J Chin Med Assoc

ORIGINAL ARTICLE

Endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of pulmonary sarcoidosis: A 9-year experience at a single center

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Abstract

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is valuable for diagnosing pulmonary sarcoidosis. We aimed to evaluate the diagnostic yield of EBUS-TBNA and cytology in sarcoidosis during the first 9 years at our institution.

Methods: Patients who underwent EBUS-TBNA for suspected sarcoidosis between January 2011 and November 2019 were identified retrospectively. EBUS-TBNA was performed with rapid on-site cytological evaluation of the samples. The final diagnosis was based on the pathology and/or cytology results, radiologic features, and clinical follow-up findings. The yield rate was analyzed annually.

Results: Eighty patients underwent 83 EBUS-TBNA procedures for suspected sarcoidosis. In total, 136 lymph nodes were sampled. The mean number of lymph node stations sampled was 2.0 ± 0.6; the mean number of needle passes per lymph node was 3.5 ± 0.8. Sixty-five patients were diagnosed with sarcoidosis, with a total of 68 procedures. Nonnecrotizing granulomatous inflammation was detected in the EBUS-TBNA samples from 49/68 procedures (yield rate: 72.1%). Of 19 patients with sarcoidosis who did not obtain a pathological diagnosis with EBUS-TBNA, epithelioid cells and/or multinuclear giant cells suggestive of granulomatous inflammation were detected in five. The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) for pathological diagnosis of sarcoidosis using EBUS-TBNA were 72.1%, 100%, 100%, and 24.0%, respectively. On using cytology, the sensitivity and NPV increased to 79.4% and 26.3%, respectively. The yield rate did not increase until 2016.

Conclusion: EBUS-TBNA is useful for diagnosing sarcoidosis. Cytology resulted in an additional yield rate of 7.3%, which improved as the number of cases increased.

Keywords: Cytology; Endobronchial ultrasound-guided transbronchial needle aspiration; Epithelioid cell; Learning curve; Sarcoidosis

1. INTRODUCTION

Sarcoidosis, which is a benign, multisystem, inflammatory disorder, remains a challenge for clinicians because of its unknown cause and heterogeneous clinical presentation.[1] Although the frequency of sarcoidosis varies according to race, sex, and age, thoracic involvement occurs in 90% patients, and bilateral hilar lymphadenopathy is the most common thoracic manifestation.[1–3] The diagnosis of sarcoidosis is not standardized and not completely accurate.[1,4] In general, the diagnosis of sarcoidosis is based on compatible clinical and radiographic images, the demonstration of nonnecrotizing granulomatous inflammation by tissue biopsy, and the exclusion of known causes that may incite granulomatous reactions.[1,4] Recently, the guidelines published by the American Thoracic Society suggested that lymph node biopsy is not necessary for patients who present with classic symptoms highly specific for sarcoidosis.[4] The recommendations for lymph node biopsy for patients with asymptomatic bilateral hilar lymphadenopathies are not available because the key determinants of the probability of sarcoidosis are still uncertain.[4] However, the regional prevalence of alternative infectious causes should be a

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 191-196.

Received April 11, 2022; accepted November 4, 2022.

doi: 10.1097/JCMA.0000000000000866.

major consideration when determining whether a biopsy should be performed. In Taiwan, histopathological proof is essential for establishing a diagnosis of sarcoidosis because of the high prevalence of tuberculosis.[5] Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), which is a minimally invasive technique that can be used to approach mediastinal and hilar lymphadenopathy or mass lesions, is valuable to the diagnosis and staging of lung cancer.[6,7] EBUS-TBNA has a lower diagnostic yield than surgical biopsy (mediastinoscopy or video-assisted thoracoscopic surgery) for sarcoidosis.[4,8] However, EBUS-TBNA remains the recommended technique for the histopathological confirmation of sarcoidosis because it is associated with better tolerance, fewer complications, and lower costs than surgical biopsy.[2,4,9] The diagnostic yield of EBUS-TBNA for sarcoidosis reported by the American Thoracic Society guideline is 87%.[4] EBUS-TBNA is an operator-dependent technique, and its diagnostic yield varies in the literature (range, 54%–93%).[8] The learning curve for this procedure is considerable; at least 40 EBUS-TBNAs should be performed to gain proficiency.[10] Rapid on-site evaluation (ROSE) can provide instant feedback regarding the adequacy of specimens, thus avoiding additional needle passes and reducing the number of complications associated with EBUS-TBNA. However, the ability of ROSE to improve the diagnostic yield is unclear.[11–13]

