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Case Report

Metastatic lung cancer with occult primary site: a difficult diagnosis

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Abstract: Occult primary non-small cell lung cancer (OP-NSCLC) is a relatively rare entity that brings difficulties in diagnosis and treatment. Accurate diagnosis depends on biopsy specimens. Often, repeated biopsies are required. Here we report a patient who underwent 3 rounds of biopsy of her cervical superficial enlarged lymph nodes to get a final diagnosis of occult metastatic lung cancer. There was no evidence of primary lesions in the lung. The patient was treated with targeted chemotherapy and survived 4 years. We emphasize the importance of repeated biopsies or resection biopsy for a definitive diagnosis. Though molecular technologies and imaging may identify a primary site, some cases have occult primaries. Adjunct examination methods such as immunohistochemistry and/or molecular methods are valuable for definite diagnosis and guiding treatment.

Keywords: Occult lung cancer, non-small cell lung cancer, repeated biopsies, definite diagnosis

Background

Occult primary non-small cell lung cancer (OP-NSCLC) is a pathological diagnosis of NSCLC based on the nodal biopsies without primary sites in the lungs by PET-CT or CT, and in which no other cancer is identified in 5 years [1]. A pathologic diagnosis is needed and is usually conclusive. The need for a pathologic diagnosis more than twice has not been reported. OP-NSCLC is very rarely reported, with no more than 100 cases. Romesser et al. found that OP-NSCLC was about 3.5% of stage III disease. Interestingly, they also found OP-NSCLC to be an independent favorable prognostic indicator in stage III patients, who usually had longer survival and lower rates of relapse. They considered that this occult group may have unique biology and represent a new entity [1]. We here present a true occult metastatic lung cancer with three rounds of biopsies and a relatively long survival time of 4 years.

Case presentation

A 61-year female with symptoms of painful left cervical lymphadenopathy for 2 months was admitted to our hospital in May 2018. She was treated with antibiotics at an outside hospital and her pain was relieved, and the size of swollen lymph nodes decreased. Not long after that, she had gradual right cervical node enlargement. Physical checkups found several lymph nodes enlarged in her bilateral cervical and supraclavicular region. Ultrasound examination found several enlarged nodes with the largest one being 2.5 cm × 2.5 cm on the left and 2.5 cm × 2.0 cm on the right with necrosis (**Figure 1A**). Computed tomography (CT) suggested a micro-nodule (8 mm) in the posterior segment of the right upper lobe of the lung was an inflammatory nodule. The multiple lymphadenopathies were suspected to be tuberculous. However, positron emission tomography revealed fluorine-18 deoxyglucose (FDG-PET-CT) accumulation in the lymph nodes of the neck, supracondylar, right iliac crest, sternal, mediastinum, and nasopharynx regions but not in the lung, so she was suspected to have lymphoma (**Figure 1B**).

Laboratory examination showed the cancer antigen 125 (CA125) to be 255.10 U/ml, and cancer antigen 153 (CA153) to be 45.50 U/ml,

