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Atypical cells in pathology of endobronchial ultrasound-guided transbronchial biopsy of peripheral pulmonary lesions: incidence and clinical significance

Chun-Ta Huang[1,2] · Yi-Ju Tsai[3] · Chao-Chi Ho[1] · Chong-Jen Yu[1]

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Abstract

Background Atypical cells may occasionally be the only pathologic finding in radial-probe endobronchial ultrasound (EBUS)-guided transbronchial biopsy (TBB) of peripheral pulmonary lesions (PPLs); however, it is uncertain how often we encounter such a situation and what clinical features can be used to identify these ambiguous PPLs, which are more likely to be malignant.

Methods From 2009 to 2016, consecutive patients referred for EBUS-guided TBB of PPLs and with pathology reports indicating atypical cells alone were included. Medical records were reviewed to extract patient demographics, clinical characteristics, procedural details and complications. The primary outcome was the final diagnosis of the PPLs on subsequent investigation. Multivariate logistic regression analysis was used to identify independent factors associated with a final malignant diagnosis.

Results One hundred sixty-five (7.2%) of 2291 patients had non-diagnostic TBB showing atypical cells. Benign and malignant diagnoses were subsequently obtained in 45 (27%) and 120 (73%) patients, respectively. The leading malignancy was lung adenocarcinoma; of note, a variety of benign lesions revealed cellular atypia on pathology, in particular, chronic inflammation, tuberculosis and pneumonia. Multivariate analysis indicated lesion appearance [solid vs. others; odds ratio (OR) 7.93; 95% confidence interval (CI) 2.94–21.40; $P<0.001$] and probe position (adjacent to vs. within; OR 3.36; 95% CI 1.11–10.15; $P=0.032$) were two significant factors predictive of a final diagnosis of malignancy.

Conclusions One out of 14 EBUS-guided TBB procedures for PPLs exhibited atypical cells on pathology. Meticulous management strategies should be formulated to deal with these instances after taking into consideration lesion appearance, probe position and patient preferences.

Keywords Biopsy · Bronchoscopy · Endobronchial ultrasound · Pathology · Peripheral pulmonary lesion

A diagnosis of peripheral pulmonary lesions (PPLs) can be achieved through a variety of modalities, such as bronchoscopy, computed tomography (CT)-guided biopsy and surgery [1, 2]. Advances in bronchoscopic techniques, including radial-probe endobronchial ultrasound (EBUS), the guide sheath, ultrathin bronchoscopy, virtual bronchoscopic navigation and electromagnetic navigation, have made transbronchial biopsy (TBB) a more appealing approach [3–6]. Among these technical advances, EBUS-guided TBB provides a fair diagnostic yield and a superior safety profile in diagnosing PPLs [2, 7, 8], and has taken the place of conventional TBB [9]. Establishing a diagnosis of malignancy is a major indication of EBUS-guided TBB; however, on occasion, the biopsy is not diagnostic and yields findings that lack sufficient cytologic and architectural atypia to differentiate benign and malignant lesions with certainty. In daily practice, it is important to understand the incidence of this situation and its clinical implications

✉ Chao-Chi Ho
ccho1203@ntu.edu.tw

[1] Department of Internal Medicine, National Taiwan University Hospital, No. 7 Chung-Shan South Rd, Taipei 100, Taiwan, Republic of China

[2] Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China

[3] Graduate Institute of Biomedical and Pharmaceutical Science, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan, Republic of China

since this information will help clinicians deal with these non-diagnostic PPLs and discuss risks with patients, so as to make informed decisions.

To our knowledge, no research exists that addresses the issues of how often we encounter atypical cells in pathology reports from EBUS-guided TBB of PPLs and what clinical or imaging features can be used to identify those patients that are more likely to have a malignant lesion, although data about atypical cells associated with CT-guided percutaneous transthoracic needle biopsy exist in the literature [10]. Our study was specifically aimed to tackle these unresolved issues.

Materials and methods

Study design and subjects

Consecutive adult patients who underwent EBUS-guided TBB of a PPL at National Taiwan University Hospital from January 2009 to December 2016 were screened for eligibility. A PPL was defined as a lesion surrounded by lung parenchyma and invisible via conventional bronchoscopy [11–13]. Patients whose pathology reports indicated atypical cells without a definitive diagnosis were included in this study. Exclusion criteria were as follows: (a) diagnosis of a PPL that was achieved via bronchial washing or brushing procedures during the same bronchoscopic session and (b) the patient was lost to follow-up before the diagnosis of a PPL could be made. This study was conducted in accordance with the amended Declaration of Helsinki. The Research Ethics Committee of National Taiwan University Hospital approved the protocol and patient informed consent was waived since data were retrospectively collected and there were no patient safety concerns throughout the study protocol.