Cytological examination has a role in the diagnosis of sarcoidosis. Recent studies have suggested that the addition of cell block cytology (CBC) and/or liquid-based cytology (LBC) can improve the diagnostic sensitivity of EBUS-TBNA.[14–16] Nevertheless, preparations for CBC increase the workload of the laboratory staff.[17] Regarding LBC, investigations have not consistently indicated its superiority over conventional smear cytology in terms of the diagnostic yield.[18,19] Additionally, LBC is not quick enough to meet the demands of ROSE, despite its simplicity.[18] Moreover, the diagnostic yield of EBUS-TBNA could be increased with conventional smears if reviewed by a cytopathologist with expertise in pulmonary diseases.[20] This study presents 9 years of experience with the diagnosis of sarcoidosis at our institution and identifies factors that may influence the diagnostic yield.

2. METHODS

2.1. Ethics statement

This study was approved by the local institutional review board (TVGH IRB No.: 2019-11-008BC). The need for informed consent was waived.

2.2. Study design and population

This was a single-center, retrospective study. We reviewed patients who underwent EBUS-TBNA for mediastinal and/or hilar lymphadenopathy at our institution between January 2011 and November 2019. Patients were referred for EBUS-TBNA if the mediastinal and/or hilar lymph node short axis was larger than 10 mm according to computed tomography (CT) results, if there was increasing fluorine-18 fluorodeoxyglucose uptake according to positron emission tomography-CT, or if the patient had lymphadenopathy of unknown cause. Patients with radiologically suspected sarcoidosis were enrolled in this study. Those who were referred for lung cancer staging or mediastinal mass and/or hilar lymphadenopathy favoring malignancy and those who were lost to follow up were excluded.

2.3. Endobronchial ultrasound-guided transbronchial needle aspiration

Real-time EBUS-TBNA was performed using a convex probe EBUS bronchoscope (BF-UC260FW; Olympus Ltd., Tokyo, Japan). Procedures were performed by interventional pulmonologists or senior trainees supervised by an experienced interventional pulmonologist. Nebulized 2% lidocaine (5 mL) followed by two puffs of 10% lidocaine spray were administered to the patients as topical anesthesia. A 1-mL aliquot of 2% lidocaine was instilled over the airways using the spray-as-you-go method. Patients who preferred to be sedated for the procedure received intravenous propofol and fentanyl, which were administered by an anesthesiologist.

The target lymph nodes were punctured with a dedicated 22-gauge TBNA needle (NA-201SX; Olympus Ltd.). The number of lymph node stations sampled and the number of aspirates per node were at the discretion of the operators. The aspirated material was expelled on glass slides and examined for the presence of "worm-like" core tissue. The core tissue was separated and transferred to a container with formalin for histopathological evaluation. The remaining lymph node aspirate material was smeared onto two slides. One slide was fixed with 95% ethanol for Papanicolaou staining, and the other was air-dried for ROSE. Cytological smears were stained using the Liu stain and interpreted by two experienced cytotechnologists certified by the Taiwan Society of Clinical Cytology. The adequacy of the sample was evaluated based on the presence of lymphocytes or lymphoid tissue, or when a specific diagnosis could be established. Granulomatous inflammation was diagnosed by cytology when the following criteria were fulfilled: clear background without necrosis; the presence of mature lymphocytes; and the presence of a tight aggregate of epithelioid histiocytes with or without multinuclear giant cells.[21,22] Small groups of epithelioid cells or scattered epithelioid cells with lymphocytes without multinucleated giant cells or necrosis were considered cytological findings consistent with sarcoidosis.[22] When no specific diagnosis was determined based on the ROSE findings, at least three punctures per lymph node were performed. The slides with positive cytological results were evaluated by experienced cytotechnologists to confirm the tight aggregate of epithelioid histiocytes as an element of granuloma during this study.

2.4. Data collection

Patient details, such as age, sex, chest radiography findings, chest CT findings, the greatest length of the sampled lymph node, and examination results, relevant to the diagnosis were recorded. The following characteristics of EBUS-TBNA were recorded: the number of lymph node stations sampled; the number of needle passes performed; anatomic location of the lymph node stations sampled; and major complications (defined as unplanned hospitalization, prolonged hospitalization, or death).[23] The final diagnosis of sarcoidosis was based on compatible cytological and/or pathological findings and negative microbiological results. For nondiagnostic cases, the final diagnosis was established through additional examinations, including CT-guided biopsy, transbronchial lung biopsy, mediastinoscopy, video-assisted thoracoscopic surgery lung biopsy, and/or clinical and radiographic follow-up for at least 1 year.

