



## Case report

## The combination of EBUS-TBNA and the PAB antibody led to a successful treatment for lung cancer in a patient with asymptomatic sarcoidosis mimicking nodal metastasis

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## ABSTRACT

Correct staging of lung cancer is important for the selection of the best therapy, but discriminating between lymphadenopathy from lung cancer and from sarcoidosis by imaging examinations is difficult. Additionally, distinguishing lymphadenopathy of sarcoidosis from sarcoid reactions which are sometimes caused by lung cancer is difficult on imaging and pathological findings. A 73-year-old woman was diagnosed as lung cancer clinical T1bN3M0 stage IIIB based on false-positive <sup>18</sup>F-fluoro-2-deoxyglucose positron emission tomography uptake. Because the effects of chemotherapy were different between the lymphadenopathy and the primary lesion, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed and revealed sarcoidosis as the cause of the lymphadenopathy with using a specific monoclonal antibody against *Propionibacterium acnes* (PAB antibody). Accordingly, the stage was changed to clinical T1bN0M0 stage IA, for which radical operation was performed. EBUS-TBNA should be performed aggressively when the effect of chemotherapy is different between lymphadenopathies and other lesions, and the PAB antibody can help to discriminate between sarcoidosis and sarcoid reactions caused by lung cancer. The combination of EBUS-TBNA and the PAB antibody is expected to be valuable in the definitive diagnosis of a lymphadenopathy for the staging of lung cancer.

## 1. Introduction

Treatment strategy for lung cancer depends on the staging; assessment of lymph node (LN) metastasis is crucial in patients with lung cancer. Sarcoidosis is reported to occasionally complicate lung cancer [1,2], but discriminating between LN metastasis from lung cancer and lymphadenopathy from sarcoidosis by imaging examinations is difficult. Additionally, distinguishing lymphadenopathy of sarcoidosis from sarcoid reactions which are sometimes caused by lung cancer is difficult on imaging and pathological findings [3]. We report a case of lung cancer with sarcoidosis, wherein LN biopsy using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) dramatically changed the treatment strategy and revealed sarcoidosis as the cause of the lymphadenopathy with using a specific monoclonal

antibody against *Propionibacterium acnes* (PAB antibody).

## 2. Case report

A 73-year-old woman presented with a chest X-ray finding of right lower lung field nodule, which was diagnosed by transbronchial lung biopsy (TBLB) as adenocarcinoma harboring epidermal growth factor receptor exon21 L858R. <sup>18</sup>F-fluoro-2-deoxyglucose positron emission tomography (<sup>18</sup>FDG-PET) showed uptake in the nodule and the multiple mediastinal and hilar LNs. Cancer stage was determined as clinical T1bN3M0 stage IIIB at another hospital. After a month of taking gefitinib (250 mg) daily, chest computed tomography (CT) showed a dramatic decrease in the size of the primary lesion from 20 to 10 mm, but the lymphadenopathy persisted (Fig. 1A–D). Because the treatment