Bronchoscopic exam

The procedures were mainly conducted by chest fellows under the supervision of experienced pulmonologists, as previously described [11–15]. In brief, after local anesthesia achieved by spray or nebulization of lidocaine into the upper airway and intramuscular administration of meperidine or fentanyl, conventional bronchoscopy with a 2.0-mm working channel was performed first to inspect the bronchial trees. EBUS was performed subsequently to locate the PPLs, and EBUS-guided TBB was commenced. The biopsies were repeated until at least four adequate samples, defined as lung specimens spilling over the surface of the biopsy forceps, were obtained [16]. On the same occasion, bronchial washings or brushings were to be performed at the discretion of the supervising pulmonologists. During the study period, rapid onsite evaluation of the biopsy samples was not performed for our patients. Throughout the procedures, oxygen was delivered to the patient via a nasal prong with oxygen saturation monitored by pulse oximetry. Given the favorable safety profile of EBUS-guided TBB, a chest X-ray was taken only as clinically indicated.

Data collection

Medical records and image studies were reviewed to extract information, including patient demographics, clinical characteristics, procedural details and complications. The primary outcome of interest was the final diagnosis of PPLs among the study population. Since lesion distribution, size and appearance, probe position, and number of biopsies per lesion have been implicated to be associated with diagnostic sensitivity of EBUS-guided TBB for PPLs, these factors were specifically retrieved for analysis [7, 14, 17–19]. Lesion distribution was classified into five anatomic lobes and lesion size was determined as the largest axial diameter on CT scans. Lesion appearance was categorized as a solid, partly solid, pure ground-glass or cavitary opacity. Probe position was classified as either within or adjacent to a PPL, as previously described [11]. Post-procedural hemorrhage was defined as significant bleeding mandating further intervention or intensive care. Post-TBB pneumothorax was defined as the presence of air in the pleural cavity and was confirmed by chest X-ray. Following EBUS-guided TBB, study subjects underwent a variety of diagnostic procedures or follow-up to establish a definitive diagnosis of PPLs. A PPL was deemed benign if its size decreased or remained unchanged after at least a 1-year follow-up.

Statistical analysis

Data are presented as number (percentage) or mean ± standard deviation per data distribution. For the primary outcome, associations with a number of variables were checked using χ^2 or Fisher's exact test for categorical variables, or Student's t test for numerical variables, as appropriate. All relevant variables were entered into multivariate logistic regression analysis without model selection to identify independent factors associated with a final diagnosis of malignancy. A P value < 0.05 was considered statistically significant and all tests were two tailed. All statistical analyses were performed using SPSS for Windows (version 15.0; SPSS Inc., Chicago, Illinois).

Results

Study patients

A total of 2291 patients underwent EBUS-guided TBB for PPLs throughout the 8-year study period. Of those, 165

(7.2%) patients who had non-diagnostic pathology results showing atypical cells were included in this study (Fig. 1). The mean age of the population was 66.1 years. The lesion size was larger than 20 mm in 90% (148/165) of patients, and the majority of PPLs appeared solid (140/165, 85%) on CT scans. In about three-fourth (123/165) of the included patients, the EBUS probe could be positioned with the lesions. The mean number of biopsies performed for each PPL was 5.3 ± 1.8. Four (2.4%) of the 165 subjects had complications, including hemorrhage ($n = 3$) and pneumothorax ($n = 1$). No procedure-related death was encountered. The baseline characteristics of the study population are displayed in Table 1.