2.5. Statistical analysis

Categorical variables are presented as the proportion, and continuous variables are expressed as the mean ± standard deviation. The diagnostic yield was defined as the sensitivity for sarcoidosis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of EBUS-TBNA for diagnosing sarcoidosis were calculated according to standard definitions. The overall and annual diagnostic yields were calculated separately. A univariate logistic regression analysis was performed to assess the factors associated with the positive diagnostic yield of EBUS-TBNA. The statistical analysis was performed using SPSS

software version 24 (IBM SPSS Inc., Armonk, NY), and $p < 0.05$ was considered statistically significant.

3. RESULTS

From January 2011 to November 2019, 83 EBUS-TBNA procedures were performed for 80 patients with radiologically suspected sarcoidosis. Two of the 80 patients underwent more than one EBUS-TBNA procedure because the diagnosis of sarcoidosis could not be confirmed without a second EBUS-TBNA procedure. One of those patients underwent a third EBUS-TBNA procedure 2 years later because there was no significant regression of mediastinal and hilar lymphadenopathy. Three patients were finally diagnosed with tuberculous adenitis, three patients were diagnosed with reactive lymphadenopathy, and nine patients were lost to follow up. Sixty-five patients were eventually diagnosed with sarcoidosis (Fig. 1).

The characteristics of the patients and procedures are detailed in Table 1. The mean age of the patients was 55 years (range, 26–80 years), and 42 (65%) were female. Based on radiological findings, 37 (57%) patients were considered to have stage I sarcoidosis, and 28 (43%) patients were considered to have stage II sarcoidosis. During 68 procedures, 136 lymph nodes were sampled. An average of 2.0 lymph node stations (standard deviation, 0.6) were sampled by performing a mean of 3.5 needle passes (standard deviation, 0.8) per lymph node. Most punctures were performed at stations 7 and 4R. Nonnecrotizing granulomatous inflammation was found in 49 pathological samples obtained during 68 EBUS-TBNA procedures (yield: 49/68; 72.1%). Epithelioid cells and/or multinuclear giant cells were detected in 24 cytological samples obtained during 68 procedures (yield: 24/68; 35.3%). We reviewed the 24 slides with positive cytological results during this study. Five were unavailable because of the absence of slides. Of the remaining 19 slides with positive cytological results, 12 exhibited a tight aggregate of epithelioid histiocytes and variable numbers of lymphocytes with or without multinuclear giant cells without necrosis (yield: 12/19; 63.2%), resulting in a diagnosis of granulomatous inflammation. Additionally, seven cases involved scattered or a small group of epithelioid cells, multinucleated giant cells, and variable numbers of lymphocytes without necrosis; these findings were considered consistent with sarcoidosis (yield: 7/19; 36.8%). Of 24 cases with positive cytological results, nonnecrotizing granulomatous inflammation was observed in the matched pathological samples of 19; the remaining five cases had nondiagnostic findings (eg, blood clots, lymphoid tissue, bronchial epithelium, etc.). Of 14 patients who had negative pathological and cytological results, sarcoidosis was confirmed using video-assisted thoracoscopic surgery for two, mediastinoscopy for two, CT-guided biopsy for one, and transbronchial lung biopsy for one. The remaining eight patients with nondiagnostic cytological and pathological findings refused further EBUS-TNBA procedures and surgical intervention. Sarcoidosis was diagnosed after at least 1 year of follow-up; it was evidenced by the typical radiographic findings of sarcoidosis, no obvious change in the mediastinal lymph node or lung parenchyma, or newly developed clinical or radiographic manifestations suggesting an alternative diagnosis.[4,24,25]

The sensitivity, specificity, PPV, and NPV of EBUS-TBNA for diagnosing sarcoidosis are provided in Table 2. The sensitivity, specificity, PPV, and NPV of EBUS-TBNA for the pathological diagnosis of sarcoidosis were 72.1%, 100%, 100%, and 24.0%, respectively. With the addition of cytology, the sensitivity and NPV of EBUS-TBNA increased to 79.4% and 26.3%, respectively. EBUS-TBNA alone was unsatisfactory for the cytological diagnosis of sarcoidosis, with sensitivity, specificity, PPV, and NPV of 35.3%, 83.3%, 96.0%, and 10.2%, respectively.

From 2011 to 2019, the diagnostic performances of pathology and cytology, individually and in combination, were evaluated annually. However, the cases from 2011 to 2015 were pooled because the average number of cases per year was fewer than five during that period. In 2016, the increase in diagnostic yield became remarkable with the increase in the number of cases (Fig. 2).