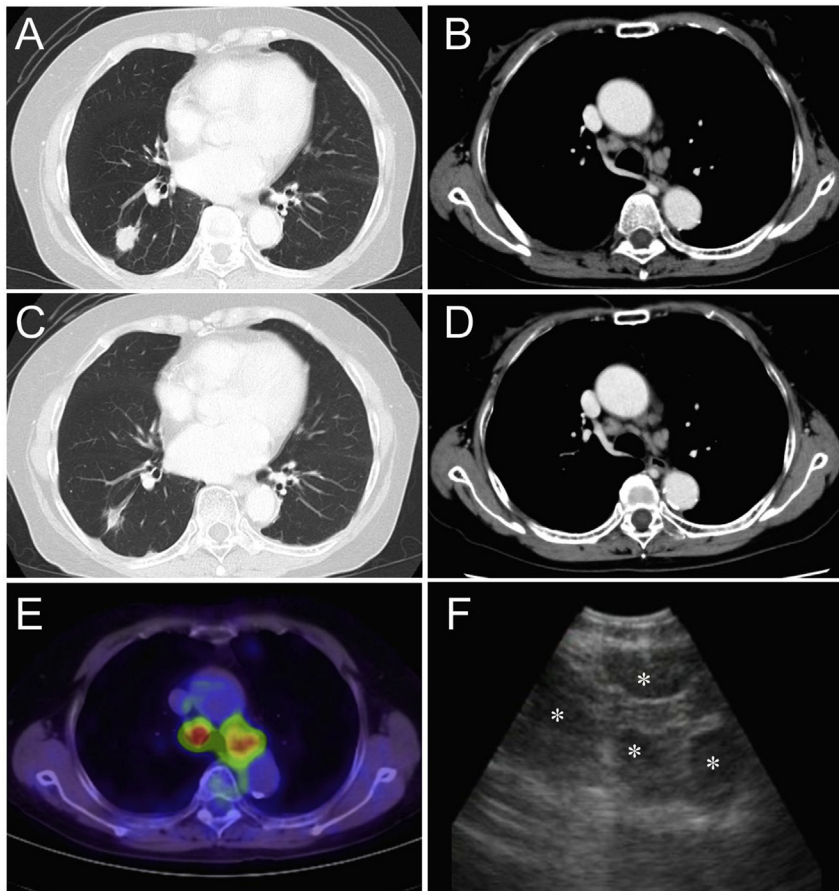
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**Fig. 1.** CT (computed tomography) scan of chest and EBUS (endobronchial ultrasound) findings. (A, B) Contrast-enhanced chest CT (computed tomography) shows a 20 mm irregularly shaped peripheral nodule in the right lower lobe and several bilateral mediastinal lymph nodes. (C, D) After treatment with gefitinib for 1 month, the primary lesion is smaller in size at 10 mm, but the lymphadenopathies remain unchanged. (E) On PET (positron emission tomography), the lymph nodes have high FDG ( $^{18}\text{F}$ -fluoro-2-deoxyglucose) uptake, with SUV max (maximum standardized uptake value) of 6.7. (F) EBUS (endobronchial ultrasound) shows several enlarged, homogeneous lymph nodes (asterisk) without coalescent or aberrant vessels in stations 4L and 4R.

effect differed between the lymphadenopathy and primary lesion, she was admitted to our hospital for definitive LN diagnosis by EBUS-TBNA.

Physical examination on admission showed normal breath sounds and no superficial lymphadenopathy. Laboratory examinations showed the following: CEA, 4.3 ng/mL; SLX, 36 U/mL; soluble IL-2 receptor, 349 U/mL; angiotensin-converting enzyme, 14.6 U/mL; and Ca, 9.2 mg/dL. Chest X-ray and contrast-enhanced CT showed an irregularly shaped peripheral nodule in the right lower lobe and several bilateral mediastinal LNs with high FDG uptake on PET (Fig. 1E).

During EBUS-TBNA, the EBUS images showed homogeneous echogenicity and straight vessels in the LNs (Fig. 1F). Two samples were individually obtained from stations 4L and 4R by EBUS-TBNA. The pathological findings showed several non-caseating epithelioid granulomas, without tumor cells (Fig. 2A). Moreover, the PAB antibody detected small round bodies in the LNs (Fig. 2B), indicating that the lymphadenopathy was caused by sarcoidosis, not sarcoid reaction. Therefore, her stage was changed to clinical T1bN0M0 stage IA.

Following the discontinuation of the gefitinib course, right lower lobectomy and regional lymphadenectomy were immediately performed (Fig. 2C). Intraoperative findings showed non-coalescent and flat mediastinal LNs, showing the same pathological findings as those of the EBUS-TBNA LN samples. The final pathologic diagnosis was stage IA lung adenocarcinoma with sarcoidosis of the mediastinal LNs (Fig. 2D–F). There were no findings suggestive of sarcoidosis in the eyes, lung parenchyma, heart, skin, etc. The patient was followed up post operation for several years.

