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Successful diagnosis of synchronous primary cancer of the lung and esophagus by endobronchial ultrasound-guided transbronchial

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► ***Case report***

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ABSTRACT

Multiple primary cancers of the esophagus and lung were mostly reported in individual cases. Most patients visited a doctor because of dysphagia or respiratory symptoms. Chest CT can determine the location of lesions but cannot clearly determine the nature of lesions. Definite diagnosis needs bronchoscopy combined with gastroscopy, lung biopsy combined with gastroscopy or surgical operation to obtain pathological tissue. Recently, we confirmed a case of multiple primary cancer of the esophagus and lung by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and shared the diagnosis and treatment process. The advantages of this technique are that endobronchial ultrasound can determine the nature of mediastinal and hilar lesions, and needle aspiration biopsy is characterized by minimal invasion and repeatable biopsy, thus providing pathological diagnosis, especially for multiple primary cancers, that avoids misdiagnosis or missed diagnosis.

Keywords: *Synchronous primary cancer, endobronchial ultrasound-guided transbronchial needle aspiration.*

INTRODUCTION

Multiple primary cancers (MPC) are usually defined as primary malignant tumors of different histological origins in one person. With the increased survival of cancer patients, the growth in life expectancy, and the development of improved diagnostic techniques, the number of patients with MPC is progressively increasing [(1)]. Primary cancers of the lung and esophagus are an unusual type of MPC. There are only a few case reports analyzing the pathogenesis, clinical features, and prognosis of patients with MPC diagnosed by bronchoscope combined with gastroscopic biopsy or surgical biopsy. Being a simple, safe, and repeatable method, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is becoming increasingly popular in the diagnosis of lung cancer and unexplained mediastinal and hilar lymphadenopathy [(2,3)]. In this paper, we report the successful diagnostic utility of EBUS-TBNA for multiple primary malignancies.

Ethics statement

This research was approved by the research ethics committees of the Affiliated Hospital of Jining Medical University. The patient was approached in accordance with approved ethical guidelines. We state that all methods in the study were performed in accordance with the relevant guidelines and regulations developed by the aforementioned ethics committees.

CASE REPORT

The patient (male; 51 years old; farmer)

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transferred from a local town hospital to our hospital due to cough and chest pain for more than 3 months. Before admission, the patient presented with cough, expectoration and prickling-like chest pain on the right side without obvious causes, accompanied by intermittent bloody sputum over 3 months ago. Recently, the patient showed poor appetite with no eating difficulties. The patient visited the Outpatient Department in our hospital, and chest CT demonstrated irregular soft-tissue shadow in the posterior mediastinum, multiple enlarged lymph nodes in the mediastinum and right pulmonary hilum, and multiple nodules in both lungs. Then, the patient was admitted because of mediastinal space-occupying lesions with unclear nature (suspected lung cancer or esophageal cancer). The patient had a smoking history of more than 30 years with 40 cigarettes/day, and a drinking history of more than 30 years with 500 g/day. After admission, chest enhanced CT examination was carried out (Somatom Definition Flash from SIEMENS, Germany, figures 1-2), and mediastinal lung cancer combined with lymph node metastasis or esophageal cancer combined with lymph node metastasis was preliminarily diagnosed. Bronchoscopy and esophagoscopy were suggested as well. Electronic bronchoscopy under moderate sedation showed carinal widening, mild stenosis of the left main bronchus and no obvious new organisms in the lumen. EBUS revealed lymph node enlargement, unclear hilum of lymph nodes and medullary structures and heterogeneous echoes at 4R/11R and irregular masses and enlarged lymph nodes below the carina. TBNA was then conducted (BF-UC260 from OLYMPUS, Japan, figures 3-5), which collected tissue samples from each area. The results of the pathological examination showed that station 4R needle aspiration biopsy showed small-cell lung cancer with necrosis (figure 6). Immunohistochemistry showed CAM5.2(+), CD56(+), CK(+), LCA(-), Ki-67 (+, 30%-40%), Syn (+), and TTF-1(+). Station 11R needle aspiration biopsy also showed small-cell lung cancer (figure 7). Immunohistochemistry showed CAM5.2(+), CK(+), and LCA(-). Mediastinal mass below the carina needle aspiration biopsy was squamous cell carcinoma (figure 8). Immunohistochemistry showed CD56 (-), P63(+), and TTF-1(-). A diagnosis of synchronous MPC was made according to the criteria of Warren and Gate [4]. Then, the endoscopic biopsy specimens showed esophageal squamous cell carcinoma (figure 9).

