The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis

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Background and study aim: Sarcoidosis is a systemic disorder of unknown cause that is characterized by a pathological hallmark, noncaseating granuloma. Bilateral hilar lymphadenopathy (BHL) is a major clinical feature, but it is sometimes difficult to exclude other diseases, especially in cases where there are no pulmonary abnormalities (stage I). Bronchoscopic transbronchial biopsy is currently a popular method by which to obtain pathological material, but its diagnostic power is insignificant. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), also attempted recently, makes the sampling of pathological material easier and better, but the diagnoses are still based on cytological findings. Our study aimed to evaluate the yield of transesophageal EUS-FNA for histological confirmation of stage I sarcoidosis.

Methods: The study was a prospective comparative study to investigate the diagnostic sensitivities of FNA cytology and FNA histology. Subjects were consecutive patients with BHL without lung lesions on chest radiographs or chest CT who were referred to our hospitals between December 2003 and April 2006. Transesophageal EUS-FNA was performed with 19-gauge needles instead of the conventional 22-gauge needles.

Results: Forty-one patients were included in this study, and both histological and cytological materials were obtained successfully by EUS-FNA in all patients. Histopathological examination of the FNA sample showed noncaseating granuloma in 34 (94.4%) of the 36 patients with a final diagnosis of sarcoidosis. In contrast, only 28 of the 36 (77.8%) were diagnosed as having sarcoidosis on the basis of cytological findings. The difference was statistically significant ($P = 0.0444$).

Conclusion: FNA histology is better suited than FNA cytology to establishing the diagnosis of stage I sarcoidosis, and EUS-FNA with a 19-gauge needle plays a important role in this process.

Sarcoidosis is a systemic disorder of unknown cause that is characterized by a pathological hallmark, the noncaseating granuloma. Bilateral hilar lymphadenopathy (BHL) is the most significant clinical feature, and is detected on chest radiograph or CT [1]. However, the diagnosis is often difficult if it is based on BHL alone without any other specific physical, imaging, or serological findings. In such cases, a pathological diagnosis is essential in order to exclude other diseases such as malignant lymphoma, metastatic tumor, and infectious diseases. Bronchoscopy with transbronchial lung biopsy (TBLB) is currently the most popular technique for this purpose [2], but its yield (40–66%) is not sufficient, particularly in cases in which there is no parenchymal involvement of the lung [3]. Transbronchial needle aspiration (TBNA) from lymph nodes together with bronchoscopy is also performed, but the sampling is sometimes difficult due to the "blind" technique of needle puncture. Although mediastinoscopy, with a high yield of 82–94.3% [4–6], can be chosen as the final diagnostic step, it is invasive, carrying a morbidity of 0.6% [7], and requires general anesthesia. Thus, the procedure requires much time, manpower, and expense. Recently, the yield of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in the diagnosis of sarcoidosis has also been reported in several publications [8–11]. Since the puncture with the needle is guided by real-time color Doppler ultrasound imaging, this procedure seems much easier and safer. However, only cytological investigations have been attempted so far because of the limited amount of material sampled.

The diagnosis of sarcoidosis was originally made from histological findings, and the diagnosis is generally more difficult to make from cytological than from histological findings. We have pre-

viously reported that using a 19-gauge needle instead of a conventional 22-gauge needle for EUS-FNA enables us to obtain a significant amount of material for histological assessment [12]. In this study, therefore, we attempted to obtain a larger amount of material by using a 19-gauge needle, and compared the diagnostic power of FNA histology to FNA cytology in patients suspected of having stage I sarcoidosis: namely, the patients with BHL without pulmonary abnormalities.

Patients and methods

Patients

This study was a prospective comparative study that employed a consecutive entry design. It was conducted at the First Department of Internal Medicine, Gifu University Hospital, between December 2003 and April 2006. Patients were referred to the hospital with suspected stage I sarcoidosis. The eligibility criteria were detection of BHL without inflammatory lesions or tumors in the lung field on chest CT. Patients with simultaneous malignant disease or active-phase tuberculosis were excluded.

The study protocol was approved by the review board for human research of Gifu University. Written informed consent was obtained from each patient on entry into the study. The study was conducted in accordance with the human and ethical principles of research set forth in the Helsinki guidelines.

