Chapter 11

Pathological Diagnosis with Endobronchial Ultrasonography — Guided Transbronchial Needle Aspiration (EBUS-TBNA)

Atsushi Kitamura and Yuichi Takiguchi

Additional information is available at the end of the chapter

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1. Introduction

The diagnosis of sarcoidosis is based on clinico-radiological findings and histological evidence of non-caseating epithelioid-cell granulomas [1]. Traditionally, if pulmonary sarcoidosis is suspected, pathological diagnostic materials are often obtained using conventional bronchoscopy together with procedures such as bronchoalveolar lavage (BAL) for evaluation of disease activity, transbronchial needle aspiration (TBNA) for hilar/mediastinal lymph node lesions, transbronchial lung biopsy (TBLB) for lung parenchymal lesions, and transbronchial biopsy (TBB) for endobronchial lesions. In most cases, however, definitive pathological diagnosis of this disease mainly depends on TBLB for lung parenchymal lesions because hilar/mediastinal lymph node lesions are often difficult to access and endobronchial lesions are uncommon. The diagnostic yield of TBLB in this disease is reportedly about 40–90% when several biopsy samples are obtained [2, 3]. When mediastinal or hilar lymphadenopathy is detected on computed tomography (CT) and cannot be diagnosed with conventional bronchoscopy, mediastinoscopy is performed to obtain histological samples. Although the diagnostic sensitivity of this procedures is >90% [4, 5], it is invasive and requires general anesthesia [5]. In this chapter, a newly developed bronchoscopic technique, endobronchial ultrasonography (EBUS)-guided transbronchial needle aspiration (EBUS-TBNA) for the definitive diagnosis of sarcoidosis is discussed.

2. EBUS-TBNA, a newly developed bronchoscopic technique

An endobronchial ultrasound, recently developed in Japan [6, 7], is a bronchoscope equipped with a convex-type ultrasound probe at the tip of the scope to simultaneously

visualize endobronchial images with optical-wavelength light and images of peribronchial structures, such as lymph nodes and vessels, with ultrasound (Figure 1). By introducing a specialized TBNA needle into the forceps channel, it is possible to obtain cytological and even histological samples [6, 7]. This technique was developed primarily as a novel minimally invasive diagnostic technique for lymph node staging of lung cancer [6, 8- 17]. As summarized in Table 1, initial research disclosed its high sensitivity and diagnostic yields for this purpose. This new technique has obviated the need for classical and invasive mediastinoscopy in many cases, and a current European guideline for lymph node staging in lung cancer primarily recommends EBUS-TBNA over mediastinoscopy [18]. Recent reports also indicate that EBUS-TBNA is a valuable diagnostic method for pulmonary sarcoidosis with hilar/mediastinal lymphadenopathy [19 - 32]. The presence of non-caseating epithelioid-cell granulomas in the lymph nodes obtained by EBUS-TBNA suggests the diagnosis of granulomatous disease including sarcoidosis.