After multidisciplinary consultation and discussion, the patient was diagnosed with esophageal squamous cell carcinoma, small cell lung cancer and mediastinal lymph node metastasis. After excluding contraindications, the patient was treated with chemotherapy for 6 cycles, with specific medication including paclitaxel (240 mg, d 1) and DDP (30 mg, d 2-5). During the treatment, conditions were assessed as stable, and the patient abandoned further treatment.

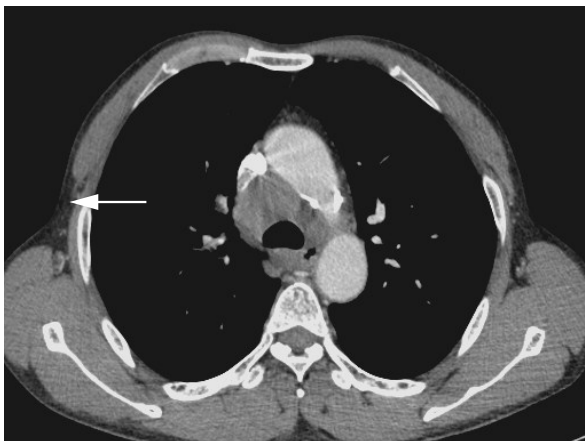


Figure 1. CT shows right lower paratracheal lymph node enlargement (station 4R, white arrow).

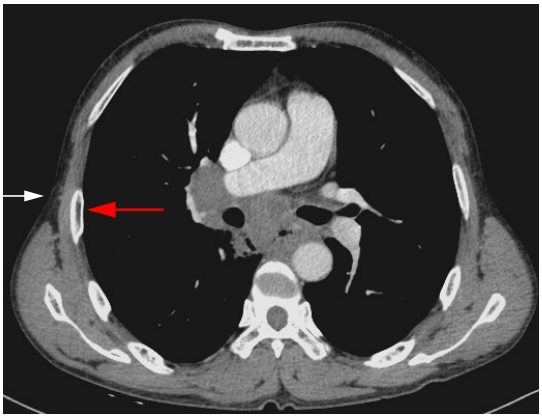


Figure 2. CT shows right hilar lymph node enlargement (station 11R, white arrow), subcarinal irregular soft-tissue shadow, enlarged lymph node, and the boundary was unclear (red arrow).

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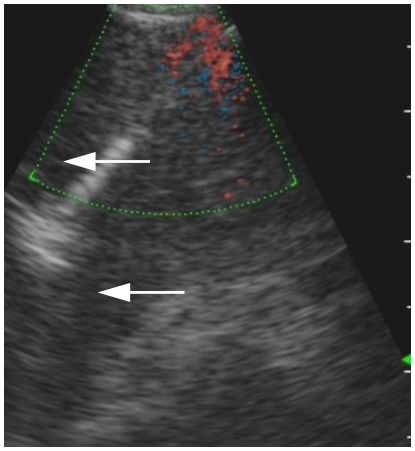


Figure 3. Endobronchial ultrasound (EBUS) shows lymph node enlargement, unclear hilum of lymph nodes and medullary structures and heterogeneous echoes (station 11 R, white arrow) during needle aspiration (red arrow).