Sampling methods

EUS-FNA was performed using an oblique-forward-viewing electronic linear scanning video echoendoscope equipped with elevator and a 2.8-mm-diameter working channel (GF-UC240P-AL5; Olympus Optical Co. Ltd., Tokyo, Japan). The echoendoscope was connected to a processor with color Doppler function (SSD-5000; Aloka Co. Ltd., Tokyo, Japan). EUS-FNA was performed with the patient under conscious sedation using 10 mg midazolam and 15 mg pentazocine, with monitoring of vital signs.

Following transesophageal EUS evaluation of mediastinal lymph nodes, under EUS guidance the most easily accessible lymph node via the esophagus was punctured. The target lesion was carefully observed, and color Doppler imaging was used to ensure that no major vessels were interposed in the puncture path. The puncture was done with a 19-gauge needle (EchoTip; Wilson-Cook, Winston-Salem, NC, USA) guided by real-time EUS imaging after the optimal puncture site was determined. The aspirated material was expelled onto glass slides by carefully reinsertion of the stylet. This material was assessed macroscopically, and whitish parts of the material were collected on another glass slide. After being divided into equal parts, half of the material was placed on a small piece of filter paper and put into formalin solution for histological examination. The remaining half was smeared on glass slides for cytological examination. Thereafter, an additional puncture was done, and all of the material recovered this time was placed in a sterilized bottle with normal saline solution for DNA detection of *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare complex* (MAC) using the polymerase chain reaction (PCR) technique [13,14]. Since neither a pathologist nor a cytologist was present on site at our institution, the puncture was repeated until whitish material was visible macroscopically. However, if no macroscopic specimen was obtained after three consecutive punctures, only smeared glass slides were sent for cytological examination.

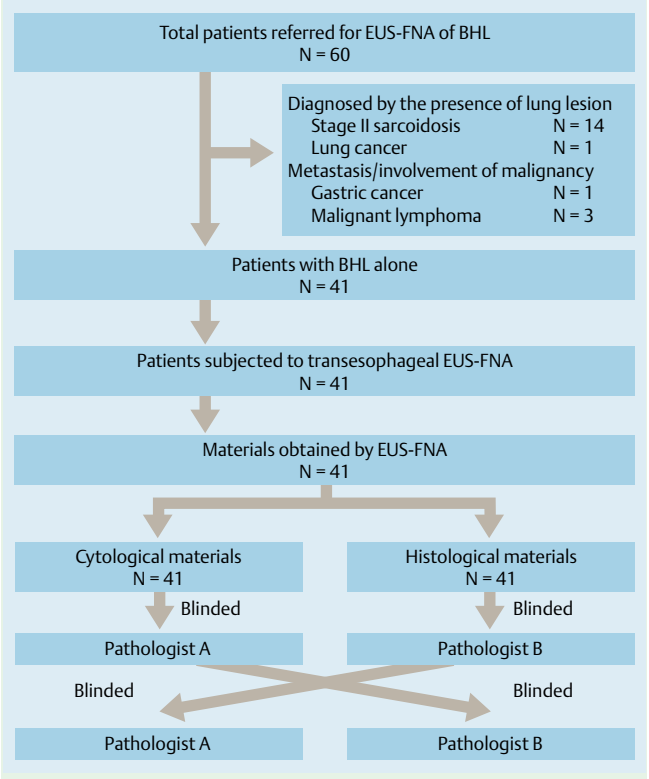

Fig. 1 Study profile.

Following preparation by laboratory staff, the cytology samples were blind-coded and carried to pathologist A. After his examination was completed, the samples were again blind-coded and distributed to pathologist B for cytological diagnosis in a crossover design as shown in **Fig. 1**. Quality evaluation of the cytology samples and the cytological diagnosis were done independently by the two pathologists. The study diagnoses and the quality assessment were regarded as established only when the two pathologists were in complete agreement. The histological diagnosis was carried out in the same blinded and crossed-over fashion.

Histological diagnoses were made on the basis of hematoxylin and eosin staining (**Fig. 2**) and cytological diagnoses on the basis of Papanicolaou staining (**Fig. 3**). If requested, immunopathological stainings were added. The procedure was performed on an outpatient basis unless the patient was already hospitalized for other medical conditions. The patients were observed for immediate complications in the outpatient recovery room for 2 hours, and contact was maintained for 24 hours after the procedure to monitor for any complications. All patients also underwent examination of serum levels of soluble interleukin-2 receptor (sIL-2R) and angiotensin-converting enzyme (ACE).