Sex, age, number of punctured lymph nodes per procedure, radiological stage, number of needle passes per node, length of the sampled lymph node, and volume (ie, product of the width multiplied by height and depth) of the sampled lymph node were examined using a univariate logistic regression analysis; however, none of these factors showed a significant association with a positive diagnostic yield.

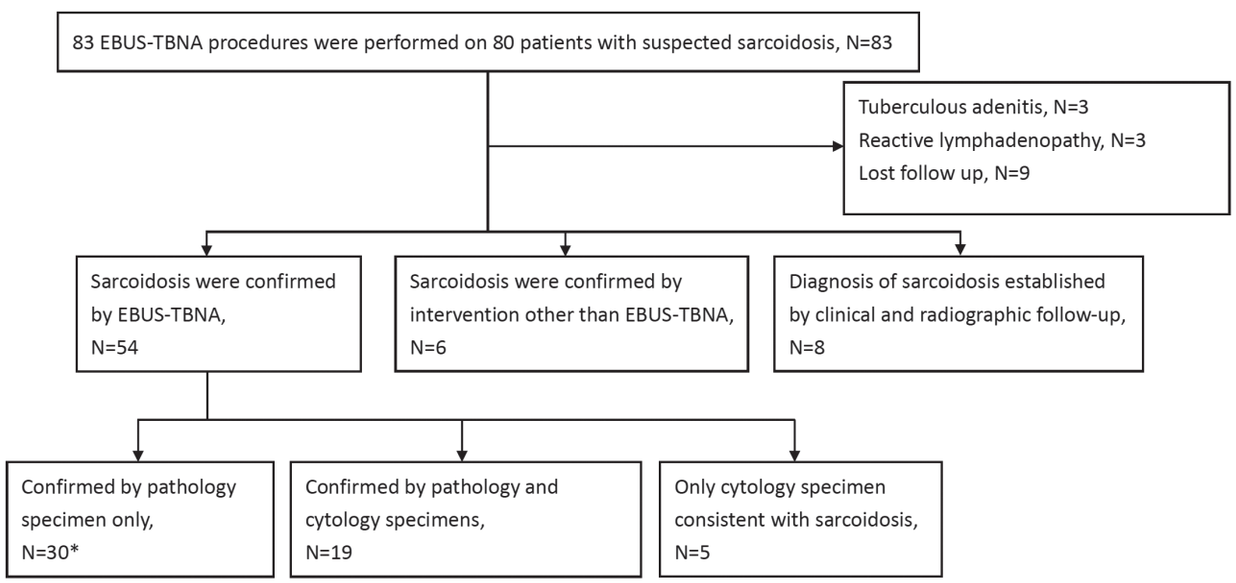

Fig. 1 Patients with mediastinal and/or hilar lymphadenopathy and suspected sarcoidosis undergoing EBUS-TBNA. *Two patients received more than one EBUS-TBNA procedure for confirming a diagnosis. Details available in the text. EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration.

Table 1

Baseline characteristics

Patient characteristics (N = 65)	
Mean age, y	54.5 (14.4)
Male/female sex (N)	23/42
Radiological stage	
I	37 [56.9]
II	28 [43.1]
III	0
IV	0
Mean number of LN stations sampled (N = 68)[a]	2.0 (0.6)
Mean number of needle passes per LN (N = 136)[b]	3.5 (0.8)
Location of lymph node stations sampled (N = 136)[b]	
Station 7	63 [46.3]
Station 4R	43 [31.6]
Station 11R	10 [7.4]
Station 10R	9 [6.6]
Station 4L	7 [5.2]
Station 11L	3 [2.2]
Station 2R	1 [0.7]
Complications (N)	
Lymph node abscess	1

Data were present as number(standard deviation) or number [%].

[a]Two patients received more than one EBUS-TBNA procedure for confirming a diagnosis. Details available in the text.

[b]Number of lymph node were sampled.

EBUS-TBNA= endobronchial ultrasound-guided transbronchial needle aspiration; LN=lymph node.