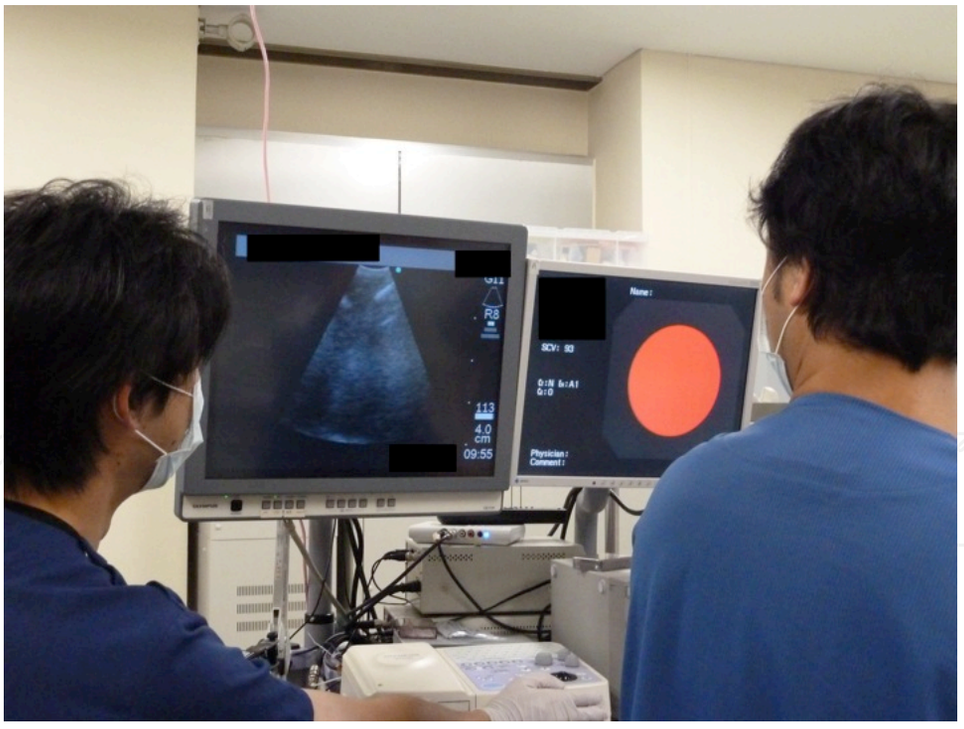

Figure 1. A bronchoscopic procedure with EBUS. The operator and assistants can view simultaneous real-time images of both endobronchus with natural light (right monitor) and peribronchial structures with ultrasonography (left monitor).

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Author	Year	No. of patients	Study design	Sensitivity (%)	Specificity (%)
Yasufuku[6]	2005	108	Prospective	94.1	100
Yasufuku[10]	2006	102	Prospective	92.3	100
Herth[11]	2006	502	Prospective	94	100
Vincent[12]	2008	146	Retrospective	99.1	100
Wallace[13]	2008	138	Prospective	69	100
Herth[14]	2008	97	Prospective	88.9	100
Ernst[15]	2008	66	Prospective	88.1	100
Petersen[16]	2009	157	Retrospective	85	100
Yasufuku[17]	2011	102	Prospective	81	100

Table 1. Recent studies for staging of lung cancer with EBUS-TBNA

3. Technique to obtain histological and cytological materials with EBUS-TBNA

EBUS-TBNA is performed under local anesthesia with mild sedation, which is comparable to conventional bronchoscopy [7 - 11]. Contrast medium-enhanced CT images are used to identify target lymph nodes. A convex-probe-equipped EBUS bronchoscope (CP-EBUS; for example, BF-UC260F-OL8; Olympus, Tokyo, Japan) supported by an ultrasound image processor (model EU-C2000; Olympus) and a dedicated 22- or 21-gauge aspiration needle (NA-201SX-4022/NA-201SX-4021; Olympus) are used (Figures 2, 3). Although 21 G and 22 G needles yield similar sensitivity in the diagnosis of malignant diseases, 22 G needles are more efficient than 21 G needles for obtaining materials from patients with sarcoidosis [33]. While the target lymph node is visualized with EBUS, a transbronchial puncture under real-time ultrasound guidance is performed with a needle equipped with an internal sheath (Figure 4). The internal sheath prevents clogging of the needle with bronchial epithelial cells. On confirming that the tip of the needle has penetrated the target lymph node, the internal sheath is removed, and rapid negative pressure is applied by aspirating with a 20-mL syringe several times. After the needle is moved back and forth inside the lymph node under real-time ultrasound guidance, it is retrieved and the internal sheath is used to expel the material aspirated in the needle (Figure 5). A histological core is first obtained in many cases; this material is placed on a small piece of filter paper for fixation in 10% buffered formalin. The internal sheath is then removed, and positive pressure is applied using an air-filled 20-mL syringe to expel the remaining material in the needle onto a glass slide, which is then smeared against another glass slide by using the squash preparation technique to yield cytological smears on 2 glass slides (Figure 6). Both histological cores and cytological specimens are obtained in many cases with this method. In our institution, tentative on-site cytological diagnosis by a cytoscreener is available. One of the

cytological slides is placed in 95% ethanol for fixation and staining with the Papanicolaou technique. The other one is air-dried, stained with a Romanowsky-type stain (Diff-Quik®), and sent for on-site evaluation. The cytoscreener ensures that the specimen is of adequate quality. Tissue sampling is repeated until sufficient material is obtained. The aspirated materials can also be dispersed into sterile saline solution for microbiological examinations, including staining and culture for bacteria, fungi, and acid-fast bacilli. In addition, polymerase chain reaction examinations can be performed for acid-fast bacilli. Histological diagnoses are based on the results of hematoxylin and eosin (H-E) staining.