Data analysis

The primary end points of this study were the sensitivities of FNA histology and cytology in the diagnosis of sarcoidosis.

The final diagnoses were based on the pathological findings, clinical symptoms, serological tests, clinical follow-up, and, if available, surgical pathology. Benign nonspecific lymphadenopathy was defined by the absence of granuloma in the biopsy specimen and spontaneous resolution or lack of progression of

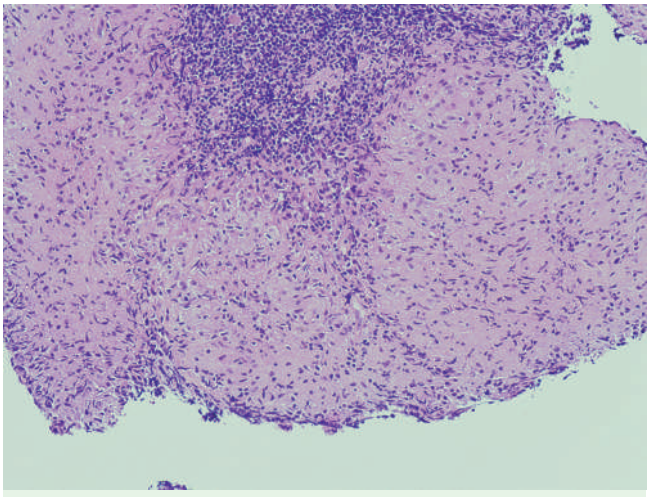

Fig. 2 Histological appearance of mediastinal lymph node obtained by EUS-FNA using a 19-gauge needle, demonstrating a noncaseating granuloma without necrosis. (Hematoxylin and eosin, original magnification × 40).

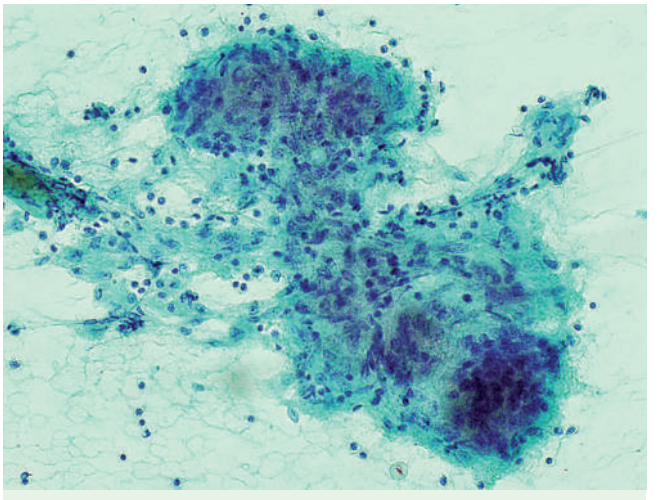

Fig. 3 Cytological appearance of mediastinal lymph node obtained by EUS-FNA using a 19-gauge needle, demonstrating clusters of epithelioid histiocytes with associated small lymphocytes. (Papanicolaou stain, original magnification × 40).

lesions, as noted on follow-up imaging studies, for at least 12 months without any deterioration of the patient's condition of health.

We calculated the sensitivities and their 95% confidence intervals (95% CI) for FNA cytology and FNA histology, and compared them using Fisher's exact test. *P* values of less than 0.05 were considered significant. We used the JMP software, version 5.0.1 (SAS Institute, Inc., Cary, NC, USA), for statistical analysis.

Results

Sixty patients were initially referred to our department to undergo EUS-FNA of BHL lesions during the study period. However, 19 of these patients were found to have lesions in addition to BHL (**Fig. 1**). In 15 patients, the presence of lung lesions was detected on chest radiograph or CT. Of these 15 patients, 14 were diagnosed as having stage II sarcoidosis and the remaining patient was diagnosed as having lung cancer. In 4 other patients,