4. DISCUSSION

The pathological demonstration of noncaseating granuloma is crucial to establishing the diagnosis of sarcoidosis for patients with mediastinal and/or hilar lymphadenopathy observed using imaging.[4] Granuloma can also be detected in cytological specimens as well-defined, tiny nodules consisting of a tight aggregate of histiocytes with a round or elliptical shape and regular contour. With an adequate specimen, whole morphological granulomas can be identified, even at low power.[21] However, the identification of elements of granuloma, such as epithelioid cells, small lymphocytes, multinucleated giant cells, and the absence of a necrotic background, can be considered consistent with sarcoidosis when typical granulomas are not identified microscopically.[21,22] Although cytological findings of granulomatous inflammation are not specific to sarcoidosis, compatible radiological features and the exclusion of alternative diseases can be used to make a diagnosis.[1,26] During the present study, the sensitivity, specificity, PPV, and NPV of EBUS-TBNA alone for the pathological diagnosis of sarcoidosis were 72.1%, 100%, 100%, and 24.0%, respectively. With the aid of cytology, the sensitivity and NPV increased to 79.4% and 26.3%, respectively. However, the specificity and PPV decreased slightly to 83.3% and 98.2%, respectively. Of 19 patients with sarcoidosis who did not receive a pathological diagnosis based on EBUS-TBNA results, typical cytological findings suggestive of sarcoidosis were observed in five patients, resulting in an additional diagnostic yield of 7.3%. EBUS-TBNA cytology alone was not satisfactory for diagnosing sarcoidosis; however, the sensitivity of the cytological diagnosis increased as the number of cases increased beginning in 2016 (Fig. 2). Our data indicate the relevance of the increasing number of cases to the diagnostic yield of sarcoidosis and the usefulness of cytology for helping to determine the diagnosis.

EBUS-TBNA has been recommended as the method of choice for pathologically confirming clinically suspected sarcoidosis.[4] Recently, the guidelines published by American Thoracic Society in 2020 were used to review several studies, and it was concluded that the diagnostic yield of EBUS-TBNA for sarcoidosis was approximately 87%.[4] A systemic review and meta-analysis reported a pooled diagnostic accuracy rate of 79%.[27] During our study, the overall yield of EBUS-TBNA alone for the pathological diagnosis from 2011 to 2019 was 72.1%, which is obviously lower than the yield reported by many studies.[4,8,27] After the first 21 procedures performed from 2011 to 2015, which resulted in an average diagnostic yield of only 52.4%, a stepwise increase in the diagnostic yield occurred, reaching 92.8% in 2018. The improvement in the diagnostic yield may have occurred because, over time, the interventional pulmonologists became more proficient, staff members in the bronchoscopy room became more familiar with the collection and processing of specimens, and cytotechnologists and pathologists accumulated more experience with the samples obtained by EBUS-TBNA. Furthermore, EBUS-TBNA has been included as a benefit offered by Taiwan's National Health Insurance since late 2015; therefore, more patients have been willing to undergo EBUS-TBNA as the front-line diagnostic procedure since 2016. The existence of the learning curve for EBUS-TBNA is well-established. Learning is heterogeneous and individualized; therefore, the exact length of the learning curve remains ambiguous, and the recommended minimum number of EBUS-TBNA procedures varies.[28–30] It has been proposed that the minimum number of procedures required to gain proficiency and achieve an accuracy rate of 90% ranges from 50 to 80.[31] However, the previous investigations of the learning curve of EBUS-TBNA were largely based on the results of patients with lung cancer. To the best of our knowledge, studies of the learning curve involving patients with suspected sarcoidosis are limited. Kubicki et al suggested that a well-trained student can achieve comparable levels of effectiveness when diagnosing sarcoidosis after independently performing 90 procedures.[32] During our study, only 65 patients were diagnosed with sarcoidosis during 9 years using fewer procedures than that suggested by Kubicki et al. However, we were able to achieve a compatible diagnostic yield. In 2019, only two cases of sarcoidosis with false-negative EBUS-TBNA results were observed in our department, thus leading to a decrease in pathological sensitivity from 92.9% in 2018 to 70% in 2019. The sensitivity of the pathological diagnosis of sarcoidosis in 2018 was competitive at 92.9% if the sensitivity in 2019, which was influenced by only two cases with false-negative results, was

Table 2

Diagnostic performances of EBUS-TBNA in the detection of sarcoidosis

	Sensitivity	Specificity	PPV	NPV
Per procedure (N = 74)[a]				
Pathology	49/68 (72.1)	6/6 (100)	49/49 (100)	6/25 (24.0)
Cytology	24/68 (35.3)	5/6 (83.3)	24/25 (96.0)	5/49 (10.2)
Combined Pathology and Cytology	54/68 (79.4)	5/6 (83.3)	54/55 (98.2)	5/19 (26.3)

Data were present as proportion (%).

[a]Patients received EBUS-TBNA except those who were lost to follow up.

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; NPV = negative predictive value; PPV = positive predictive value.