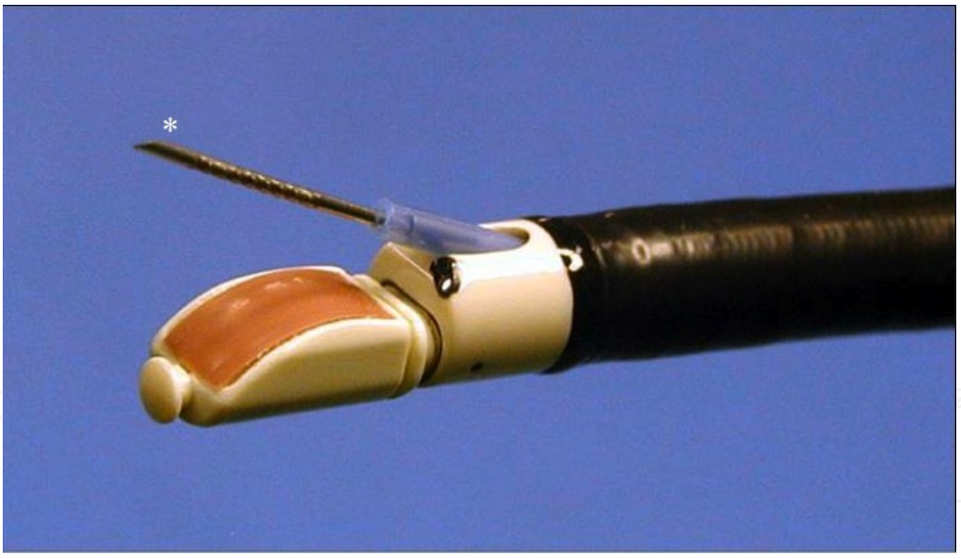

Figure 2. The tip of the endobronchial ultrasound equipped with an aspiration needle (asterisk). The needle is protruded for demonstration.

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Figure 3. The control head of an endobronchial ultrasound is similar to that of a conventional bronchoscope except for a sophisticated needle aspiration kit that enables operators to control internal and outer sheaths separately.

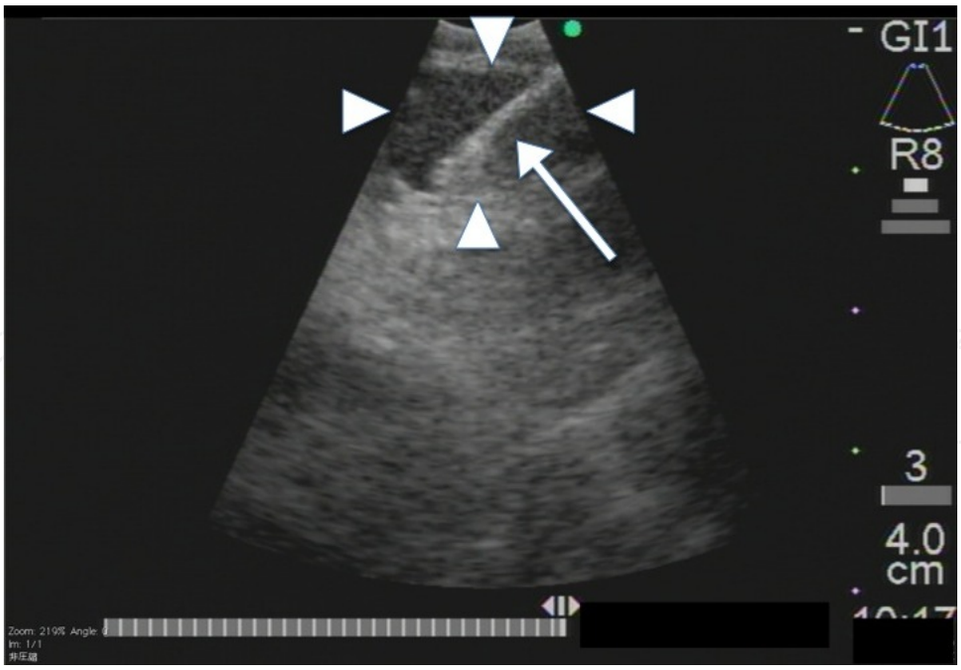

Figure 4. An ultrasound image showing an enlarged lymph node (hypoechoic area; arrowheads) and an aspiration needle (arrow) inserted into the lymph node. On ensuring that the tip of the needle is inside the target lymph node, negative pressure is applied and the needle is moved back and forth inside the lymph node to obtain material for pathological examination.