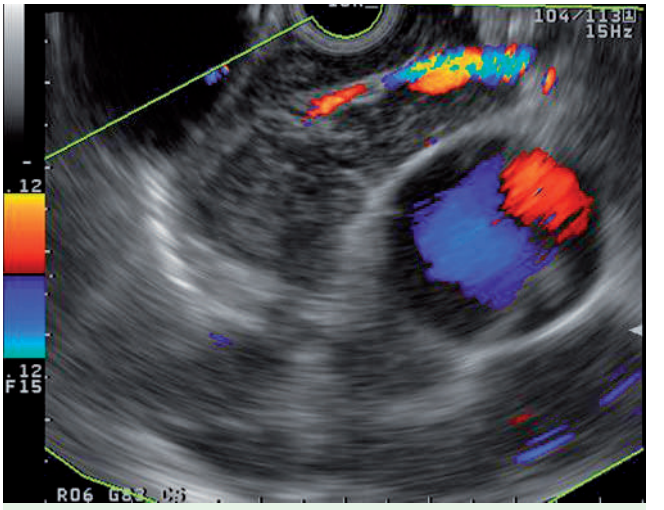

Fig. 4 EUS findings of a patient with sarcoidosis, demonstrating clustered, well-demarcated, and homogeneous isoechoic lymph nodes with central hyperechoic strand including vessels in the subcarinal region.

coexisting malignancies were found: malignant lymphoma in 3 and gastric cancer in 1, detected by modalities other than EUS-FNA; in these patients the BHL lesions were diagnosed as involvement or metastasis (**Fig. 1**).

A total of 41 patients with BHL alone on chest radiograph and chest CT fulfilled the inclusion criteria and were enrolled in this study. The participants were 22 women and 19 men; their median age was 54 years (range 21 – 84 years). Subjective symptoms were recorded in 10 patients: chest pain in 5, blurred vision in 4, and fever in 1. The remaining 31 patients (75.6%), however, had no clinical symptoms; in these patients the BHL was found incidentally on imaging during a periodic health examination or follow-up for another disease. Serum ACE concentration was 17.9 ± 8.2 IU/L (mean ± standard deviation; normal range 8.3 – 21.4 IU/L) and serum sIL-2R 1031 ± 720 U/mL (normal range 145 – 519 U/mL). Only 11 patients (26.8%) presented with increased levels of serum ACE, while 30 patients (73.2%) presented with increased sIL-2R. Nine patients (22.0%) had previously undergone a non-diagnostic bronchoscopy.

Enlarged mediastinal lymph nodes were easily detected by EUS in all patients. EUS findings in these lymph nodes were: clustered in 32 patients, well-demarcated in 39, homogeneously isoechoic in 36, and with a central hyperechoic strand including vessels in 14 patients (**Fig. 4**). Needle puncture was successful in all patients, and the targeted lymph nodes were located in the subcarinal (n = 38), the left hilar (n = 1), the right hilar (n = 1), and the left paratracheal regions (n = 1). The median length of the long axis of the lymph nodes was 37 mm (range 17 – 75 mm), and the median length of the short axis 19 mm (range 5 – 42 mm). Macroscopically visible material was obtained in all cases; the mean number of passes was 2.4 (range 2 – 4). Thirty-four patients (83.0%) underwent the procedure as outpatients.

Pathological results of specimens biopsied by EUS-FNA

Sufficient and adequate materials for determining histological diagnoses were obtained from 39 patients (95.1%) (**Fig. 5**). Noncaseating granulomas were found on histological examination in 34 patients (82.9%). The PCR detection tests for *M. tuberculosis* and MAC were negative in all these patients, and they were diagnosed with sarcoidosis. One patient was diagnosed with lymphoma, classified as follicular B-cell lymphoma (grade