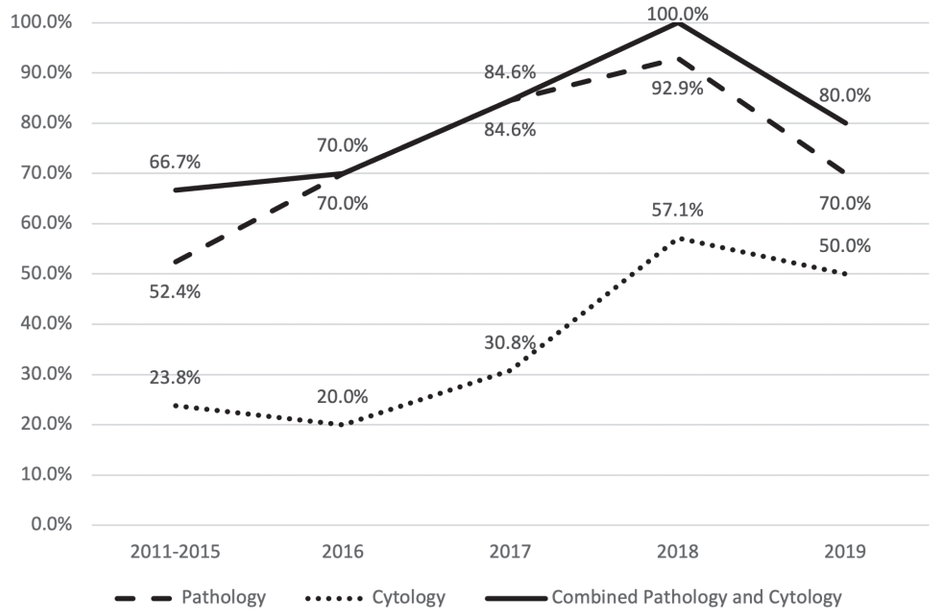

Fig. 2 Diagnostic yield of EBUS-TBNA revealed increasing annually. EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration.

neglected. In our department, the interventional pulmonologists performed EBUS-TBNA not only for patients with sarcoidosis but also for patients with lung cancer or other malignancies. From 2011 to 2019, more than 800 patients underwent EBUS-TBNA in our department. This number was sufficiently large and allowed interventional pulmonologists to achieve satisfactory performance.

The sensitivity (93.69%) of EBUS-TBNA for diagnosing sarcoidosis reported by Sun et al. was higher than that reported by many studies; this is partially attributable to the addition of cytology to pathology for the diagnosis and the participation of an experienced cytologist.[33] It has been proposed that the diagnostic yield of EBUS-TBNA can be further increased when the results are reviewed by a cytopathologist who specializes in lung diseases.[20] The diagnosis of benign lung diseases may be more dependent on the experience of cytopathologists.[34] Cytology alone is not sensitive enough to diagnose sarcoidosis, with a sensitivity of 22% reported for one cohort.[26] The addition of LBC can increase the diagnostic yield of EBUS-TBNA for cases of suspected sarcoidosis.[26] Comparable with the diagnostic yield reported by Chee et al, the present study showed that the cytological sensitivity for sarcoidosis was 23.8% during 2011 to 2015. The yield of EBUS-TBNA alone for the cytological diagnosis of sarcoidosis increased to more than 50% beginning in 2018, because the number of cases gradually increased. However, this study showed that the addition of LBC to determine the cytological diagnosis did not result in any benefits (data not shown). LBC samples are mostly stained with Papanicolaou stain, which is not designed to identify epithelioid cells or giant cells. Our data suggested that the increase in the number of cases improved the experience of the cytotechnologists; therefore, they became more proficient at recognizing granulomatous inflammation, even in conventional smears.

The benefits of ROSE for EBUS-TBNA remain debatable. A meta-analysis indicated that the use of ROSE failed to improve the diagnostic yield or reduce the procedure time of EBUS-TBNA, but that it could lead to fewer needle passes during EBUS-TBNA and fewer additional bronchoscopic procedures to make a final diagnosis.[13] To achieve a higher diagnostic yield with EBUS-TBNA for pulmonary sarcoidosis without ROSE, many investigations have recommended more passes for each patient.[33,35] Sun et al reported higher sensitivity than many other investigations, with an average number of passes per patient of 7.17.[33] It can be expected that more passes lead to more time and probably more complications during EBUS-TBNA. At our institution, ROSE has been used since the introduction of EBUS-TBNA. Although no definite benefit for the diagnostic yield of ROSE for sarcoidosis was observed, ROSE did provide the adequacy of specimens in time, thereby avoiding additional needle passes and reducing the time spent performing EBUS-TBNA. Furthermore, EBUS-TBNA cytology specimens may serve as a feasible source of material for non-small cell lung cancer genotyping because of its promising reliability, which can benefit patients without a viable biopsy sample.[36] ROSE is beneficial for interventional pulmonologists and pathologists because it can ensure that adequate cells are obtained for molecular testing.

