



Transesophageal endosonography in the diagnosis of sarcoidosis: a narrative review

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Background and Objective: Transesophageal endosonography, including endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA), has been applied to the diagnosis of benign as well as malignant diseases. This narrative review summarizes the recent use of EUS-(B)-FNA in diagnosing sarcoidosis.

Methods: A comprehensive and systematic online literature search of PubMed was conducted using the keywords (“sarcoidosis”), and (“EUS” OR “EUS-FNA” OR “EUS-B” OR “EUS-B-FNA” OR “endoscopic ultrasound guided fine needle aspiration” OR “endoscopic ultrasound using the EBUS scope guided fine needle aspiration” OR “endoscopic ultrasound using the EBUS bronchoscope” OR “transesophageal” OR “transesophageal endoscopic ultrasound guided fine needle aspiration” OR “transesophageal bronchoscopic ultrasound guided fine needle aspiration”).

Key Content and Findings: Most EUS-FNA procedures were performed under moderate sedation, primarily using midazolam, with 22-gauge needles. The diagnostic sensitivity of sarcoidosis in mediastinal lymph node sampling is as high as 75–100% for EUS-FNA and 70–86% for EUS-B-FNA, much higher than that of traditional bronchoscopic procedures, such as transbronchial lung biopsy (TBLB) and conventional transbronchial needle aspiration (TBNA). The complications associated with EUS-(B)-FNA have thus far included only a few cases of mediastinitis, successfully treated with antibiotics, as well as lymph node hematoma, and sore throat.

Conclusions: EUS-FNA and EUS-B-FNA provide high diagnostic yields in patients with sarcoidosis. The safety profile is acceptable, although there is a slight risk of infectious complications. EUS-B-FNA, a minimally invasive and well-tolerated procedure, offers a viable alternative to endobronchial ultrasound-guided TBNA (EBUS-TBNA) for the diagnosis of sarcoidosis, particularly in patients with cough and poor respiratory function; this procedure can easily be performed by pulmonologists.

Keywords: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA); endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA); sarcoidosis

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Introduction

The clinical manifestations of sarcoidosis are often non-specific. The granulomatous inflammation seen in sarcoidosis is also associated with other diseases that

present with similar findings, including tuberculosis, fungal infections, lymphoma, lung cancer, and berylliosis, all of which must be excluded (1,2). Thus, to avoid false-positive results, a definitive diagnosis requires both clinical and

radiologic confirmation, including evidence of noncaseating granuloma of the involved tissue (3).

In patients with lesions that do not involve the skin or peripheral lymph nodes and thus cannot be easily sampled, transbronchial lung biopsy (TBLB) was recommended in the previous American Thoracic Society guidelines published in 1999 (2). However, the diagnostic yield of this procedure is only ~65% (40–90%) and a pathological diagnosis cannot be made in one-third of the cases (4,5). In addition, TBLB is occasionally associated with pneumothorax (incidence of 1–5%) and bleeding (9%) (6). Transbronchial needle aspiration (TBNA), as a conventional bronchoscopic approach, has a diagnostic yield similar to that of TBLB (42–76%) (7–9). Mediastinoscopy was once the next step in patients not diagnosed by TBLB or TBNA, as the reported diagnostic yield is as high as 82–97% (10–12), but the procedure is invasive and requires hospitalization and general anesthesia.

The development of endosonography, including endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided TBNA (EBUS-TBNA), has dramatically changed the evaluation of hilar-mediastinal lesions. The high accuracy and safety of endosonography for diagnosing benign as well as malignant lesions is now well established (13,14). As sarcoidosis is characterized by enlarged hilar and mediastinal lymph nodes, endosonography has proven useful in obtaining tissue specimens for its diagnosis, as demonstrated in several studies. The advantages of EBUS-TBNA are that it allows real-time TBNA and the locations of the needle and the target lesion on ultrasound images can be simultaneously confirmed. Given its high diagnostic yield (71–94%) and excellent safety (15–23), EBUS-TBNA is now recommended as the first-line method of tissue sampling in patients with suspected sarcoidosis (3). Although the reported diagnostic accuracy of EUS-FNA for accessible mediastinal lesions is comparable to that of EBUS-TBNA, a recent guideline (3) did not refer to its use for tissue sampling in sarcoidosis. This narrative review summarizes the current application of EUS-FNA and endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) in diagnosing thoracic sarcoidosis. We present this article in accordance with the Narrative Review reporting checklist (available at <https://med.amegroups.com/article/view/10.21037/med-24-37/rc>).