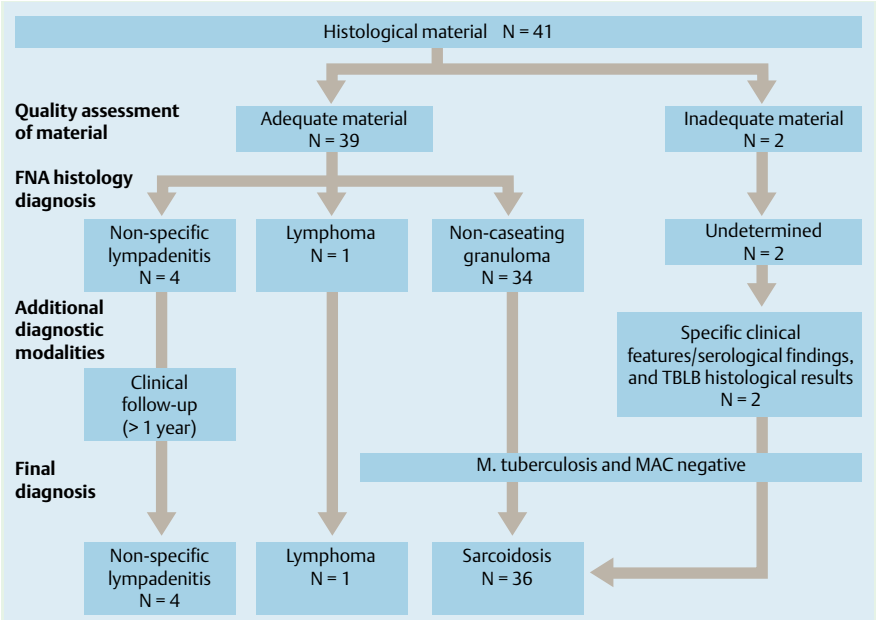

Fig. 5 Study execution profile: FNA histological assessment.

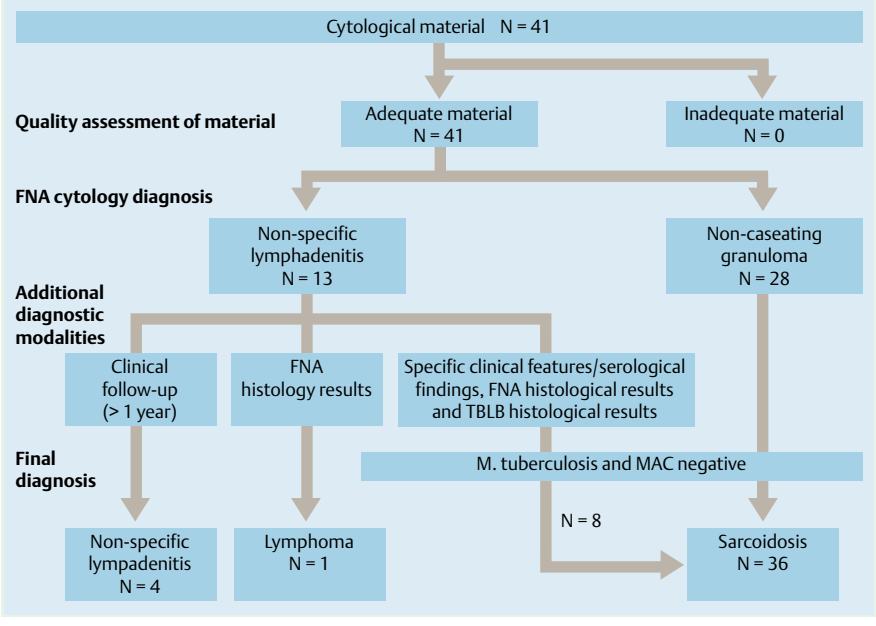

Fig. 6 Study execution profile: FNA cytological assessment.

1) on the results of immunohistochemical staining. The remaining four patients did not show any specific findings, including granuloma, and in these cases the diagnosis given was nonspecific lymphadenitis.

In two cases, adequate material could not be obtained (**Fig. 5**). However, noncaseating granuloma was found in the TBLB specimen in one patient, and he was later diagnosed with sarcoidosis. Another patient was also later diagnosed with sarcoidosis, on the basis of developing uveitis and an increased serum level of ACE.

The four patients diagnosed with nonspecific lymphadenitis were observed every 3–6 months after EUS-FNA; the median duration of follow-up was 22 months (range 18–33 months). The final follow-up data of these patients were collected in September 2007. Lymph node sizes had decreased in one patient. The remaining three patients showed neither an increase in lymph node size nor other changes on follow-up CT, and no additional clinical symptoms appeared.

Thirty-six patients had a final diagnosis of sarcoidosis (**Fig. 5**). Of these, 34 were diagnosed on the basis of histological findings obtained by EUS-FNA. In contrast, only 28 patients were diagnosed on the basis of cytological findings (**Fig. 6**). There was no disagreement between the two pathologists in any of the cases regarding the cytological diagnosis, histological diagnosis, and quality assessment of the FNA specimens. The sensitivity, specificity, and accuracy of FNA histology and FNA cytology in diagnosing sarcoidosis were respectively 94.4% (95% CI 81.9–98.5) and 77.8% (95% CI 61.9–88.3; $P = 0.0444$), 100% (95% CI 56.6–100) and 100% (95% CI 56.6–100), and 95.1% (95% CI 83.9–98.7) and 80.5% (95% CI 66.0–89.8) (**Table 1**).

