Usefulness of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration in Distinguishing Sarcoidosis from Recurrent Cancer in Patients with Lymphadenopathy after Surgery

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Objective: Endobronchial ultrasound-guided transbronchial needle aspiration is a new minimal-invasive test for investigating mediastinal and hilar lymphadenopathy. It is sometimes difficult to distinguish between a recurrent malignant lymph node and lymphadenopathy due to sarcoidosis in patients who develop lymphadenopathy after surgery for a malignant tumor.

Methods: Between December 2009 and October 2012, we performed endobronchial ultrasound-guided transbronchial needle aspiration in 13 selected patients with a suspected recurrence in the mediastinum and/or hilum of the lung after surgical resection of a malignant tumor. We examined their medical records to obtain information on the diagnosis, the sizes of lymph nodes, the number of needle passes and other complications.

Results: Definitive diagnoses were made using endobronchial ultrasound-guided transbronchial needle aspiration in 10 patients (three lung adenocarcinomas, one prostate carcinoma, one renal cell carcinoma, one neuroendocrine tumor and four sarcoidosis). Pathological specimens showing non-caseating granulomas led to the diagnosis of sarcoidosis in four patients; their previous malignancies had been papillary adenocarcinoma of the thyroid, carcinoma of the gingiva, thymoma and bladder cancer, but no recurrences were observed. The median of the longest diameter in 15 lymph nodes was 22 mm (range 13–35), and the median number of needle passes was two times (range 1–5) without severe complications.

Conclusions: Endobronchial ultrasound-guided transbronchial needle aspiration might be useful in differentiating between benign lymphadenopathy, including sarcoidosis, and cancer recurrence in patients with mediastinal or hilar lymphadenopathy after surgical resection of a malignant tumor.

Key words: endobronchial ultrasound-guided transbronchial needle aspiration, sarcoidosis, mediastinal and hilar lymphadenopathy, lymph node metastasis

INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) allows real-time assessment and biopsy of mediastinal and hilar lymph nodes and therefore often obviates the need for mediastinoscopy (1,2). In fact, EBUS-TBNA appears to be at least as effective as mediastinoscopy for mediastinal staging of non-small-cell lung cancer and has a lower rate of complications, making it the initial procedure of choice at many institutions (3). The ability of EBUS-TBNA to identify granuloma in the work-up of patients with suspected...
sarcoidosis has been reported recently (4). Other reports indicate that EBUS-TBNA is highly efficacious and safe in helping to make a sarcoidosis diagnosis (5). Sarcoidosis is a multi-system disorder of unknown etiology that is characterized based on the clinicoradiological findings and histological evidence of non-caseating epithelioid cell granulomas (6). In this study, we report on four patients with suspected cancer-related lymphadenopathy who were diagnosed with sarcoidosis using EBUS-TBNA.

PATIENTS AND METHODS

Patients
We reviewed EBUS-TBNA cases performed at Okayama University Hospital between December 2009 and October 2012. We selected 13 patients with a suspected recurrence in the mediastinum and/or hilum of the lung after surgical resection of a malignant tumor. Both chest radiography and computerized tomography (CT) prior to a bronchoscopic examination revealed at least one enlarged mediastinal or hilar lymph node with a long axis > 10 mm in all patients. The diagnostic criteria for sarcoidosis were based on the American Thoracic Society consensus panel report (7). The study was approved by the Institutional Ethics Committee of Okayama University Hospital (No. 1641).

Procedures
All bronchoscopic procedures were performed on an inpatient basis under local anesthesia with mild conscious sedation. Intramuscular injection of hydroxyzine pamoate (25 mg) and atropine (0.25 mg) was used as pretreatment. Five milliliters of 2% lidocaine were sprayed into the pharynx, and 5 ml of 2% lidocaine was administered through a cannula during the procedures. The patients were monitored by electrocardiography, pulse oximetry and blood pressure readings without the presence of an anesthesiologist. The bronchoscope was inserted orally during midazolam-induced conscious sedation. A conventional flexible bronchoscope (BF-260 bronchovideoscope; Olympus, Tokyo, Japan) was used, and intubation was achieved using a siliconized, uncuffed tracheal tube with an inside diameter of 7.5 mm (Portex; Smiths Medical, St. Paul, MN, USA). Following conventional bronchoscopy, EBUS-TBNA was performed using an endobronchial ultrasound bronchoscope with a convex probe (BF-UC260F-OL8; Olympus).