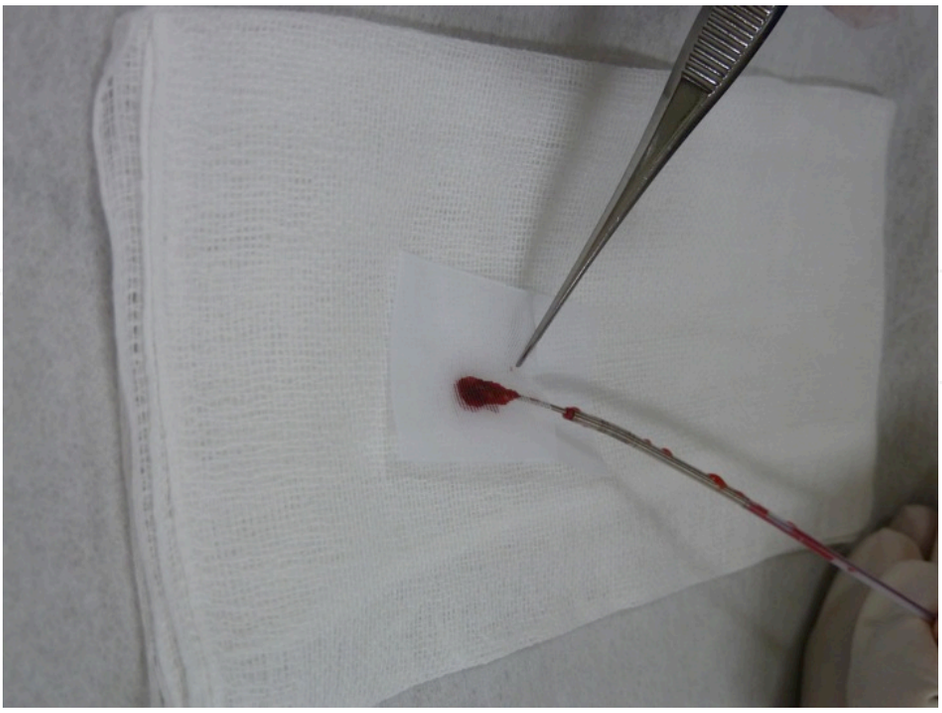

Figure 5. Aspirated material inside the needle is expelled by inserting the inner sheath. Usually a histological core is obtained, and the material is collected on a filter paper for fixation in formalin solution.

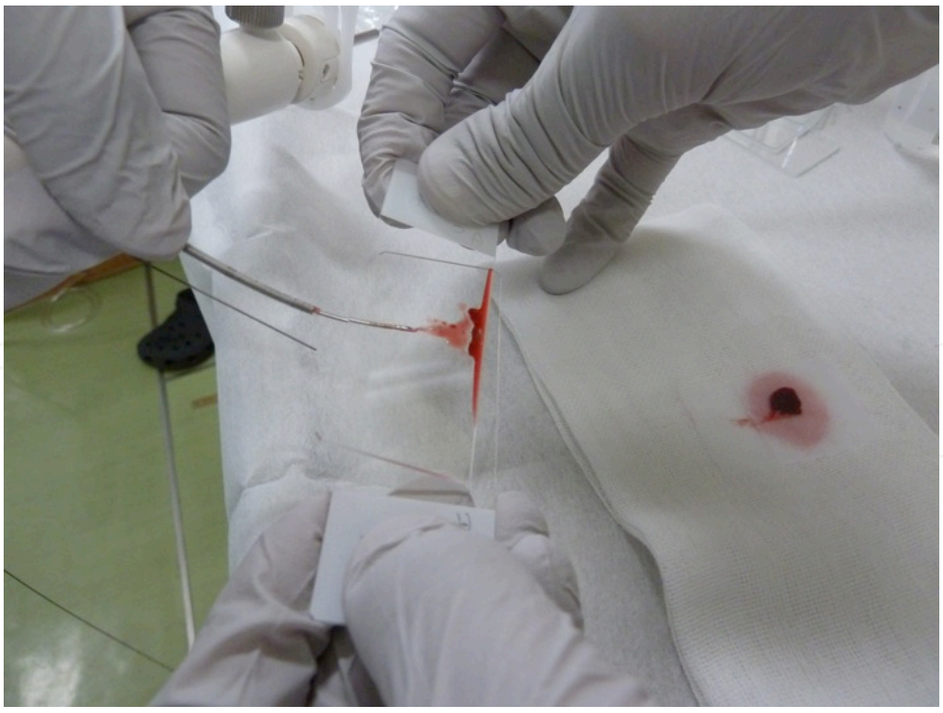

Figure 6. After obtaining the histological core, the inner sheath is removed. An abrupt positive pressure is used to expel remaining material inside the needle for cytological samples, which are obtained on 2 glass slides by using the squash preparation technique.