Clinical courses of the patients finally diagnosed with sarcoidosis

Of the 36 patients finally diagnosed with sarcoidosis, 3 were started on steroid therapy owing to aggravation of uveitis (n = 2) and chest pain (n = 1). The remaining 33 patients were followed up regularly without medication. Among these patients,

Table 1 Comparison of diagnostic results for bilateral hilar lymphadenopathy (BHL): FNA histology vs. FNA cytology

Diagnosis	Final*	FNA histology	FNA cytology
Sarcoidosis	36	34 (94 %)†	28 (78 %)‡
Lymphoma	1	1	0
Nonspecific lymphadenitis	4	4	13
Undetermined	0	2	0
Total	41	41	41

* Final diagnoses were based on pathological findings, clinical symptoms, serological tests, clinical follow-up, and, if available, surgical pathology.
† Numbers in parentheses indicate diagnostic sensitivity for sarcoidosis.
‡ $P = 0.04$ as compared to FNA histology using Fisher's exact test.
Diagnostic specificity and accuracy for sarcoidosis are, respectively: FNA histology, 100 % and 95 %; FNA cytology, 100 % and 80 %.

BHL showed a decreasing tendency in 3, no significant changes in 26, and an increasing tendency in 4. In 2 of the 4 patients in whom an increasing tendency was seen, the sarcoidosis progressed to stage II with the appearance of an interstitial shadow in the lung fields on their chest CT.

Complications

Early complications related to the procedure occurred in one patient. She had chest pain the day after the EUS-FNA and was diagnosed with mediastinitis on the basis of blood examinations and CT findings. Her symptoms resolved within 1 week with conservative treatment with antibiotics.

Discussion

EUS-FNA has now been recognized as a safe and accurate procedure for sampling intramural and extramural lesions of the gastrointestinal tract. In cases of mediastinal lymphadenopathy, EUS-FNA has been proved to be helpful for the preoperative nodal staging of lung cancer and for the diagnosis of lymphadenopathy of unknown etiology, since posterior mediastinal lymph nodes are readily accessible by this technique [15 – 19].

BHL occurs in several diseases, including infectious, inflammatory, and malignant, but the most common cause is sarcoidosis [20]. BHL is found in up to 90 % of patients with sarcoidosis [1]. According to a joint statement on sarcoidosis by the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), the diagnosis of sarcoidosis requires a compatible clinical picture, histological demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histological or clinical picture [21]. The clinical pictures of sarcoidosis vary, and the patients sometimes have no symptoms and show no abnormal laboratory data.

For example, ACE is a relatively specific biochemical marker of sarcoidosis, but the sensitivity is quite low. Especially, patients' ACE levels are significantly lower in stages I and III than in stage II [22]. In fact, increased levels of serum ACE were shown in only 11 (30.6 %) of the 36 patients finally diagnosed with sarcoidosis in our study. On the other hand, 26 (72.2 %) of the patients showed increased levels of sIL-2R, which is a supporting marker of lymphoma, so we measured it to exclude lymphoma. However, in fact, the level of sIL-2R is also increased in sarcoidosis patients, and its sensitivity was reported by Grutters et al. as 79 % [23]. In addition, the sIL-2R level was significantly higher in stage I compared to stage III.

In patients without any clinical features, a pathological investigation is essential for the diagnosis of sarcoidosis. TBLB is currently the most popular technique for sampling the histopathological material [2], but the yield is not optimal, especially in patients without parenchymal involvement of the lung, namely suspected stage I sarcoidosis [3].