RESULTS

Eight males and five females (median age, 65 years; range 51–80 years) were included, and 15 lymph nodes were recorded and aspirated. The mean length of the long axis of the enlarged lymph nodes was 22 mm (range 13–35 mm) as measured by CT imaging. Fourteen enlarged lymph nodes were located in the mediastinal region, and one lymph node was found in the hilum of the lung. The most common lymph node station was the subcarinal station 7 (9/15, 60%). The median number of needle passes was two (range 1–4), without severe complications. Definitive diagnoses were made using EBUS-TBNA in 10 patients (three lung adenocarcinoma, one prostate carcinoma, one renal cell carcinoma, one neuroendocrine tumor and four sarcoidosis), and no pathological diagnosis was made in three patients (Table 1).

Pathological specimens showing non-caseating granulomas led to a sarcoidosis diagnosis in four patients. Lymphadenopathy was identified by closely evaluating chest radiographs or CT scans. Although the patients had histories of papillary adenocarcinoma of the thyroid, carcinoma of the gingiva, thymoma and bladder cancer, no recurrences or second malignancies were found during the follow-up. Data for the patients with sarcoidosis are summarized in Table 2. Serum levels of soluble interleukin-2 receptor were within the normal limits (<500 U/ml) or slightly elevated, and the interferon-gamma release assay (QuantiFERON®-TB Gold: QFT) results were negative. Other granulomatous diseases were excluded by reviewing patient’s history and the microbiological results. All patients had stage I disease according to the chest radiographic staging (7), with no other organ involvement. The four cases are described as follows.

Case 1
A 53-year-old woman who had undergone a thyroidectomy for papillary adenocarcinoma of the thyroid showed mediastinal and bilateral hilar lymphadenopathy on chest CT (Fig. 1A) and positron emission tomography (PET) (Fig. 1B) performed 7 years after surgery. The specimen obtained by EBUS-TBNA (Fig. 1C) revealed non-caseating granulomas (Fig. 1D). The lymphadenopathy regressed during 29 months after the diagnosis.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
</tr>
<tr>
<td>Male/female ratio, n</td>
<td>8/5</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>65 (51–80)</td>
</tr>
<tr>
<td>Enlarged lymph node stations (4R/4L/#7/#11), n</td>
<td>3/2/9/1</td>
</tr>
<tr>
<td>Longest diameter in the lymph node (range), mm</td>
<td>22 (13–35)</td>
</tr>
<tr>
<td>Diagnosis by EBUS-TBNA, n</td>
<td></td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>4</td>
</tr>
<tr>
<td>Indefinite</td>
<td>3</td>
</tr>
</tbody>
</table>

4L, left lower paratracheal node; 4R, right lower paratracheal node; #7, subcarinal nodes; #11, N1 nodes; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.
CASE 2

A 60-year-old woman had undergone a gingivectomy for carcinoma of the gingiva 13 years ago. She had mediastinal and bilateral hilar lymphadenopathy on chest CT (Fig. 2A) and PET (Fig. 2B). Non-caseating granulomas (Fig. 2C) were observed in the specimen obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) revealed non-caseating granulomas. (D) Hematoxylin–eosin staining, ×200.

The lymphadenopathy improved over 26 months.

CASE 3

A 62-year-old man who had undergone an extended thymectomy for thymoma 7 months previously showed mediastinal and bilateral hilar lymphadenopathy on chest CT and PET (Fig. 2B). Non-caseating granulomas (Fig. 2C) were observed in the specimen obtained by EBUS-TBNA (Fig. 2D). The lymphadenopathy decreased during the subsequent 20 months.

