin-fixed histological cores were obtained.^[7]

The improved diagnostic yield in granulomatous diseases when CBs are used is due to the fact that when the specimen is allowed to clot, recognition of granulomas is easier than with smear preparations.^[8,9] Wang *et al.* found that in 37 patients who underwent EBUS-TBNA, 100% of CBs showed nonnecrotizing granulomas, compared to only 27% in smears.^[9] This may be because the smearing of samples between two slides disrupts the epithelioid groups in the FNA samples; this does not tend to occur during CB preparation as sedimentation and paraffin embedding do not disrupt the histological structure.^[5]

Although CB is accepted as a standard procedure for diagnosis of granulomatous diseases such as sarcoidosis, it has yet to be cleared for malignancy.

Nathan *et al.*^[8] reported the importance of CB for the diagnosis and categorization of tumors. Previous studies on CBs obtained with EBUS-TBNA showed that CB contributed to diagnosis when combined with smear, but it is more important for subtyping.^[3,4,10]

Additionally, as a previous study revealed, CB provides material suitable for genetic analysis.^[11] Targeted therapies are becoming more important in lung cancer treatment^[12] and the current guidelines recommend their subclassification and genetic analysis, especially for non-small cell lung cancer.^[13] Thus, CBs should be obtained in all cases of suspected malignancy. Consistent with the previous studies, in our study CB slightly increased the diagnostic yield of EBUS-TBNA for malignancy. However, CBs obtained during EBUS-TBNA provided additional information for subtyping of cancer with IHCS, as in other studies.^[11-13]

CONCLUSION

In conclusion, we showed that CBs increase the diagnostic yield of EBUS-TBNA in sarcoidosis and enable subclassification of malignancy. Therefore, all efforts should be made to obtain sufficient samples for CB preparation in all patients with suspected granulomatous diseases or malignancy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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