Methods

A comprehensive and systematic online literature

search of PubMed was conducted using the keywords (“sarcoidosis”), and (“EUS” OR “EUS-FNA” OR “EUS-B” OR “EUS-B-FNA” OR “endoscopic ultrasound guided fine needle aspiration” OR “endoscopic ultrasound using the EBUS scope guided fine needle aspiration” OR “endoscopic ultrasound using the EBUS bronchoscope” OR “transesophageal” OR “transesophageal endoscopic ultrasound guided fine needle aspiration” OR “transesophageal bronchoscopic ultrasound guided fine needle aspiration”). From the initially identified 35,324 articles related to sarcoidosis, 296 articles were retrieved. After the exclusion of those that did not include mediastinal disease, 258 articles remained. Editorials, comment, letters, proceedings, books, and abstracts were also excluded. The majority of the articles were related to EBUS-TBNA. After the list was narrowed to articles with at least 10 cases of sarcoidosis diagnosed by EUS-FNA and EUS-B-FNA, 15 articles were finally reviewed. The search strategy is summarized in *Table 1*.

Procedures

The results regarding the use of EUS-FNA and EUS-B-FNA in diagnosing sarcoidosis are summarized in *Table 2* (18,24–35) and *Table 3* (36–38). In most studies, EUS-FNA was performed with the patients under moderate sedation, mainly using midazolam, but in a few studies the patients were placed under deep sedation using propofol. Because EUS endoscopes have a larger working channel than EBUS bronchoscopes, a variety of needles are available. The reliability of the cytological diagnosis of sarcoidosis has been well established. In most studies, 22-gauge needles were used, but a few studies used 19-gauge needles. In a prospective study, Iwashita *et al.* prepared cytological and histological specimens obtained using a 19-gauge needle, and each specimen was blindly evaluated by pathologists (29). The sensitivity of histological specimens in EUS-FNA was significantly higher than that of cytological specimens (94.4% *vs.* 77.8%, $P=0.0444$). The subcarinal lymph nodes were the most frequently examined, followed by the left paratracheal lymph nodes. The subaortic, para-esophageal, and intra-abdominal lymph nodes, which are inaccessible by EBUS-TBNA, were evaluated only rarely.

Diagnostic performance of EUS-FNA

In 1999, Mishra *et al.* published the first report of the

Table 1 Search strategy summary

Items	Specification
Date of search	May 18, 2024
Databases and other sources searched	PubMed
Search terms used	("sarcoidosis"), and ("EUS" OR "EUS-FNA" OR "EUS-B" OR "EUS-B-FNA" OR "endoscopic ultrasound guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS scope guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS bronchoscope" OR "transesophageal" OR "transesophageal endoscopic ultrasound guided fine needle aspiration" OR "transesophageal bronchoscopic ultrasound guided fine needle aspiration")
Timeframe	January 1, 1938 to May 18, 2024
Inclusion and exclusion criteria	Inclusion criteria: original article, research article, full paper, English language Exclusion criteria: editorial, comments, letters, proceedings, books, abstracts, non-English papers, less than 10 cases of sarcoidosis diagnosed
Selection process	First author conducted the selection process, initial literature review, assessed all of the identified studies based on the eligibility criteria. Both authors reviewed the final list of studies included in the review

EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; EUS-B-FNA, endoscopic ultrasound with bronchoscope-guided fine-needle aspiration; EBUS, endobronchial ultrasound.

