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Role of additional endobronchial biopsy in enhancing diagnostic accuracy for sarcoidosis

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Abstract. *Background and Aim:* The identification of nonnecrotizing granulomas is essential for the diagnosis of sarcoidosis. For this purpose, the effectiveness of transbronchial lung biopsy (TBLB) and transbronchial needle aspiration (TBNA) is established; however, the role of endobronchial biopsy (EBB) remains uncertain. This study aimed to assess the additional diagnostic value of EBB and factors affecting its diagnostic yield for the diagnosis of sarcoidosis. *Methods:* This retrospective cross-sectional study included 46 patients who were preliminarily diagnosed with sarcoidosis and admitted to the Department of Respiratory Medicine of Shizuoka Saiseikai General Hospital between August 2016 and April 2023. Among them, 25 patients who underwent EBB were divided into EBB (diagnosed by EBB) and nonEBB (diagnosed by TBLB, TBNA, or clinically) groups. The patient background characteristics were analyzed to identify factors affecting the diagnostic yield of EBB. *Results:* The diagnostic yield of EBB alone was 24% (6 of 25 patients). There were no significant differences in the patients' background characteristics between the two groups. When EBB was added, the diagnostic yield of TBLB increased from 47.8% to 60.9% and that of TBNA increased from 52.6% to 57.9%. In three patients, EBB alone provided histological diagnosis. *Conclusions:* Although EBB alone had a relatively low diagnostic yield, it led to a diagnosis in some cases. Combining TBLB or TBNA with EBB may enhance overall diagnostic yield.

Key words: sarcoidosis, endobronchial biopsy, diagnostic yield, biopsy techniques, bronchoscopy

Introduction

Sarcoidosis is a multisystemic inflammatory disorder of unknown origin that is characterized by noncaseating epithelioid cell granulomas. The diagnosis of sarcoidosis relies on a combination of compatible clinical findings, histological evidence of noncaseating epithelioid cell granulomas, and the exclusion of other diseases with similar histological or clinical features. Respiratory involvement is the most common manifestation, often affecting the alveolar region, peribronchial vessels, and hilar and mediastinal lymph nodes; biopsy of these areas is crucial for the diagnosis of sarcoidosis. Endobronchial biopsy (EBB) is a minimally invasive diagnostic technique—which has been reported by studies in Europe and the U.S. to be safe—that has few complications and enhances the diagnostic yield of fiberoptic bronchoscopy (1-4). In patients with sarcoidosis, the diagnostic yield of EBB alone ranged from 20% to 61% (5). Meanwhile, transbronchial needle aspiration (TBNA) is effective for sampling hilar and mediastinal lymph nodes, whereas transbronchial lung biopsy (TBLB) is useful for examining alveolar regions. A systematic review and meta-analysis showed excellent diagnostic performance of endobronchial ultrasound-guided TBNA, with a pooled diagnostic yield of 79% and sensitivity of 84%. The American Thoracic Society (ATS)/European Respiratory Society

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(ERS)/World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) statement on sarcoidosis recommends TBLB as the first choice for tissue sampling because of its high diagnostic rate (6). Herein, we aimed to evalutate the added diagnostic value of EBB in combination with TBNA or TBLB in the histological diagnosis of sarcoidosis. In addition, we investigated the factors affecting the diagnostic yield of EBB.

Materials and Methods

Study subjects

A total of 46 consecutive patients diagnosed with sarcoidosis between August 2016 and April 2023 at Shizuoka Saiseikai General Hospital, Japan, were reviewed. The diagnosis and assessment of organ involvement followed the ATS/ERS/WASOG consensus statement and the Diagnostic Standard and Guideline for Sarcoidosis of the Japan Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) (8). The study population was ethnically homogeneous, comprising only Japanese patients. All patients underwent standard evaluation, including medical history, physical examination, chest radiography, computed tomography, and laboratory tests. The serum studies included assessments of various inflammatory markers, such as angiotensin-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), and lysozyme levels. All bronchoscopy procedures were performed under local anesthesia with 2% lidocaine and mild sedation with intravenous midazolam. All patients underwent standard conventional fiberoptic bronchoscopy using several diagnostic modalities, including bronchoalveolar lavage (BAL), TBLB, TBNA, and EBB. The appearance of the airways was recorded as either normal or abnormal, which was defined as the presence of hypervascularity, submucosal nodules, or both; 2–3 specimens were taken from these abnormal areas. In patients with normal-appearing airways, 2–3 specimens were taken from the mucosa of the secondary or main carina.

Data collection

Clinical, radiological, and laboratory data, including BAL and pathological information, were retrospectively obtained from the electronic medical records. The number of organ involvement was recorded according to the definition provided in the Diagnostic Standard and Guideline by JSSOG (8). Hilar or mediastinal lymphadenopathy was excluded from the definition of lung involvement.