The present study had certain limitations. First, this was a retrospective study conducted at a single center. The number of patients was limited, and the diagnostic yield was based on a small sample size. Second, pathology slides were not reviewed by pathologists who specialized in lung diseases, especially benign lung diseases, which could have lowered the diagnostic yield. Third, cytopathologists who specialized in lung diseases were not immediately available during EBUS-TBNA procedures; however, ROSE and cytological examinations were performed by experienced cytotechnologists during this study. Fourth, the rate of finding a whole morphological granuloma using cytology was lower than that reported by previous studies.[22] Possible reasons why a whole morphological granuloma was rarely found during the present study include the relatively small needle size (22-gauge instead of 19-gauge),[27,37,38] lack of core tissue for cytology smears, limited number of cases of sarcoidosis, and limited experience of the cytotechnologists. As they gain experience, our cytotechnologists may feel increasingly confident recognizing elements of granuloma, and even a whole morphological granuloma.

In conclusion, EBUS-TBNA is a valuable technique for diagnosing sarcoidosis. We found that interventional pulmonologists at our center have to overcome a steep learning curve to achieve a satisfactory diagnostic yield when the number of patients is

limited. Cytology for conventional smears is helpful for diagnosing sarcoidosis, resulting in an additional diagnostic yield of 7.3% during this study. An increase in the number of cases can help cytotechnologists recognize granulomatous inflammation. The diagnostic yield may further increase when both interventional pulmonologists and pathologists become more familiar with EBUS-TBNA and the specimens indicating sarcoidosis.

ACKNOWLEDGMENTS

This article received partial financial support by the R2100200 Taipei Veterans General Hospital industry-academia cooperation project.