usefulness of EUS-FNA in diagnosing sarcoidosis (39), based on the cytological diagnosis of sarcoidosis in 6 of 108 patients who underwent EUS-FNA of the mediastinal lymph nodes. Subsequently, several investigators reported the diagnostic efficacy of EUS-FNA in patients with sarcoidosis. In 13 studies, 4 involving patients with mediastinal lymphadenopathy (24,26,31,33) and 9 limited to patients with suspected sarcoidosis (18,25,27-30,32,34,35), the reported sensitivities ranged from 75% to 100% (Table 2). The results are comparable to those obtained with EBUS-TBNA [71–94% (15-22)] or mediastinoscopy [82–97% (10-12)].

Three studies evaluated the diagnostic yield of EUS-FNA in patients with negative bronchoscopy results. Tournoy *et al.* performed EUS-FNA in 18 patients with negative bronchoscopy [TBLB, TBNA, endobronchial biopsy (EBB)] for sarcoidosis and reported a sensitivity of 94% in 16 patients (18). In a crossover study, Gnass *et al.* performed EUS-FNA in 21 patients with negative TBNA or EBUS-TBNA results; sarcoidosis was diagnosed in 9 patients whereas EBUS-TBNA did not identify any additional cases among 5 patients with negative EUS-FNA results (34). In a crossover study, Kocoń *et al.* reported that EUS-FNA was of diagnostic utility in 7 of 8 patients with negative bronchoscopy results (combined EBUS-TBNA, TBLB, EBB and TBNA), and EBUS-TBNA in 2 of 8 patients with negative bronchoscopy results (combined

EUS-FNA, TBLB, EBB and TBNA) (35).

As granulomatous inflammation is associated with many diseases besides sarcoidosis, including tuberculosis and fungal infections, there is a risk of false-positive results, but such cases are rare. In a study investigating the usefulness of EUS-FNA in differentiating between tuberculosis and sarcoidosis, including 30 cases of sarcoidosis and 28 cases of tuberculosis, 3 tuberculosis cases were initially misdiagnosed as sarcoidosis based on the cytology obtained with EUS-FNA (31).

Diagnostic performance of EUS-B-FNA

Despite the high diagnostic utility of mediastinal lymph node biopsy by EUS-FNA, the procedure is limited by the need for a skilled endoscopist and specialized equipment, such as an ultrasound endoscope and needle. An EBUS bronchoscope, equipped with a miniaturized convex probe at its tip, shares a mechanism similar to an EUS endoscope. Therefore, the transesophageal EUS-FNA procedure can be performed using an EBUS bronchoscope; this technique is termed EUS-B-FNA (40). Considering the familiarity of pulmonologists with EBUS bronchoscopy, they may find it easier to perform EUS-B-FNA than to perform EUS-FNA. In addition, EUS-FNA is better tolerated and less invasive than EBUS-TBNA (41).