Diagnostic criteria

The diagnostic criteria were based on the aforementioned JSSOG guidelines in 2015 (8). In the histological diagnosis group, noncaseating epithelioid cell granulomas were detected on the biopsy specimens obtained from any organ of the body, and the granulomas of known origin and local sarcoid reactions were ruled out. In addition, the following characteristic laboratory findings and systemic involvement were thoroughly investigated: (1) bilateral hilar lymphadenopathy, (2) elevated ACE or lysozyme serum level, (3) elevated sIL-2R serum level, (4) markedly increased uptake on gallium-67 scintigraphy or ^{18}F-fluorodeoxyglucose positron emission tomography, and (5) elevated lymphocyte ratio and CD4/CD8 ratio of >3.5 in the BAL fluid. In the clinical diagnosis group, no noncaseating epithelioid cell granulomas were pathologically identified. However, there were highly suggestive clinical findings of sarcoidosis in more than one organ (e.g., respiratory, ocular, and cardiac) and the presence of more than one of the five enumerated items.

Statistical analysis

Continuous variables were expressed as median (range) unless otherwise stated and were compared using the Mann–Whitney U test. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, as appropriate. Statistical analyses were performed using the software EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.0.2) (9). More precisely, EZR is a modified version of R commander (version 2.0–3), designed to add statistical functions frequently used in biostatistics. A p value of <0.05 was considered statistically significant.

Results

Characteristics of patients with sarcoidosis

Of the 46 patients during the study period, 21 who did not undergo EBB were excluded. Those

in whom the histological diagnosis of sarcoidosis was made by EBB were defined as the EBB group (n = 6), whereas those diagnosed by other means were defined as the nonEBB group (n = 19). The clinical characteristics of the patients in each group are presented in Table 1. Compared with the nonEBB group, the EBB group tended to be younger (median age, 49.5 years vs. 65 years, p = 0.176) and comprise more women (5 of 6 [83.3%] vs. 9 of 19 [47.4%], p = 0.18) and had a higher proportion of patients with more than two organs involved or extrapulmonary involvement. There were no significant differences in chest radiography and laboratory findings between the two groups. Moreover, the bronchoscopy findings, including the BAL cell fraction and CD4/CD8 ratio and the presence of endobronchial hypervascularity or submucosal nodules, were similar between the two groups.

Table 1. Patients Characteristics

	All (n=25)	**EBB group (n=6)**	**Non-EBB group (n=19)**	***p*-value**
Age				
Median (range)	60 [24-83]	49.5 [24-83]	65 [29-81]	0.176
Sex, n (%)				
Male	14 (56.0)	1 (16.7)	10 (52.6)	0.18
Female	11 (44.0)	5 (83.3)	9 (47.4)	
Radiographic stage, n (%)				
I	7 (28.0)	2 (33.3)	5 (26.3)	0.139
II	15 (60.0)	2 (33.3)	13 (68.4)	
III	3 (12.0)	2 (33.3)	4 (21.1)	
Organ involvement, n (%)				
One organ	9 (36.0)	1 (16.7)	8 (42.1)	0.588
Two organs	10 (40.0)	3 (50)	7 (36.8)	
Three organs <	6 (24.0)	2 (33.3)	4 (21.1)	
ACE (U/L)				
Median [range]	19.1 [8.0-37.9]	22.5 [11.9-26.0]	17.6 [8.0-37.9]	0.4
Lysozyme (μg/mL)				
Median [range]	8.4 [3.9-17.6]	6.8 [6.4-7.1]	8.8 [3.9-17.6]	0.395
sIL-2R (U/mL)				
Median [range]	728 [286-2710]	703 [487-967]	703 [286-2710]	0.77
BAL, Median [range]				
TCC (×10^6/mL)	1.2 [0.4-3.4]	1.0 [0.5-3.0]	1.34 [0.4-3.4]	0.368
Lymphocyte (%)	25.7 [6.2-63.8]	30.1 [14.0-39.6]	24.7 [6.2-63.8]	0.581
Macrophage (%)	70.6 [36.2-86.8]	66.4 [59.2-85.4]	71.7 [36.2-86.8]	0.739
Neutrocyte (%)	0.8 [0-25.2]	1.6 [0-5.0]	0.6 [0-25.2]	0.199
Eosinophile (%)	0.2 [0-3.2]	0.2 [0-1.4]	0.2 [0-3.2]	0.727
BAL, Median[range]				
CD4/CD8 ratio	5.4 [1.7-15.4]	4.1 [2.7-9.7]	5.6 [1.7-15.4]	0.415
FOB, n (%)				
hypervascularity +/–	20 (80.0 / 5 (20.0)	6 (100) / 0 (0)	14 (73.7) / 5 (26.3)	0.289
nodule +/–	23 (92.0) / 2 (8.0)	6 (100) / 0 (0)	17 (89.5) / 2 (10.5)	>0.99