CASE 4

A 77-year-old woman who had undergone a total cystectomy for bladder cancer had mediastinal and bilateral hilar lymphadenopathy on chest CT and PET performed 2 years

Table 2. Patients with sarcoidosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Previous malignancy (disease stage)/interval between malignancy and sarcoidosis</th>
<th>Serum level of interleukin-2 receptor/interferon-gamma release assay result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/F</td>
<td>Papillary adenocarcinoma of the thyroid (Stage I)/7 years</td>
<td>379 U per ml/Negative</td>
</tr>
<tr>
<td>2</td>
<td>60/F</td>
<td>Carcinoma of the gingiva (Stage IV)/13 years</td>
<td>368 U per ml/Negative</td>
</tr>
<tr>
<td>3</td>
<td>62/M</td>
<td>Thymoma (Stage II)/7 months</td>
<td>368 U per ml/Negative</td>
</tr>
<tr>
<td>4</td>
<td>77/F</td>
<td>Bladder cancer (Stage III)/2 years</td>
<td>680 U per ml/Negative</td>
</tr>
</tbody>
</table>

F, Female; M, Male.

Figure 1. A patient with papillary adenocarcinoma of the thyroid had mediastinal and bilateral hilar lymphadenopathy on chest computed tomography (CT) (A) and positron emission tomography (PET) (B) scans 7 years after surgery. (C) The specimen obtained by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) revealed non-caseating granulomas. (D) Hematoxylin–eosin staining, ×200.
postoperatively. EBUS revealed an enlarged #7 lymph node. The biopsy specimen revealed the presence of non-caseating granulomas. The lymphadenopathy remained unchanged radiographically for 8 months.

DISCUSSION

EBUS-TBNA has emerged as an accurate, minimally invasive and safe technique for assessing undiagnosed mediastinal and hilar lymphadenopathy. Samples can be imaged and directly visualized, resulting in a high diagnostic yield (2,8). The present study demonstrated that EBUS-TBNA for mediastinal and/or hilar lymphadenopathy was useful in distinguishing between a recurrent malignant lymph node and lymphadenopathy due to sarcoidosis.

Sarcoidosis is a multi-system disorder of unknown etiology, and some patients with sarcoidosis develop cardiac or neurological dysfunctions. About 1–5% of patients with chronic sarcoidosis die of respiratory failure or cardiac or neurological dysfunction (7). Although systemic steroid therapy is considered in cases of progressive disease, pathological confirmation of sarcoidosis is required to exclude other possible diseases. In the present study, sarcoidosis diagnoses were established based on the clinical and radiological findings and were confirmed by histological evidence of non-caseating granulomas (7). An association between cancer and granulomatous inflammation exists, but its cause remains unclear (9–11). Sarcoidosis has long been speculated to be a local immune response to a neoplasm (12). In other reports, non-caseating granulomas were caused by chemical exposure, infections, foreign bodies and granulomatous diseases (13,14). During follow-up in our patients, we found no evidence that the non-caseating granulomas were caused by an infection or a sarcoid-like reaction induced by cancer recurrence/second malignancy.

We described four patients with sarcoidosis who were diagnosed by EBUS-TBNA after surgical resection of a malignant tumor. Although only four cases were evaluated, this report highlights the clinical importance of pathologically confirming a diagnosis of mediastinal or hilar lymphadenopathy after curative treatment of cancer, in order to avoid unnecessary chemotherapy or radiotherapy for a presumed tumor recurrence. EBUS-TBNA might be a valuable tool for diagnosing cases such as those described here.

This study has a major limitation. Confirmation of the results in a large-scale prospective trial based on the clinical practice is needed because the small sample size is not suitable for statistical analysis calculating sensitivity or specificity.

In conclusion, EBUS-TBNA might be useful in differentiating between benign lymphadenopathy, including sarcoidosis, and cancer recurrence in patients with mediastinal or hilar
lymphadenopathy after surgical resection of a malignant tumor.

Conflict of interest
None declared.

References