The results obtained with EUS-B-FNA in diagnosing

Table 2 Studies using EUS-FNA in patients with suspicion of sarcoidosis

Author	Year	Study design	Sedation	Needle size (G)	Size of LN, mm [†]	No. of passes	LN examined	Stage	No. of patients examined	No. of patients with sarcoidosis	No. of patients with sarcoidosis diagnosed by EUS-FNA	Sensitivity for diagnosing sarcoidosis, %	Complications	Other
Fritscher-Ravens (24)	2000	Retrospective	Moderate sedation	22	NA	NA	NA	NA	153	16	16	100	No	False positive result: 1
Fritscher-Ravens (25)	2000	Prospective	NA	22	24 [10–41]	NA	#4R, #5, #7, #8	I, II, III	19	18	18	100	No	False positive result: 1
Wildi (26)	2004	Retrospective	NA	22	18 [5–40]	≥4	Subcarinal, AP window, paratracheal, para-aortal	NA	124	28	25	89	No	
Annema (27)	2005	Prospective	Moderate sedation	22	25 [5–40]	Mean 3	Lt paratracheal, AP window, subcarinal, para-esophageal	I, II	51	50	41	82	No	
Michael (28)	2008	Retrospective	Moderate/deep sedation	22/25	NA	Mean 5.3 per lesion	Subcarinal/mediastinal/intra-abdominal	NA	21	21	18	86	Mild sore throat: 1	Intra-abdominal LN: 7
Iwashita (29)	2008	Prospective	Moderate sedation	19	19 [5–42]	Mean 2.4	Subcarinal, left/right hilar, left paratracheal	I	41	36	34	94.4	Mediastinitis: 1	
Tournoy (18)	2010	Prospective	Moderate/deep sedation	22	NA	NA	NA	NA	18	17	16	94	No	TBB + EBB/TBNA: 121; EBUS-TBNA: 54
von Bartheld (30)	2010	Retrospective	Moderate sedation	22	NA	Mean 3.9	#2R, #4L, #4R, #5, #7, #8	I, II	100	91	79	87	Mediastinitis: 1; local hematoma: 1; sore throat: 1	
Fritscher-Ravens (31)	2011	Prospective	NA	22	[5–42]	≥3 (2 for cytology, 1 for bacteriological analysis)	Mostly subcarinal, AP window	I, II	71	30	30	100	No	False positive result: 3
von Bartheld (32)	2013	Randomized	Moderate/deep sedation	22	NA	Mean 5.21	NA	I, II	102	NA	NA	88	Mediastinal abscess	EBUS-TBNA: 56; bronchoscopy: 149
Jamil (33)	2014	Retrospective	NA	19/22/25	15 [7–33]	Median 3	NA	NA	160	32	25	78.1	NA	
Gnass (34)	2015	Randomized	Moderate sedation	22	≥10	3–5	NA	I, II	36	35	31	88.6	No	EBUS-TBNA: 36; TBNA: 43
Kocor (35)	2017	Randomized	Moderate sedation	22	NA	3–6	#4L, #7	I, II	51	NA	NA	75	No	EBUS-TBNA: 55

[†], mean or median [range]. #2R, right upper paratracheal; #4R, right lower paratracheal; #4L, left lower paratracheal; #5, subaortic; #7, subcarinal; #8, paraesophageal. EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; G, gauge; LN, lymph nodes; NA, not available; AP, aortopulmonary; Lt, left; TBB, transbronchial biopsy; EBB, endobronchial biopsy; TBNA, transbronchial needle aspiration; EBUS-TBNA, endobronchial ultrasound-guided-transbronchial needle aspiration.

Table 3 Studies on EUS-B-FNA in patients suspected of sarcoidosis

Author	Year	Study design	Sedation	Needle size (G)	Size of LN, mm [†]	No. of passes	LN examined	Stage	No. of patients examined	No. of patients with sarcoidosis	No. of patients with sarcoidosis diagnosed by EUS-FNA	Sensitivity for diagnosing sarcoidosis, %	Complications	Other
Oki (36)	2013	Prospective	Moderate sedation	21	13.6 [6.8–28.7]	Mean 3.3 per lesion	#2L, 3p, #4R/L, #7, #8, #10L	I, II	33	29	25	86	No	
Filarecka (37)	2020	Prospective	Moderate sedation	22	15.2	3–5	#2R/L, #4R/L, #7, #8	I, II	50	47	33	70.21	No	
Crombag (38)	2022	Randomized	Moderate/deep sedation	22/25	18 [15–22]	≥5	#2R, #4R/L, #7, #8, #9	I, II	358	141	115	82	No	EBUS-TBNA: 185

[†], mean or median [range]. #2L, left upper paratracheal; #2R/L, right/left upper paratracheal; 3p, retrotracheal; #4R/L, right/left lower paratracheal; #7, subcarinal; #8, paraesophageal; #9, pulmonary ligament; #10L, left hilar. EUS-B-FNA, endoscopic ultrasound with bronchoscope-guided fine-needle; G, gauge; LN, lymph node; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; EBUS-TBNA, endobronchial ultrasound-guided-transbronchial needle aspiration.