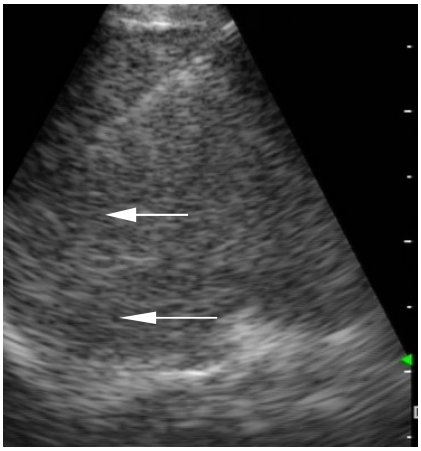


Figure 4. Endobronchial ultrasound (EBUS) shows lymph node enlargement, unclear hilum of lymph nodes and medullary structures and heterogeneous echoes (station 4 R, white arrow) during needle aspiration (red arrow).

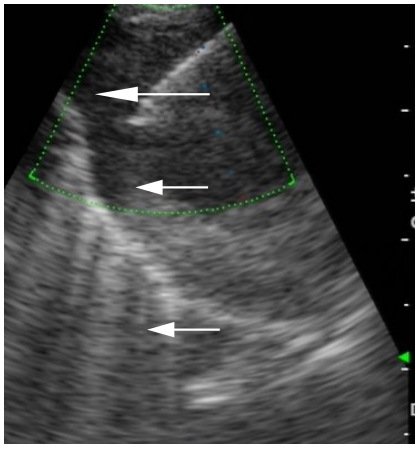


Figure 5. Endobronchial ultrasound (EBUS) shows subcarinal irregular masses and enlarged lymph nodes (white arrow) during needle aspiration (red arrow).

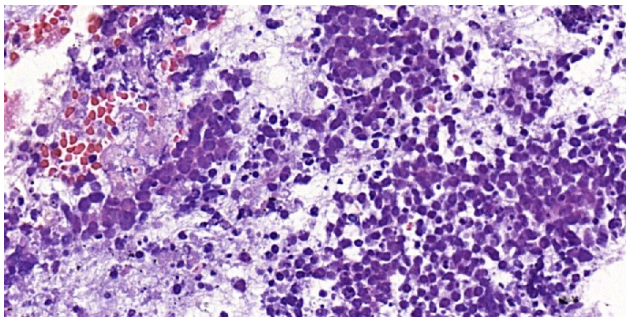


Figure 6. Station 4R: Pathological findings show small-cell lung cancer (H & E staining ×400, black arrow).

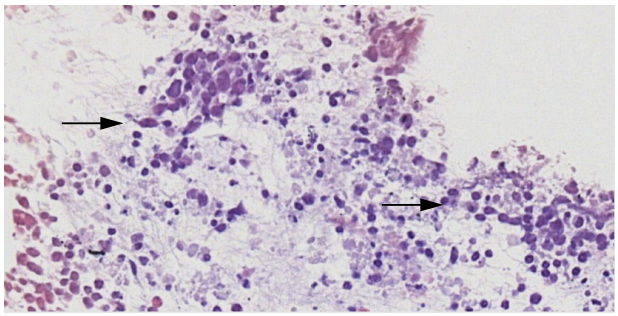


Figure 7. Station 11R: Pathological findings shows small-cell lung cancer (H & E staining ×400, black arrow).

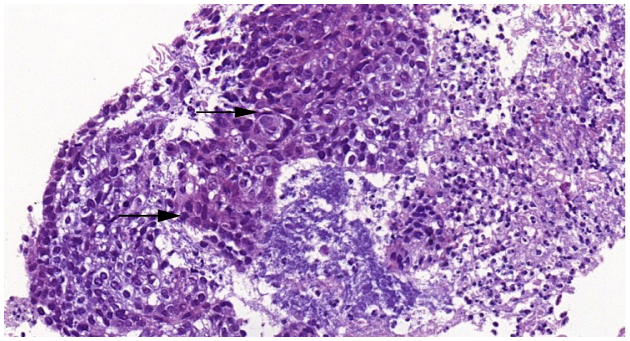


Figure 8. Mediastinal mass below carina: Pathological findings show squamous cell carcinoma (H & E staining ×400, black arrow).