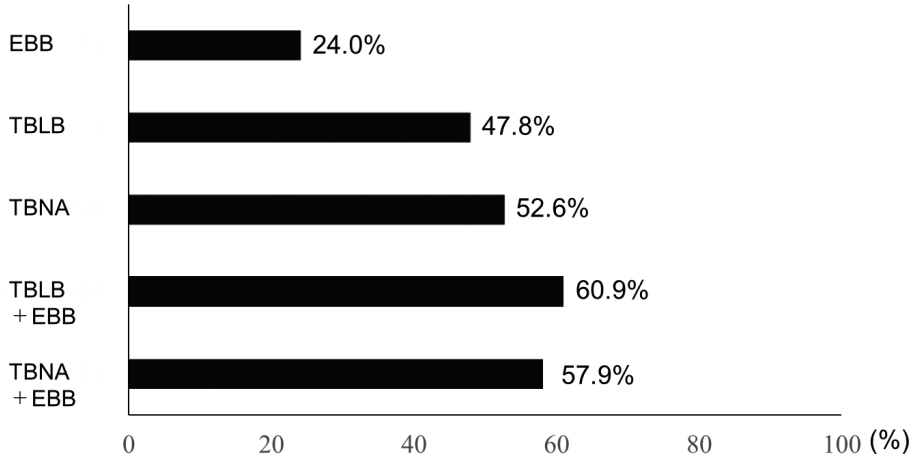

Figure 1. Utility of EBB combined with TBLB/TBNA

Table 2. Univariate analysis of factors associated with EBB diagnostic yield

	Odds ratio	95% CI	p-value
Age	0.963	0.911-1.02	0.179
Sex [Male]	0.18	0.0175-1.85	0.149
Organ involvements	2.13	0.691-6.560	0.188
ACE	1.02	0.899-1.16	0.749
sIL-2R	1	0.998-1.00	0.597
Lysozyme	0.773	0.436-1.37	0.379
BAL Lymphocyte	0.999	0.940-1.06	0.983
BAL CD4/8	0.886	0.674-1.17	0.387
Radiographic stage	0.714	0.0985-5.18	0.739

*CI: confidential interval

Diagnostic yield of EBB for sarcoidosis

The diagnostic yield of EBB alone was 24.0% (6 out of 25 patients), which was lower than those of TBLB (47.8%) and TBNA (52.6%). Notably, in three cases, the histological diagnosis of sarcoidosis was made by EBB alone and not by TBLB or TBNA. Moreover, when EBB was added, the diagnostic yield increased from 47.8% to 60.9% for TBLB (+13.1%) and from 52.6% to 57.9% for TBNA (+5.3%) (Figure 1). None of the patients suffered from a complication during any of the bronchoscopic procedures.

Factors associated with EBB diagnostic yield

The factors associated with the detection of granulomas using EBB were examined via logistic regression analysis. Age; sex; number of affected organs; serological markers, including ACE and sIL-2R; BAL findings; and chest radiograph findings, were not predictive of the diagnostic yield of EBB (Table 2).

Discussion

EBB is an established minimally invasive technique that enables sampling of the proximal airways under direct vision (10). The diagnostic yield of EBB for sarcoidosis ranges from 20% to 61% (5) and can increase in cases with macroscopic mucosal abnormalities. However, even in the absence of typical sarcoidosis characteristics, histological analysis may reveal granulomas in EBB samples. In sarcoidosis, submucosal lesions range from seemingly normal mucous membranes to those resulting in hypervascularity or submucosal nodules. In our study, hypervascularity was present in 80% of the patients, and submucosal nodules were identified in 92% of the patients. These findings did not correlate with the diagnostic yield of EBB, indicating that the presence of submucosal abnormalities did not contribute to the diagnostic yield of sarcoidosis. In this study, the diagnostic yield of EBB alone was comparable with that reported in previous studies. When EBB was added to TBLB and TBNA, the diagnostic yields increased by 13.1% and 5.3%, respectively. The wide variation in the reported diagnostic yield of EBB might be largely accounted for by the ethnic differences among the patients studied (11). In this study, we addressed this issue by analyzing an ethnically homogenous group.