### 3. Discussion

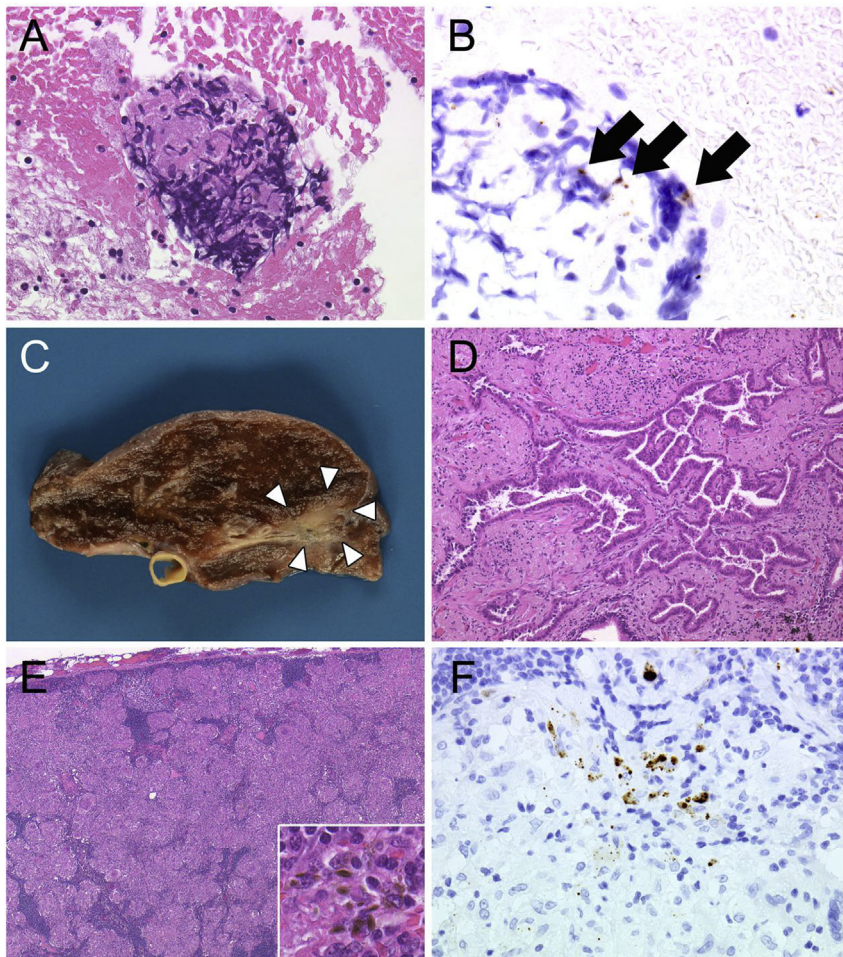
In this case, a false-positive  $^{18}\text{F}$ FDG-PET uptake on initial assessment mistakenly staged a lung cancer patient as having nodal metastasis. However, instead, EBUS-TBNA revealed a diagnosis of concomitant

mediastinal LN sarcoidosis with using the PAB antibody, which led to restaging that rendered the lung adenocarcinoma operable.

Patients with sarcoidosis were previously reported to develop lung cancer 2–3 times more frequently than patients without sarcoidosis [1,2]; although this observation remains controversial [4], we sometimes encounter such cases. Lung cancer and sarcoidosis can present with mediastinal and hilar lymphadenopathy, but distinguishing between them is difficult with using CT, although with FDG-PET [5]. Conversely, EBUS-TBNA can help in discriminating between lung cancer and sarcoidosis, as demonstrated herein. Indeed, EBUS-TBNA was previously reported to be valuable for the diagnosis of sarcoidosis (diagnostic accuracy = 91.4%) [6]. Moreover, EBUS-TBNA is reported to have a higher diagnostic accuracy (98%) for LN metastasis from lung cancer [7].