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BAL followed by TBLB with conventional bronchoscopy is performed before EBUS-TBNA [22,28] when required.

4. Sensitivity and specificity of EBUS-TBNA in the diagnosis of sarcoidosis

Table 2 summarizes the results of recent reports and shows a diagnostic sensitivity for sarcoidosis of EBUS-TBNA ranging from 56% to 94% [19 - 32]. Non-caseating epithelioid-cell granulomas on histological examination of EBUS-TBNA specimens have high sensitivity and specificity for sarcoidosis at stages 1 and 2. Nakajima et al. [22], Oki et al. [28], and Kitamura et al. [29] reported that the sensitivity of EBUS-TBNA for stage 1 and 2 sarcoidosis is much higher than that of TBLB from the lung parenchyma.

Author	Year	No. of patients	Study design	Histology		Cytology		Histology & Cytology	
				Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Garwood[19]	2007	48	Prospective	-	-	-	-	85	-
Oki[20]	2007	14	Prospective	57	-	65	-	78	-
Wong[21]	2007	61	Prospective	-	-	-	-	92	-
Nakajima[22]	2009	32	Retrospective	63	-	71	-	91	-
Tremblay[23]	2009	24	Prospective	-	-	-	-	83	-
Eckardt[24]	2010	43	Retrospective	-	-	-	-	77	-
Tournoy[25]	2010	54	Prospective	-	-	-	-	56	-
Navani[26]	2011	27	Prospective	-	-	-	-	85	-
Plit[27]	2011	37	Retrospective	-	-	-	-	84	-
Oki[28]	2012	54	Prospective	-	-	-	-	94	-
Kitamura[29]	2012	72	Retrospective	72	97	65	94	88	92

- : not available

Table 2. Recent studies for diagnosis of sarcoidosis with EBUS-TBNA

5. Diagnostic validity for sarcoidosis of epithelioid-cell clusters on cytological examination

Cytological evaluation has been reported in the diagnosis of sarcoidosis with conventional TBNA, trans-esophageal ultrasound-guided biopsy [34 - 40], and EBUS-TBNA [41,42]; however, the validity of the diagnostic criteria has not been defined.

Epithelioid-cell clusters suggesting the presence of granulomas are defined by variably-sized loose collections of non-pigmented epithelioid or spindle-cell histiocytes that are usually accompanied by lymphocytes [31]. Typical cytological findings are shown in Figures 7 to 10, together with their corresponding histological findings obtained from the same aspiration. The validity of cytological evaluation in the diagnosis of sarcoidosis, however, was not well-defined. To elucidate the diagnostic validity of epithelioid-cell clusters on cytological examination, we performed a study in which cytological samples from 72 patients with sarcoidosis and 116 control patients with malignant lung diseases mainly of primary lung cancer (with lymphadenopathy eventually proven to be metastasis free) were evaluated independently by 2 cytoscreeners and a pathologist, all blinded to patient information. The results included excellent inter-observer variability and a high specificity of 94.0%, indicating validity of cytological diagnosis of sarcoidosis [29]. Our study also uncovered a very high rate (87.5% or 63/72) of pathological proof of epithelioid-cell granulomas when cytological and histological evaluations with EBUS-TBNA-obtained materials were combined. Validity of cytological diagnosis of sarcoidosis might be applicable to other organs.