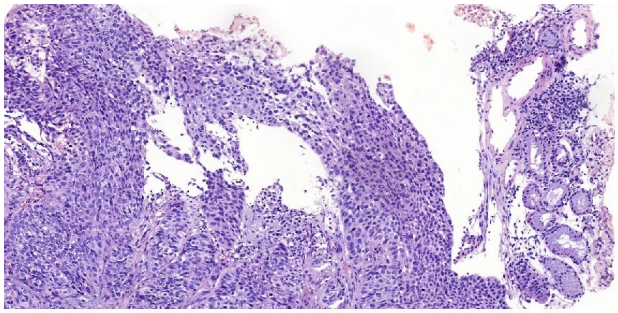


Figure 9. Pathological findings show esophageal squamous cell carcinoma (H & E staining ×400, black arrow).

DISCUSSION

Multiple primary cancers, also known as multiplicity carcinoma, refer to two or more unrelated malignant tumors that occur simultaneously or successively in one patient that may occur in different parts of the same organ or system or in different organs or systems [4]. Multiple primary cancers were first reported by Billroth in 1889, and then reports on multiple

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primary cancers increased gradually. The incidence of multiple primary cancers in all malignant tumors is 3.2%-7.5% abroad and 0.3%-3.5% in China [5]. Although both esophageal cancer and lung cancer are common clinical malignant tumors in China, the reported cases of multiple primary cancers of the esophagus and lung are rare. At present, most reports on lung cancer and esophageal cancer are published by Japanese scholars. They found that when many patients with esophageal squamous cell carcinoma combined with another primary squamous cell carcinoma, the most common site was the head and neck. However, lung squamous cell carcinoma was rarely reported [6]. Ishii [7] reported that the incidence of primary lung cancer combined with esophageal cancer was 0.54%-3.2%.

For patients with multiple primary cancers of the esophagus and lung, the following three aspects should be considered in clinicopathological diagnosis. First, patients with esophageal cancer combined with lung cancer are mainly characterized by symptoms of esophageal cancer, manifested as dysphagia of different degrees, chest pain, bloody sputum, cough and fever. Due to relatively hidden pulmonary lesions, pulmonary space-occupying lesions are often found only in the routine preoperative examination of the esophagus and further confirmed as primary lung cancer. Second, in patients with lung cancer combined with esophageal cancer [7, 80], esophageal cancer is usually induced by radiation therapy for lung cancer, and their imaging manifestations are marked with mediastinal fibrosis at an interval of 11 months to 13 years [8]. Third, the lung is one of the most prone sites for metastasis of esophageal cancer, especially lymph node metastasis, and imaging alone cannot diagnose. The treatment principles of primary lung cancer and metastatic tumors are essentially different, and the prognosis is quite different. Therefore, we should actively obtain pathological basis to distinguish primary lung cancer from metastatic tumors.

The patient was initially diagnosed with mediastinal space-occupying lesions with unclear nature (mediastinal lung cancer combined with hilar lymph node metastasis or esophageal cancer combined with mediastinal lymph node metastasis). Optional diagnostic methods include the following. First, bronchoscopy, especially EBUS-TBNA, can obtain definite histopathological diagnosis and staging of hilar and mediastinal lesions from multiple parts at once and can provide an opportunity for gene detection in nonsmall-cell lung cancer. Such as epidermal growth factor receptor (EGFR) and anaplastic lymphatic kinase (ALK). Second, esophageoscopy and esophageal biopsy can obtain pathology, and transesophageal ultrasound can also realize needle aspiration biopsy (EUS-FNA)of mediastinal lymph nodes but cannot detect 4R or 11R or obtain tissue samples. Combined with chest CT, the pathological characteristics of 4R and 11R lymph nodes play an important role in the diagnosis. EBUS-TBNA is needed to clarify the pathological characteristics. Finally, mediastinoscopy is an alternative method that cannot reach posterior mediastinal and hilar lymph nodes. In addition, due to surgical risks and complications, it cannot be repeated in the same patient [9]. After consideration, the patient chose to undergo bronchoscopy firstly. No significant airway lesions were found during general bronchoscopy. Then, endoscopic ultrasound-guided biopsy was performed for mediastinal and hilar lesions, and pathology confirmed simultaneous multiple primary cancers. Since this disease is rare, diagnosis should be careful. Subsequent esophagoscopy also confirmed esophageal squamous cell carcinoma. A systematic review of the literature was performed via PubMed by Muker [6]. The literature on simultaneous lung and esophageal cancer is sparse. Most reports were from Japan. Most patients were in their 50s to 60s (range, 46–80). Most were male (62 of 69; 89.9%) with SCC as the histology for all esophageal tumors and most (42 of 60; 70%) lung tumors. Most of the remaining lung tumors were adenocarcinoma (12 of 60; 90%), and SCC-SCLC was rare (2 of 60; 3%).