Table 1 Patient characteristics

Variables	Benign lesions $n = 45$	Malignant lesions $n = 120$	*P* value
Age (years)	67.8 ± 10.8	65.4 ± 12.6	0.245
≤65	21 (47)	63 (53)	0.504
>65	24 (53)	57 (48)	
Male sex	25 (56)	57 (48)	0.357
Lesion distribution			
Right upper lobe	9 (20)	36 (30)	0.034
Right middle lobe	1 (2.2)	15 (13)	
Right lower lobe	15 (33)	20 (17)	
Left upper lobe	15 (33)	30 (25)	
Left lower lobe	5 (11)	19 (16)	
Lesion size, mm	34 ± 10	37 ± 17	0.283
≤20	2 (4.4)	15 (13)	0.159
>20	43 (96)	105 (88)	
Lesion appearance			
Solid	29 (64)	111 (93)	<0.001
Others[a]	16 (36)	9 (7.5)	
Probe position			
Within	40 (89)	83 (69)	0.010
Adjacent to	5 (11)	37 (31)	

[a]Partly solid, pure ground-glass or cavitary

Diagnoses of the PPLs

Benign and malignant diagnoses were subsequently obtained for 45 (27%) and 120 (73%) patients, respectively (Table 2). The diagnostic modalities included CT-guided biopsy ($n = 62$), video-assisted thoracoscopic surgery ($n = 56$), repeat EBUS-guided TBB ($n = 12$), distant biopsy ($n = 11$), mediastinal lymph node sampling via linear-probe EBUS-guided transbronchial needle aspiration ($n = 6$), microbiology ($n = 4$), serology ($n = 1$) and clinical/radiologic follow-up ($n = 13$). The leading malignancy associated with the presence of atypical cells on pathologic examination was

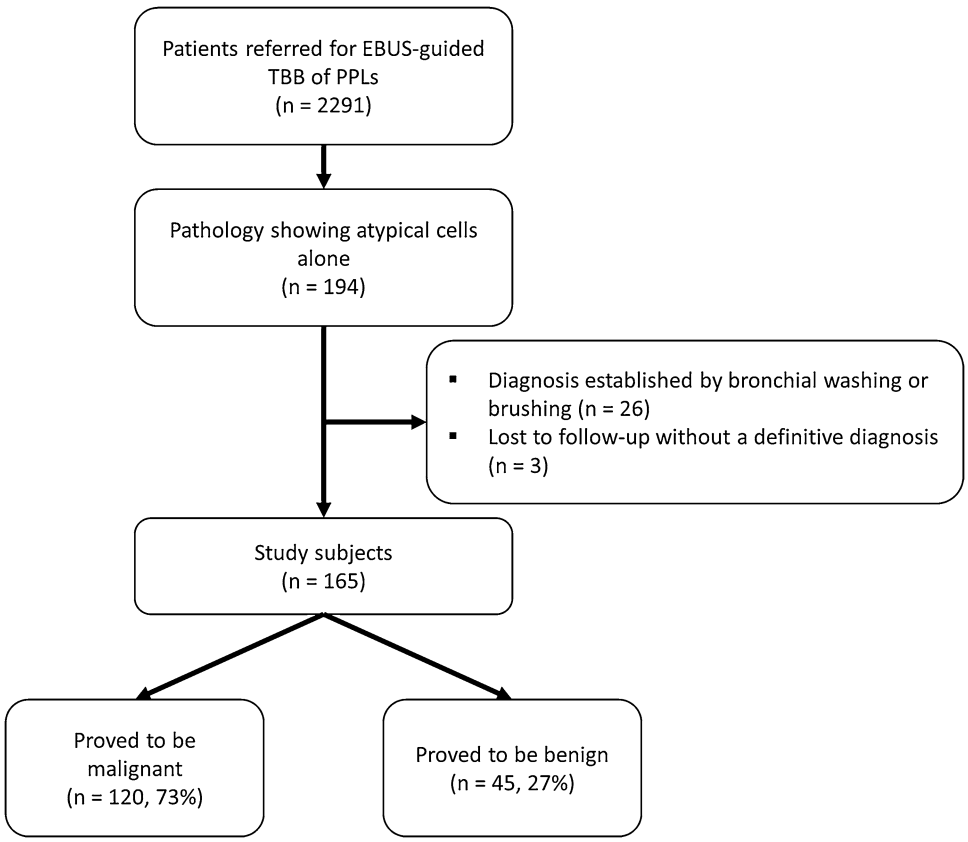

Fig. 1 Study flow diagram. *EBUS* endobronchial ultrasound, *TBB* transbronchial biopsy, *PPL* peripheral pulmonary lesion