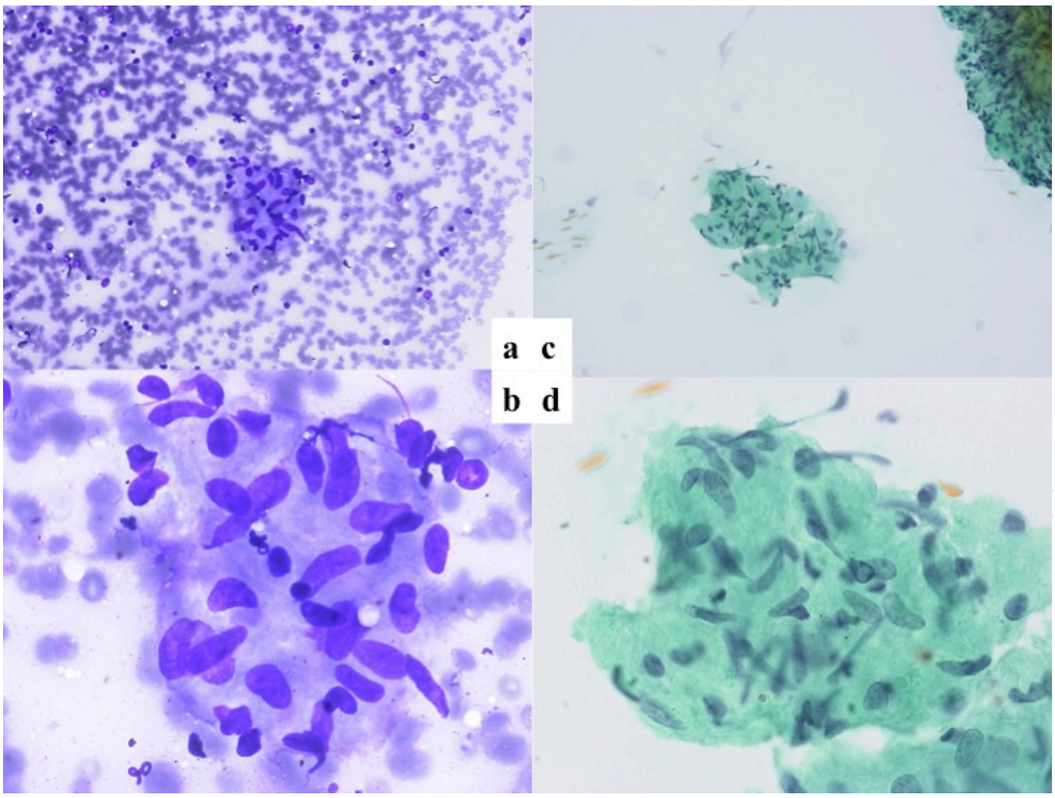

Figure 7. Typical epithelioid-cell clusters in a cytological specimen, with Diff-Quik staining (a and b) and Papanicolaou staining (c and d). They were obtained from the same lymph node in a patient with sarcoidosis. The original magnifications were ×100 (a and c) and ×400 (b and d).

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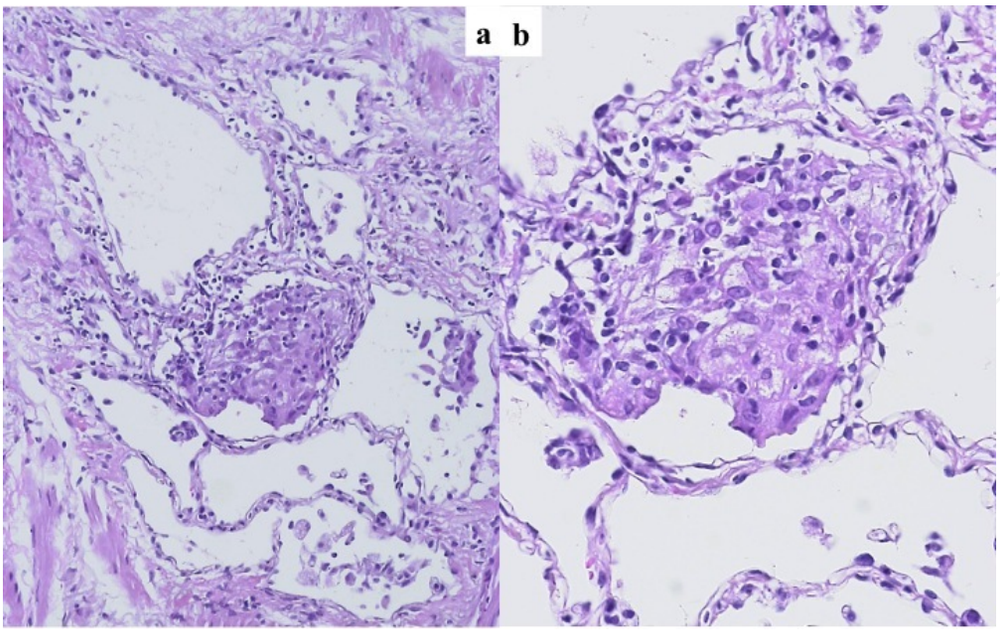

Figure 8. Histological findings of a histological core obtained from the same patient whose cytological findings are shown in Figure 7. Histological findings characteristic of a non-caseating epithelioid-cell granuloma are shown (H-E stain; original magnification of ×100 in a and ×200 in b).