EBUS-TBNA played a key role in the clinical and pathological diagnosis of the patient. Airway ultrasonography could locate the three lesions indicated by chest CT. The obtained

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ultrasonographic characteristics of these lesions were consistent with malignant lesions. Furthermore, the ideal pathological tissues were obtained by sequential sampling at the three sites. If esophagoscopy is performed first, esophageal squamous cell carcinoma combined with mediastinal lymph node metastasis will be diagnosed. Generally, ultrasound-guided bronchoscopy may be abandoned, leading to missed diagnosis. The emergence of endobronchial ultrasonography provides us with a new method and tool for the diagnosis and staging of thoracic diseases. It can provide information on lesions, including echoes, edges, shape and size, to help with differential diagnosis. EBUS-TBNA, as a new minimally invasive diagnostic method of the chest, has been widely applied because of its repeatable biopsy and minimal invasiveness [10]. Its indications include the mediastinal lymph node staging of malignant lung tumors, diagnosis of intrapulmonary and mediastinal space-occupying lesions, and enlargement of mediastinal or hilar lymph nodes with unknown causes. EBUS-TBNA shows good sensitivity and specificity in determining mediastinal lymph node metastasis of malignant tumors. Moreover, a meta-analysis with 11 studies including a total of 1,299 patients also revealed that EBUS-TBNA showed sensitivity of 93% and specificity of 100% in detecting mediastinal lymph node metastasis [11].

Combined with the experience of this patient, we conclude that for patients with suspected malignant lesions accompanied by mediastinal and/or hilar lymph node enlargement and masses in CT images, pathological biopsy is recommended for definite diagnosis, which is essential for distinguishing primary lung cancer, esophageal cancer and metastasis. Considering that the upper mediastinal paratracheal lymph node (4R) is also the most common site of lymph node metastasis in thoracic esophageal cancer [12], and both tumors might be involved in these lymph nodes, the determination of pathological type can assist in staging, and EBUS-TBNA played a key role in diagnosis in this patient. Although our patient was definitively diagnosed, according to the location and pathological characteristics of esophageal cancer and lung cancer, surgery could not be conducted, and thus, chemotherapy was performed.

MPC occur rarely; however, consistent with the increased availability of diagnostic techniques, the number of patients diagnosed with MPC is increasing. Clinicians should strengthen their understanding of MPC and pay attention to the observation of chest CT and bronchoscopy, and bronchoscopy should not be satisfied with the discovery of a major lesion, as it may miss other lesions. The comprehensive and careful examination of multifocal lung disease should be performed to prevent blind or one-sided diagnoses. In the recent medical literature, to our knowledge, there are no cases of MPC that have been successfully diagnosed by EBUS-TBNA. EBUS-TBNA is a minimally invasive, safe, and cost-effective technique with a high diagnostic yield [10]. This case suggests that EBUS-TBNA is a useful modality for the diagnosis of mediastinal or hilar lymph node lesions in patients with MPC. We believe that accurate evaluation of mediastinal and hilar lymph nodes by EBUS-TBNA is a major determinant of effective treatment.

Conflicts of interest**:** *Declared none.*

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