Table 2 Final diagnoses

Diagnoses	No. (%) of patients ($n=165$)
Malignant lesions	120 (73)
Adenocarcinoma	86 (52)
Squamous cell carcinoma	7 (4.2)
Metastasis	6 (3.6)
Lymphoma	4 (2.4)
Small cell carcinoma	4 (2.4)
Carcinoma	3 (1.8)
Non-small cell carcinoma	3 (1.8)
Others	7 (4.2)
Benign lesions	45 (27)
Chronic inflammation	8 (4.8)
Tuberculosis	8 (4.8)
Pneumonia	7 (4.2)
Cryptococcosis	2 (1.2)
Mycetoma	2 (1.2)
Nontuberculous mycobacteriosis	2 (1.2)
Organizing pneumonia	2 (1.2)
Sarcoidosis	2 (1.2)
Others	12 (7.3)

lung adenocarcinoma. Of note, a variety of benign lesions exhibited atypical cells on pathology; among them, chronic inflammation, tuberculosis and pneumonia were the three most common.

Factors associated with malignant diagnoses

Univariate analysis (Table 1) indicated a difference between benign and malignant lesions in the lobar distribution and appearance of the PPLs, and in the position of the EBUS probe. The number of biopsies among the benign and malignant PPLs was similar, with a mean of 5.2 ± 1.4 vs. 5.3 ± 1.9 per lesion, respectively ($P=0.986$). In the multivariate analysis (Table 3), only lesion appearance [solid vs. others; odds ratio (OR) 7.93; 95% confidence interval (CI) 2.94–21.40; $P<0.001$] and probe position (adjacent to vs. within; OR 3.36; 95% CI 1.11–10.15; $P=0.032$) were associated with a final diagnosis of malignancy. In other words, patients with both high-risk features (33/38, 87%) were far more likely than those with neither of the two features (5/21, 24%) to have malignant lesions on subsequent investigation.

Discussion

The main findings of this study are (a) the incidence of atypical cells on EBUS-guided TBB of PPLs was 7.2%; (b) the majority (73%) of patients with this pathology were eventually found to have a malignant diagnosis; (c) atypical cells, found on pathology of TBB of PPLs, were not uncommonly seen in benign lesions, particularly chronic inflammation, tuberculosis and pneumonia; (d) a solid lesion appearance and position of the EBUS probe adjacent to a PPL were two high-risk features suggesting the presence of malignancy in the end for these patients.

Although the diagnosis of PPLs in most patients undergoing EBUS-guided TBB will be definitively benign or malignant [7], the present study found that 7.2% of the TBB resulted in a pathology diagnosis of atypical cells. Previously published data of atypical cells in percutaneous transthoracic needle lung biopsy showed a slightly higher percentage of 15.5% and a slightly lower percentage of malignancy in those atypical cell samples (62.5%), as opposed to the current study [10]. There are several reasons why a biopsy could yield the diagnosis of the presence of atypical cells, and among them, the limited amount of tissue available for examination in a small piece of biopsy specimen may be a major factor. The increased use of minimally invasive biopsy techniques for investigating PPLs has led to the consequence that in a significant number of cases, the pathologic findings are equivocal. The correct recognition of malignancy or a specific benign process relies on fulfilling diagnostic criteria that have been developed through a detailed and comprehensive inspection of a large surgical specimen [20–22]. Thus, the typical architectural or cytologic features needed for an accurate diagnosis of either a benign or malignant lesion are not readily seen in a small sample [23]. Our study, for the first time, shows how often pathologists are confronted with a dilemma when trying to

Table 3 Multivariate logistic regression model for patient and clinical features associated with a final diagnosis of malignancy

Characteristics		OR	95% CI	*P* value
Age	> 65 years vs. ≤65 years	0.74	0.34–1.61	0.441
Sex	Male vs. female	0.66	0.30–1.43	0.289
Lesion distribution	Upper lobes vs. non-upper lobes	1.67	0.75–3.70	0.206
Lesion size	> 20 mm vs. ≤20 mm	0.30	0.06–1.60	0.159
Lesion appearance	Solid vs. others	7.93	2.94–21.40	< 0.001
Probe position	Adjacent to vs. within	3.36	1.11–10.15	0.032

CI confidence interval, *OR* odds ratio

reach a definitive diagnosis of EBUS-guided TBB of PPLs, and then report an inconclusive result of atypical cells.