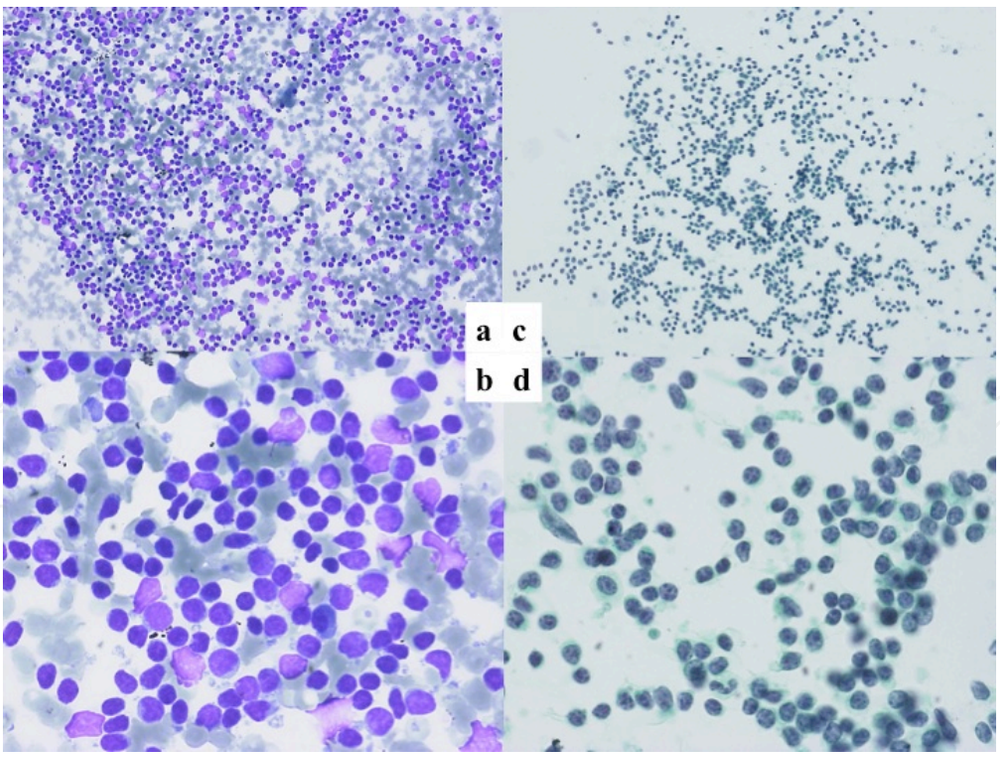

Figure 9. Normal lymph node findings shown in a cytological specimen, with Diff-Quik staining (a and b) and Papanicolaou staining (c and d). They were obtained from the same lymph node in a control patient. The original magnification were ×100 (a and c) and ×400 (b and d).