Several reports have discussed the yield of EUS-FNA to confirm the pathological diagnosis of sarcoidosis [8 – 11]. Mishra et al. [11] were the first to report, in 1999, that, among 108 consecutive patients who underwent EUS-FNA of mediastinal lymph nodes, cytological evidence of sarcoidosis was obtained in 6. Fritscher-Ravens et al. [8] reported the first prospective study of the diagnostic value of EUS-FNA in sarcoidosis. In their study, 19 patients suspected of having sarcoidosis were investigated using EUS-FNA, and the overall diagnostic accuracy and sensitivity of EUS-FNA cytology in the diagnosis of sarcoidosis were 94 % and 100 %, respectively. However, the number of subjects in these two studies was small. Wildi et al. [10] reviewed retrospectively the data on 124 patients with mediastinal lymphadenopathy of unknown origin. Among them, 25 patients were diagnosed with sarcoidosis by EUS-FNA cytology, and the sensitivity and specificity of EUS-FNA were 89 % and 96 %, respectively. Annema et al. [9] also assessed the yield of EUS-FNA for the diagnosis of sarcoidosis in a large patient group. In this study, 51 patients with suspected stage I and II sarcoidosis underwent EUS-FNA, and the diagnosis of sarcoidosis was confirmed in 41 of 50 patients (82 %), with the final diagnosis of sarcoidosis from cytological findings.

In these four studies, EUS-FNA was performed mainly using 22-gauge needles, and the pathological diagnoses were determined on the basis of cytological findings. Although the value of cytology in the diagnosis of sarcoidosis seems to be established [24,25], the fact is that only a limited number of centers prefer to use it routinely. Because the diagnosis of sarcoidosis was originally defined by histological evidence of noncaseating epithelioid cell granulomas, it is more difficult to diagnose sarcoidosis on the basis of cytological than on the basis of histological findings. Cytological diagnosis therefore requires a well-trained cytopathologist. For these reasons, we tried to confirm the diagnosis of sarcoidosis on the basis of histological findings. We have already reported a high yield of EUS-FNA using 19-gauge needles for the histological diagnosis. In our previous study, the overall accuracy of EUS-FNA histology using 19-gauge needles for unknown lymphadenopathy was 98 %, and histopathological classification of lymphoma was possible in 88 % of cases [12]. For this reason, we also used 19-gauge needles in this study. As a result, 34 (94.4 %) of 36 sarcoidosis patients showed noncaseating granuloma on histological examination by EUS-FNA (**Fig. 5**). In contrast, only 28 patients (77.8 %) were diagnosed with sarcoidosis on the basis of cytological findings (**Fig. 6**). The sensitivity was significantly higher in the histological diagnosis ($P = 0.0444$) (**Table 1**).

The biggest limitation of this study is that no further histological investigations such as mediastinoscopy and thoracotomy were performed in any of the patients. However, in order to exclude other granulomatous diseases before deciding on the final diagnosis of sarcoidosis, DNA detection tests for *M. tuberculosis* and MAC using the PCR technique were routinely performed on the aspirated material in our study, and the results were negative in all cases. Pneumoconioses, such as berylliosis, were excluded in

the absence of any occupational history of exposure to beryllium and dust in all patients, and histoplasmosis is not endemic in Japan. A sarcoidal reaction from malignant diseases was considered unlikely because of the long-term follow-up (more than 6 months). As for the four patients diagnosed with nonspecific lymphadenitis from adequate material obtained by EUS-FNA, no granulomas or fibrotic changes were seen in the biopsied specimens, and the patients' clinical courses over more than 12 months also made sarcoidosis unlikely. Nevertheless, a diagnosis of sarcoidosis cannot be excluded completely in these patients. Assuming that all of those patients with nonspecific lymphadenitis were false negatives, the sensitivity of EUS-FNA would be 85.0%.

Several EUS findings have been reported as specific features of sarcoidosis: (i) clustered, (ii) well-demarcated, and (iii) homogeneous isoechoic lymph nodes, and (iv) hyperechoic strands including vessels [9,11]. The sensitivities of these findings were 83%, 94%, 86%, and 36%, respectively, in the 36 patients finally diagnosed with sarcoidosis in this study. However, these features were also found in 40%, 100%, 100%, and 20%, respectively, of the remaining 5 patients who were *not* diagnosed with sarcoidosis. Therefore, these findings may be useful to differentiate sarcoidosis from malignancy in lymph nodes, but it is still considered difficult to discriminate sarcoidosis from other benign diseases on the basis of EUS findings.

In conclusion, a histological assessment is better suited than a cytological assessment alone to establishing a diagnosis of stage I sarcoidosis, and EUS-FNA with a 19-gauge needle plays a significant role in this process.

Competing interests: None

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