Selecting the most effective treatment for lung cancer is based on the clinical stage. Particularly, the lung cancer treatment guidelines recommended against curative resection for patients with N3 [8]; therefore, the presence of nodal metastasis is an important factor to guide treatment decisions. Accordingly, the treatment strategy can change based on staging using EBUS-TBNA. Moreover, EBUS-TBNA can help when the effect of chemotherapy is different between the lymphadenopathy and other lesions. Therefore, in such patients (our case), EBUS-TBNA should immediately be performed.

The lymphadenopathy of lung cancer is caused by metastasis and sarcoid reactions, tumor-related tissue reactions that can lead to the formation of non-caseating epithelioid granulomas in the LNs of a malignant tumor, the tumor itself, and non-regional tissues [9]. The frequency of sarcoid reactions in patients with lung cancer was reported in the range of 1.3%–3.2% [10–12]. The formation of epithelioid granulomas is speculated to be caused by an immunologic hypersensitivity reaction that is elicited by antigenic factors from the tumor cells [9]. Distinguishing lymphadenopathy of sarcoidosis from sarcoid



**Fig. 2.** Specimen detail from EBUS-TBNA (endobronchial ultrasound-guided transbronchial needle aspiration) and operation. (A) Photomicrographs of the EBUS-TBNA (endobronchial ultrasound-guided transbronchial needle aspiration) lymph node specimens show tiny crushed tissue fragments with incorporated spindle cells, which histologically imply epithelioid cell granuloma. (B) Small round bodies are detected by PAB antibody (a specific monoclonal antibody against *Propionibacterium acnes*), which imply immunopositivity for *Propionibacterium acnes*. (C) Gross examination of the cut surface of the resected lung shows a light brown-colored tumor (white arrowheads). (D) The tumor is histologically diagnosed as papillary adenocarcinoma surrounded by marked fibrosis that suggested a therapeutic effect for cancer. (E) Histologic examination of the simultaneously dissected lymph nodes shows abundant non-caseous epithelioid cell granulomas with Langerhans-type giant cells and several Hamazaki–Wesenberg bodies (inset), but there is no fibrosis or foamy macrophages, both of which histologically indicated the therapeutic effect. (F) The lymph nodes contain small round bodies detected by the PAB antibody.

reactions is difficult on imaging and pathological findings [13]; however, this distinguishing is possible with the PAB monoclonal antibody, which is specific for *P. acnes*. *P. acnes* detections at the lesion site of sarcoidosis are reported [14], and the pathogenic mechanism of sarcoidosis was inferred to be related to an allergic immunoreaction to *P. acnes* [15]. Therefore, the PAB antibody is useful in detecting *P. acnes*; remarkably, positive reaction products were observed in 88% of cases with lymphadenopathy of sarcoidosis but not in cases with sarcoid reactions and tuberculous lymphadenitis [3]. Accordingly, as demonstrated in this case, the use of the PAB antibody can diagnose concomitant sarcoidosis in lung cancer patients and allow the choice of an adequate treatment to improve the prognosis.

The presence of small round bodies detected by the PAB antibody is previously reported in lung samples obtained by video-assisted thoracic surgery (74%) and TBLB (48%) [3]. However, its use for EBUS-TBNA LN samples remains unclear. In our case, small round bodies were observed in the LN samples obtained by EBUS-TBNA. Therefore, in patients with lung cancer complicated by sarcoidosis who are inoperable, the combination of EBUS-TBNA and the PAB antibody can provide the diagnosis and stage and distinguish between sarcoidosis and sarcoid reactions.

In conclusion, this case demonstrated the potential use of EBUS-TBNA when the effect of chemotherapy is different between a lymphadenopathy and other lesions. In samples that reveal the presence of non-caseating epithelioid granulomas, the PAB antibody can help to discriminate between sarcoidosis and a sarcoid reaction. Accordingly, the combination of EBUS-TBNA and the PAB antibody is expected to be valuable in the definitive diagnosis of a lymphadenopathy for the staging of lung cancer.

#### Conflict of interest

The authors declare no conflicts of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2018.10.014>.

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