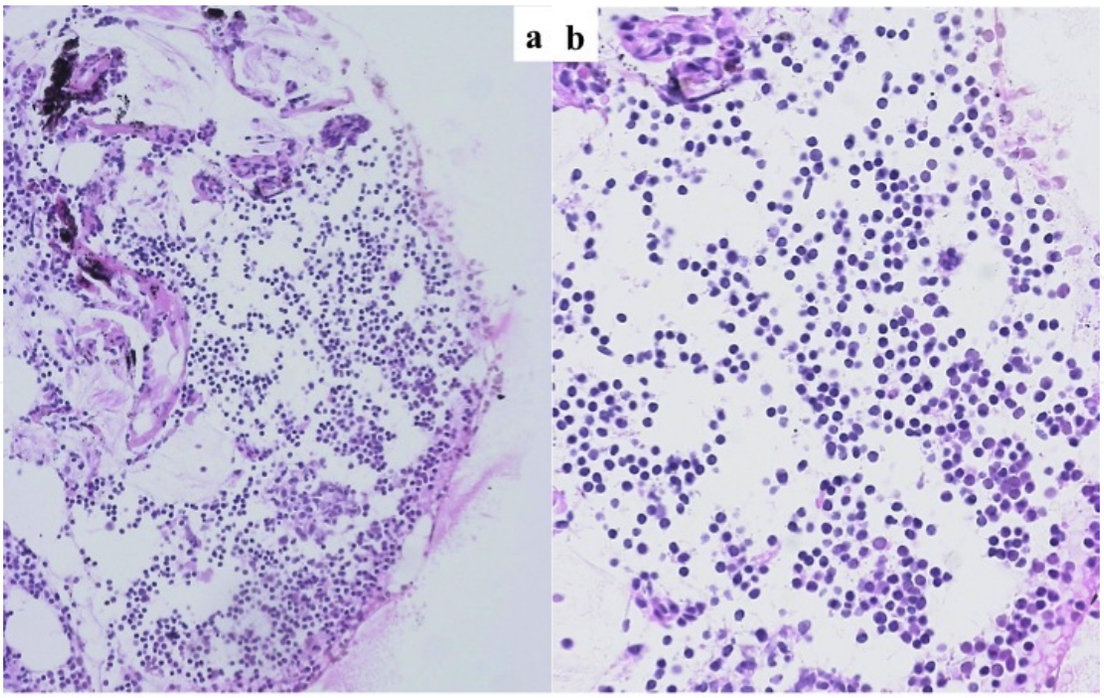

Figure 10. Histological findings of a histological core obtained from the same patient whose cytological findings are shown in Figure 9. Although the structure has partially disintegrated probably because of tissue damage inside the aspiration needle, normal lymph node architecture is observed without evidence of epithelioid-cell granuloma or malignant cells (H-E stain; original magnification of ×100 in a and ×200 in b).

6. Epithelioid-cell granulomas in lymphadenopathy with lung cancer

Non-caseating epithelioid-cell granulomas may be seen in draining lymph nodes in various malignant diseases. These relatively uncommon histological findings, which are not systemic sarcoidosis, have been termed sarcoid reactions [43]. Sarcoid reactions are also seen in lung malignancy with a reported incidence of 1.2–4.3% [44- 46]. This value was 6.0% in our study [29], that is, cytological evaluation of the EBUS-TBNA samples revealed epithelioid-cell clusters in lymph nodes from 7 patients out of the 116 patients with primary lung cancer whose lymphadenopathy was eventually proven to be metastasis free. Sarcoid reactions probably reflect an immune response to tumor antigens due to T-cell mediated immune responses [47]. The tumor antigens are thought to be carried by lymphatic vessels to the draining lymph nodes, causing sarcoid reactions in situ [43]. Although uncommon, it is very important that this is considered in the pathological diagnosis of sarcoidosis. There is no report on differentiating sarcoidosis from sarcoid reactions on the basis of histological and/or cytological findings. Clinical differentiation of sarcoid reaction from sarcoidosis, however, may not be difficult because of the presence of primary lesion and asymmetric distribution of the hilar/mediastinum lymphadenopathy. Nevertheless, it should be stressed that sarcoid reaction potentially misleads N staging of the lung cancer.

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7. Future directions

As discussed in the above sections, EBUS-TBNA results in a very high rate (>80%) of pathological proof of sarcoidosis provided enlarged hilar/mediastinal lymph nodes are accessible. The technique has been reported to be very safe because target lymph nodes and surrounding vessels are easily visualized with ultrasound images. In contrast, the sensitivity of TBLB of pulmonary parenchymal lesions is reportedly much lower than that with EBUS-TBNA. In fact, it was 34.5% (or 20/58) in our study [29], where only 58 patients out of the 72 patients with sarcoidosis were evaluated with TBLB because of absent pulmonary lesions in the imaging studies and/or possible complications. TBLB is potentially invasive; consequently, the procedure may be complicated with massive bleeding or pneumothorax. These possible complications may justify avoiding TBLB in the diagnosis of sarcoidosis when EBUS-TBNA is available. Excluding certain conditions where proof of pulmonary parenchymal lesions is required, prioritizing EBUS-TBNA over TBLB would be reasonable. Advances in this new technology might change the diagnostic practices in sarcoidosis.

In addition, easier access to involved lymph nodes with EBUS-TBNA may provide new opportunities to obtain biomarkers for elucidating pathogenesis of the disease. In fact, Nakajima et al. [48] and Sakairi et al. [49] were successful with this technique in detecting various gene mutations in patients with lung cancer. Similar advances with the same technique in the field of sarcoidosis and other granulomatous diseases would be realistic. We anticipate that sarcoidosis, an unpleasant refractory disease, will be conquered by applied investigation and personalized care in the future.

Author details

Atsushi Kitamura[1,2] and Yuichi Takiguchi[1]

*Address all correspondence to: takiguchi@faculty.chiba-u.jp

1 Department of Medical Oncology, Graduate School of Medicine, Chiba University, Japan

2 Department of Respiratory Medicine, St. Luke's International Hospital, Japan

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