To date, no studies that have investigated the relationship between atypical cells in EBUS-guided TBB and the subsequent diagnosis of malignancy have been reported. The present work indicates that approximately three-fourth of PPLs with pathology showing atypical cells were later proved to be malignant. This information suggests that under most circumstances, an invasive diagnostic procedure for PPLs should be planned if EBUS-guided TBB finds only atypical cells. In addition to malignancy, cells may exhibit atypia in certain benign processes. In tissue repair, benign epithelial cells display some morphologic attributes of malignant cells, such as enlarged nuclei and prominent nucleoli [23]. This reparative atypia could be particularly conspicuous in association with inflammatory mass lesions, such as granulomatous inflammation [24]. Specific infections, e.g., aspergillosis, may also lead to significant cellular atypia [23]. In line with these observations, chronic inflammation, tuberculosis and pneumonia were the most common benign PPLs associated with atypical cells on EBUS-guided TBB in this study. Of note, more than one in four PPLs with cellular atypia was ultimately considered to be benign lesions. Thus, taking the relevant clinical context into consideration is paramount when interpreting a pathology result of cellular atypia, since it may be possible to postpone or even avoid invasive studies in this subgroup of patients with PPLs.

As stated above, it would be practically useful to understand the clinical and radiologic characteristics predictive of benign or malignant PPLs, after atypical cells are identified in EBUS-guided TBB. Our study herein found two significant features that can pertain to a malignant diagnosis in PPLs, namely a solid PPL and a PPL with the probe positioned at its edge. A barrage of evidence has indicated that lesion appearance has nothing to do with the diagnostic yield of EBUS-guided TBB [12–14, 17]. However, in lung cancer screening studies, a pulmonary nodule, either partly solid or pure ground-glass, is more likely to be malignant than a solid one [25]. This is contradictory to our findings that solid PPLs with atypical cells on TBB are a high-risk predictor for a subsequent malignant diagnosis. Our study subjects were highly specific and selected; therefore, a general observation may not be applicable to this particular population. The discrepancy reinforces the importance and value of the current study.

EBUS probe position is a well-recognized variable associated with the diagnostic yield of TBB for PPLs [12–14, 18, 26, 27]. A probe located adjacent to the PPL has a remarkably lower diagnostic yield than that of a probe placed within the PPL. The present study revealed that PPLs with cellular atypia on TBB had significantly higher odds of a malignant diagnosis when the EBUS probe was positioned adjacent to, rather than within, the lesions. The reasons behind the finding are not entirely clear. A plausible explanation is that tissue samples acquired from the PPLs via EBUS-guided TBB may be less likely to provide adequate and sufficient material for pathology investigation if the probe can only be located adjacent to the PPLs (rather than within the PPLs). Therefore, the specimens would not be sufficient to allow the pathologist to be confident enough to make a definitive diagnosis of PPLs, but only to report an ambiguous result, i.e., atypical cells. Taken together, the findings of this study indicate two significant elements—lesion appearance and probe position—should be considered when encountering a pathology report of atypical cells on EBUS-guided TBB, to formulate appropriate management strategies for patients with PPLs.

A number of limitations to the present work should be mentioned. First, the study presents results from a single institution, and further confirmation from other organizations or settings is required. Yet, as the pioneer study in this field, we hope our findings will encourage more large-scale and elaborate studies to explore this issue. Second, given the retrospective nature of this study and the lack of standardization of the interpretation of pathologic findings, inter-observer variability in making a diagnosis of atypical cells may exist among pathologists. However, this is a common and real-world phenomenon, and may, therefore, support the generalizability of our study. Third, auxiliary bronchoscopic procedures, such as fluoroscopy or a guide sheath, were not used in our study cohort; thus, it is uncertain whether our findings remain valid when ancillary tools are coupled with EBUS-guided procedures. However, this is also one of our study's strengths, in that it allows us a unique opportunity to do the observation specifically related to EBUS-guided TBB.

In conclusion, atypical cells on pathology were observed in one out of 14 EBUS-guided TBB procedures for PPLs, and these non-diagnostic lesions were mainly found to be malignant on subsequent investigation. Of note, cellular atypia may also be the pathologic finding of PPLs in certain benign processes, in particular, chronic inflammation, tuberculosis and pneumonia. Two significant features, lesion appearance and probe position, would help differentiate benign from malignant PPLs. Thus, in dealing with a pathology report of atypical cells in EBUS-guided TBB specimens, meticulous management strategies, e.g., invasive studies or conservative observations, should be formulated for the PPLs after taking into consideration the two aforementioned important clinical features and patient preferences.

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Compliance with ethical standards

Disclosures Drs. Chun-Ta Huang, Yi-Tu Tsai, Chao-Chi Ho, and Chong-Jen Yu have no conflicts of interest or financial ties to disclose.

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