sarcoidosis are summarized in Table 3. Oki *et al.* evaluated the diagnostic utility of EUS-B-FNA in a prospective study of 33 patients with suspected stage I/II sarcoidosis; they reported a diagnostic yield of 86% (36). Filarecka *et al.* evaluated EBUS-TBNA followed by EUS-B-FNA in 50 patients with suspected stage I/II sarcoidosis. The sensitivity of EBUS-TBNA, EUS-B-FNA, and its combination was 76.6%, 70.2%, and 91.7%, respectively (37). Crombag *et al.* published a large multicenter international randomized trial in 2022 that included 358 patients with suspected stage I/II sarcoidosis. The study randomized 185 patients to EBUS-TBNA and 173 to EUS-B-FNA; 306 patients (86%) were ultimately diagnosed with sarcoidosis. The detection rate and sensitivity based on the detected granulomas were 70% and 78% for EBUS-TBNA and 68% and 82% for EUS-B-FNA, respectively; the differences between the two groups were not significant (38).

Safety of EUS-FNA and EUS-B-FNA

Of the 13 studies on EUS-FNA, a small number of cases reported serious complications, including mediastinitis (2 cases) and mediastinal abscess (1 case) (29,30,32). Although the safety of EUS-FNA has been well established, the risk of infectious complications in sarcoidosis patients should be kept in mind. In a case series of 252 patients with sarcoidosis who underwent EUS-FNA, 5 developed mediastinal abscess, with 4 patients requiring surgical treatment (42). The other reported complications associated with EUS-FNA were all minor ones, such as sore throat and hematoma.

In three studies of EUS-B-FNA, no complications were reported. Severe cough or oxygen desaturation, which often occur during EBUS-TBNA, are less common during EUS-B-FNA. In the study by Oki *et al.*, oxygen desaturation occurred in only 6% of patients (36). Pulmonologists unfamiliar with transesophageal procedures should be cautious when performing EUS-B-FNA in patients with suspected esophageal varices, esophagitis, and esophageal stenosis (43). These conditions may increase the risk of complications during the procedure.

Will EUS-FNA become the method of choice for tissue sampling in sarcoidosis?

As sarcoidosis often involves the hilar-mediastinal lymph nodes and lungs, patients are often managed by pulmonologists. However, while pulmonologists are able

to easily perform bronchoscopy, including EBUS-TBNA, TBLB, TBNA, and EBB, they are often not familiar with the handling of an EUS endoscope. The diagnostic performance of EUS-FNA is comparable to that of EBUS-TBNA; consequently, under certain circumstances, such as the availability of experienced endoscopists and an EUS-endoscope or sampling from EUS- but not EBUS-accessible lesions, it is a useful alternative to EBUS-TBNA when diagnosing sarcoidosis. EUS-B-FNA overcomes the limitation of EUS-FNA and offers an alternative to EBUS-TBNA (44,45). Although there is a learning curve, pulmonologists experienced in EBUS-TBNA can learn and perform EUS-B-FNA relatively easily (46,47). Pulmonology trainees should gain experience with EBUS, EUS-B-FNA, and EUS-FNA techniques (40). EUS-B-FNA offers the advantages of being minimally invasive and well-tolerated, even in patients with cough and poor respiratory function. Given the high tolerability and diagnostic efficacy of EUS-B-FNA, it is an effective technique available to pulmonologists when mediastinal sampling is required.

Conclusions

EUS-FNA and EUS-B-FNA are highly accurate procedures for diagnosing sarcoidosis. The reported safety profile is acceptable, although the risk of infectious complications should be considered. In particular, given its ease of performance by pulmonologists, EUS-B-FNA offers a useful alternative to EBUS-TBNA in the diagnosis of sarcoidosis.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://med.amegroups.com/article/view/10.21037/med-24-37/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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