REFERENCES

1. Statement on Sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS board of directors and by the ERS executive committee, February 1999. *Am J Respir Crit Care Med* 1999;**160**:736–55.
2. Navasakulpong A, Auger M, Gonzalez AV. Yield of EBUS-TBNA for the diagnosis of sarcoidosis: impact of operator and cytopathologist experience. *BMJ Open Respir Res* 2016;**3**:e000144.
3. Polverino F, Balestro E, Spagnolo P. Clinical presentations, pathogenesis, and therapy of sarcoidosis: state of the art. *J Clin Med* 2020;**9**:2363.
4. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;**201**:e26–51.
5. Lu CW, Lee YH, Pan YH, Chang HH, Wu YC, Sheng WH, et al. Tuberculosis among migrant workers in Taiwan. *Global Health* 2019;**15**:18.
6. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;**143**:e211S–50S.
7. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax* 2009;**64**:757–62.
8. Agrawal A, Ghori U, Chaddha U, Murgu S. Combined EBUS-IFB and EBUS-TBNA vs EBUS-TBNA alone for intrathoracic adenopathy: a meta-analysis. *Ann Thorac Surg* 2022;**114**:340–8.
9. Trisolini R, Verhoeven RLJ, Cancellieri A, De Silvestri A, Natali F, Van der Heijden EHFM. Role of endobronchial ultrasound strain elastography in the identification of fibrotic lymph nodes in sarcoidosis: a pilot study. *Respirology* 2020;**25**:1203–6.
10. Bolliger CT, Mathur PN, Beamis JF, Becker HD, Cavaliere S, Colt H, et al; European Respiratory Society/American Thoracic Society. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. *Eur Respir J* 2002;**19**:356–73.
11. Trisolini R, Baughman RP, Spagnolo P, Culver DA. Endobronchial ultrasound-guided transbronchial needle aspiration in sarcoidosis: beyond the diagnostic yield. *Respirology* 2019;**24**:531–42.
12. Muthu V, Sehgal IS, Dhooria S, Prasad KT, Gupta N, Aggarwal AN, et al. Endobronchial ultrasound-guided transbronchial needle aspiration: techniques and challenges. *J Cytol* 2019;**36**:65–70.
13. Sehgal IS, Dhooria S, Aggarwal AN, Agarwal R. Impact of rapid on-site cytological evaluation (rose) on the diagnostic yield of transbronchial needle aspiration during mediastinal lymph node sampling: systematic review and meta-analysis. *Chest* 2018;**153**:929–38.
14. Qiu T, Zhu H, Cai M, Han Q, Shi J, Wang K. Liquid-based cytology preparation can improve cytological assessment of endobronchial ultrasound-guided transbronchial needle aspiration. *Acta Cytol* 2015;**59**:139–43.
15. Iwashita T, Yasuda I, Doi S, Kato T, Sano K, Yasuda S, et al. The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis. *Endoscopy* 2008;**40**:400–5.
16. 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.
17. Sadullahoğlu C, Yaman B, Veral A, Nart D. The diagnostic value of cell blocks in Liquid-Based Cytology of bronchial aspiration and bronchial brushing materials. *Cytopathology* 2018;**29**:156–62.
18. Hou G, Yin Y, Wang W, Wang QY, Hu XJ, Kang J, et al. Clinical impact of liquid-based cytology test on diagnostic yields from transbronchial needle aspiration. *Respirology* 2012;**17**:1225–8.
19. Nalwa A, Walia R, Singh V, Madan K, Mathur S, Iyer V, et al. Comparison of conventional smear and liquid-based cytology preparation in diagnosis of lung cancer by bronchial wash and transbronchial needle aspiration. *J Cytol* 2018;**35**:94–8.
20. Tremblay A, Stather DR, MacEachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest* 2009;**136**:340–6.
21. Cancellieri A, Leslie KO, Tinelli C, Patelli M, Trisolini R. Sarcoidal granulomas in cytological specimens from intrathoracic adenopathy: morphologic characteristics and radiographic correlations. *Respiration* 2013;**85**:244–51.
22. Smojver-Jezek S, Peros-Golubicić T, Tekavec-Trkanjec J, Mazuranić I, Alilović M. Transbronchial fine needle aspiration cytology in the diagnosis of mediastinal/hilar sarcoidosis. *Cytopathology* 2007;**18**:3–7.
23. Žemaitis M, Musteikienė G, Miliauskas S, Pranys D, Sakalauskas R. Diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration cytological smears and cell blocks: a single-institution experience. *Medicina (Kaunas)* 2018;**54**:19.
24. Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J* 2021;**58**:2004079.
25. Sève P, Pacheco Y, Durupt F, Jamilloux Y, Gerfaud-Valentin M, Isaac S, et al. Sarcoidosis: a clinical overview from symptoms to diagnosis. *Cells* 2021;**10**:766.
26. Chee A, Khalil M, Stather DR, MacEachern P, Field SK, Tremblay A. Cytologic assessment of endobronchial ultrasound-guided transbronchial needle aspirates in sarcoidosis. *J Bronchology Interv Pulmonol* 2012;**19**:24–8.
27. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. *Respir Med* 2012;**106**:883–92.
28. Medford ARL. Learning curve for endobronchial ultrasound-guided transbronchial needle aspiration. *Chest* 2012;**141**:1643.
29. Stather DR, Chee A, MacEachern P, Dumoulin E, Hergott CA, Gelberg J, et al. Endobronchial ultrasound learning curve in interventional pulmonary fellows. *Respirology* 2015;**20**:333–9.
30. Folch E, Majid A. Point: are >50 supervised procedures required to develop competency in performing endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal staging? Yes. *Chest* 2013;**143**:888–91.
31. Medford AR. Learning curve for EBUS-TBNA: longer than we may think. *Respiration* 2015;**90**:173.
32. Kubicki P, Szlubowski A, Jastrzębski D, Czyżewski D, Ziora D. Comparison of the diagnostic effectiveness between an expert and a student in the diagnosis of sarcoidosis by transbronchial biopsy of mediastinal lymph nodes under the control of endosonography. *Adv Respir Med* 2021;**89**:241–6.
33. Sun J, Yang H, Teng J, Zhang J, Zhao H, Garfield DH, et al. Determining factors in diagnosing pulmonary sarcoidosis by endobronchial ultrasound-guided transbronchial needle aspiration. *Ann Thorac Surg* 2015;**99**:441–5.
34. Medford ARL, Bennett JA, Free CM, Agrawal S. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): applications in chest disease. *Respirology* 2010;**15**:71–9.
35. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest* 2007;**132**:1298–304.
36. Martin-Deleon R, Teixido C, Lucena CM, Martinez D, Fontana A, Reyes R, et al. EBUS-TBNA Cytological samples for comprehensive molecular testing in non-small cell lung cancer. *Cancers (Basel)* 2021;**13**:2084.
37. Jones RC, Bhatt N, Medford ARL. The effect of 19-gauge endobronchial ultrasound-guided transbronchial needle aspiration biopsies on characterisation of malignant and benign disease. The Bristol experience. *Monaldi Arch Chest Dis* 2018;**88**:915.
38. Kanth S, Pickering EM, Sachdeva A, Holden VK. Endobronchial ultrasound needles: does size matter? *Shanghai Chest* 2020;**4**:24.