Ishii et al. reported that EBB of normal-appearing airways, along with TBLB, did not improve the diagnostic yield of sarcoidosis in Japan (12). However, in their study, only 2 of 18 cases had completely normal endobronchial findings; this seemed to be similar to our cases; however, their diagnostic yield of EBB alone was only 6% (1 of 18). Therefore, even in Asian populations, EBB can be considered valuable in the diagnosis of sarcoidosis, especially when combined with TBLB or TBNA. The average age of sarcoidosis onset is 40–55 years, with a younger peak age at diagnosis in men (30–50 years) than in women (50–60 years). Our study showed that the diagnostic yield of EBB did not differ significantly according to age and sex. Moreover, although chest radiographic classification and the number of organs involved were reported to be important predictors of the progression of sarcoidosis(13,14), these factors were not found to affect the diagnostic yield of EBB significantly. There were several limitations in this study. First, Of the 46 cases diagnosed with sarcoidosis by bronchoscopy, the analysis was performed in 25 cases which endobronchial biopsy was performed, and EBB was not performed in all cases. The decision to perform EBB was left to the decision of the attending physician in each case, but unfortunately not in all cases. Patient characteristics were compared between biopsied and unbiopsied groups. No significant differences were found in airway abnormalities, cough, frequency of EBUS-TBNA due to adenopathy, or radiographic stage between the two groups. Additionally, our study did not include any extra-pulmonary sarcoidosis cases without pulmonary symptoms. Second, this was a single-institution, uncontrolled, retrospective study. Third, all patients included in this study were Japanese; our results may not be applicable to all because ethnic and genetic factors can influence the histological diagnostic yield of EBB. Forth, this study could not validate pulmonary function parameters, including forced vital capacity and forced expiratory volume in 1 second. In conclusion, the addition of EBB may increase the histological diagnostic yield of pulmonary sarcoidosis. Currently, there is no consensus on the use of EBB among patients suspected of having pulmonary sarcoidosis. Our results suggest that the addition of EBB may increase the histological diagnostic yield for pulmonary sarcoidosis. Further investigations with a larger sample size are needed.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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References

1. Armstrong JR, Rajke JR, Kvale PA, et al. Endoscopic findings in sarcoidosis: characteristics and correlations with radiographic staging and bronchial mucosa yield. Ann Otol Rhinol Laryngol. 1981;90:339-43. doi: 10.1177/000348948109000410.
2. Bjemer L, Thunell M, Rosenhall L, et al. Endobronchial biopsy positive sarcoidosis: relation to bronchoalveolar lavage and course of disease. Respir Med. 1991;85:229-34. doi: 10.1016/s0954-6111(06)80085-5.
3. Bilaceroglu S, Perim K, Gunel O, et al. Combining transbronchial aspiration with endobronchial and transbronchial biopsy in sarcoidosis. Monaldi Arch Chest Dis. 1999;54:217-23. PMID: 10441973.
4. Shorr AF, Torrington KG, Hnatiuk OW, et al. Endobronchial biopsy for sarcoidosis: a prospective study. Chest. 2001;120:109-14. doi: 10.1378/chest.120.1.109.
5. Benzaquen S, Aragaki-Nakahodo AA. Bronchoscopic modalities to diagnose sarcoidosis. Curr Opin Pulm Med. 2017;23:433-8. doi: 10.1097/MCP.0000000000000398.
6. Trisolini R, Lazzari Agli L, Tinelli C, De Silvestri A, Scotti V, Patelli M. Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosis of sarcoidosis in clinically unselected study populations. Respirology. 2015;20:226-34. doi: 10.1111/resp.12449.
7. American Thoracic Society, European Respiratory Society, World Association of Sarcoidosis and Other Granulomatous Disorders. Statement on sarcoidosis. Am J Respir Crit Care Med. 1999;160:736-55. doi: 10.1164/ajrccm.160.2.ats4-99.
8. The Japanese Society of Sarcoidosis and Other Granulomatous Disorders. Diagnostic standard and guideline for sarcoidosis-2006. Jpn J Sarcoidosis Granulomatous Disord. 2007;27:89-102.
9. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-8. doi: 10.1038/bmt.2012.244.
10. Dziedzic DA, Peryt A, Orlowski T. The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis. Clin Respir J. 2017;11:58-63. doi: 10.1111/crj.12304.
11. Torrington KG, Shorr AF, Parker JW. Endobronchial disease and racial differences in pulmonary sarcoidosis. Chest. 1997;111:619-22. doi: 10.1378/chest.111.3.619.
12. Ishii H, Otani S, Iwata A, et al. Limited role of auxiliary endobronchial biopsy in the diagnosis of Japanese patients with sarcoidosis. Tohoku J Exp Med. 2011;223:119-23. doi: 10.1620/tjem.223.119.
13. Scadding JG, Mitchell DN. Sarcoidosis. London: Chapman and Hall; 1985.
14. Inoue Y, Inui N, Suda T, et al. Cumulative incidence and predictors of progression in corticosteroid-naïve patients with sarcoidosis. PLoS One. 2015;10(11):e0143371. doi: 10.1371/journal.pone.0143371.