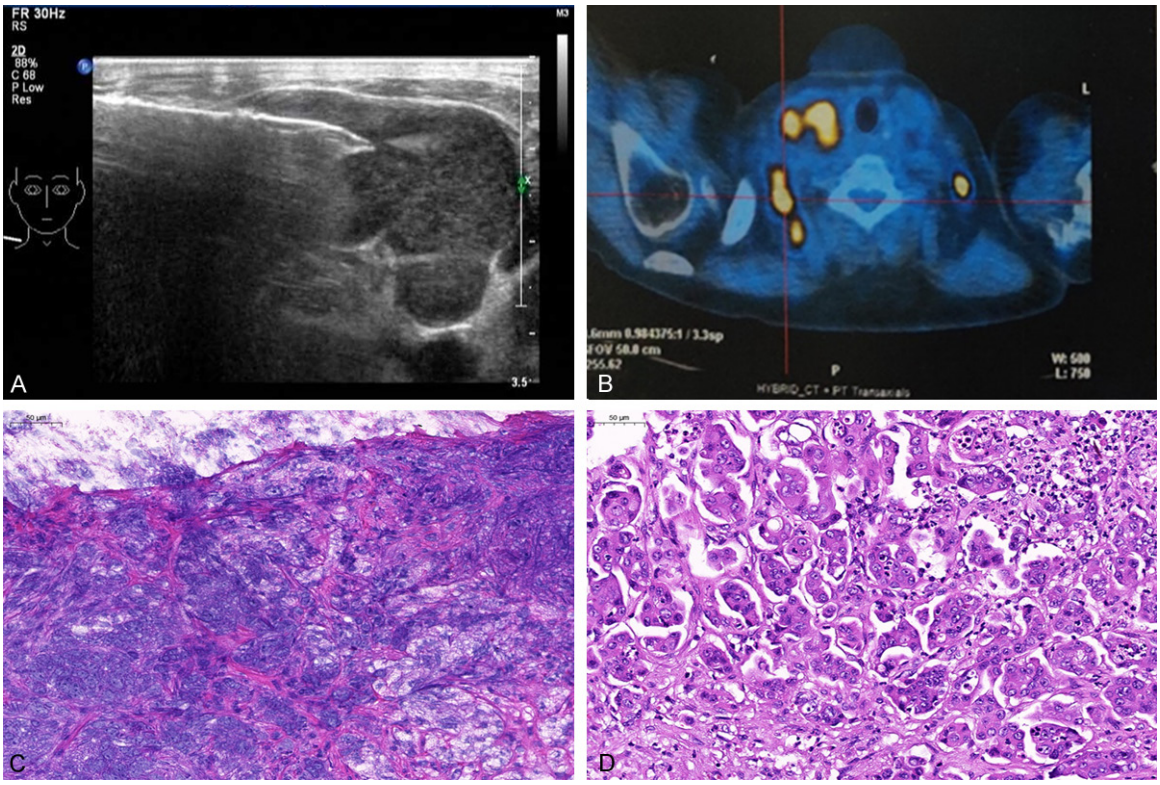

Figure 1. Ultrasound, PET-CT, and histological images. A: Ultrasound-guided biopsy of the enlarged right lymph nodes; B: PET-CT showed the high uptake of the bilateral cervical lymph nodes; C: Histologic picture of the abundant mucinous material without tumor cells (Hematoxylin and eosin stain); D: Micropapillary adenocarcinoma in the lymph node (Hematoxylin and eosin stain).

with serum Fe: 518.00 ng/ml, which were above normal levels. She had a history of hypertension for 5 years and had no other abnormalities.

The patient underwent a core needle biopsy guided by ultrasound for the first time in the enlarged lymph node of her right neck. Microscopically, there was only a large amount of mucus in the biopsied fibrous connective tissue, with no epithelial cells, and no lymphocytes identified (**Figure 1C**). We and the consulted experts suspected a benign disease such as thyroid disease, or a metastatic mucus-producing malignant tumor such as mucinous adenocarcinoma or chondrosarcoma. The patient underwent thyroid function tests and the infectious indices which found the thyroid peroxidase raised above to 1300.00 U/ml, C-reactive protein 26.70 mg/L, and immunoglobulin E 362.20 IU/ml. These abnormal tests did not explain the enlarged lymph nodes and their high FDG uptakes. Since the true tumor may have been missed, the patient got another core biopsy of the enlarged lymph nodes on the contralateral side of her neck. To our surprise, it showed the same picture as before and the pathological diagnosis was the same. The clinicians became confused about the next steps of treatment. After a multidisciplinary team discussion, a third resection biopsy of a relatively smaller left subclavian lymph node was done. In the resected lymph node, histopathologic examination revealed a large area of necrosis and at the periphery of the node micropapillary adenocarcinoma was identified (**Figure 1D**). Since PET-CT did not reveal any suspicious primary location, we did thorough immunohistochemistry to trace the origin. The lesion was positive for: thyroid transcription factor-1 (TTF-1), cytokeratin 7 (CK7) (**Figure 2A**), cytokeratin 5/6 (CK5/6), epithelial membrane antigen (EMA), Napsin A, P53, cytokeratin 19 (CK19), c-met, epidermal growth factor receptor (EGFR), Galectin-3, Programmed death-ligand 1 (PD-L1), anaplastic lymphoma kinase (ALK) (**Figure 2B**), Napsin A (**Figure 2C** and **2D**). The lesion was negative for: calretinin, P16, Wilms tumor

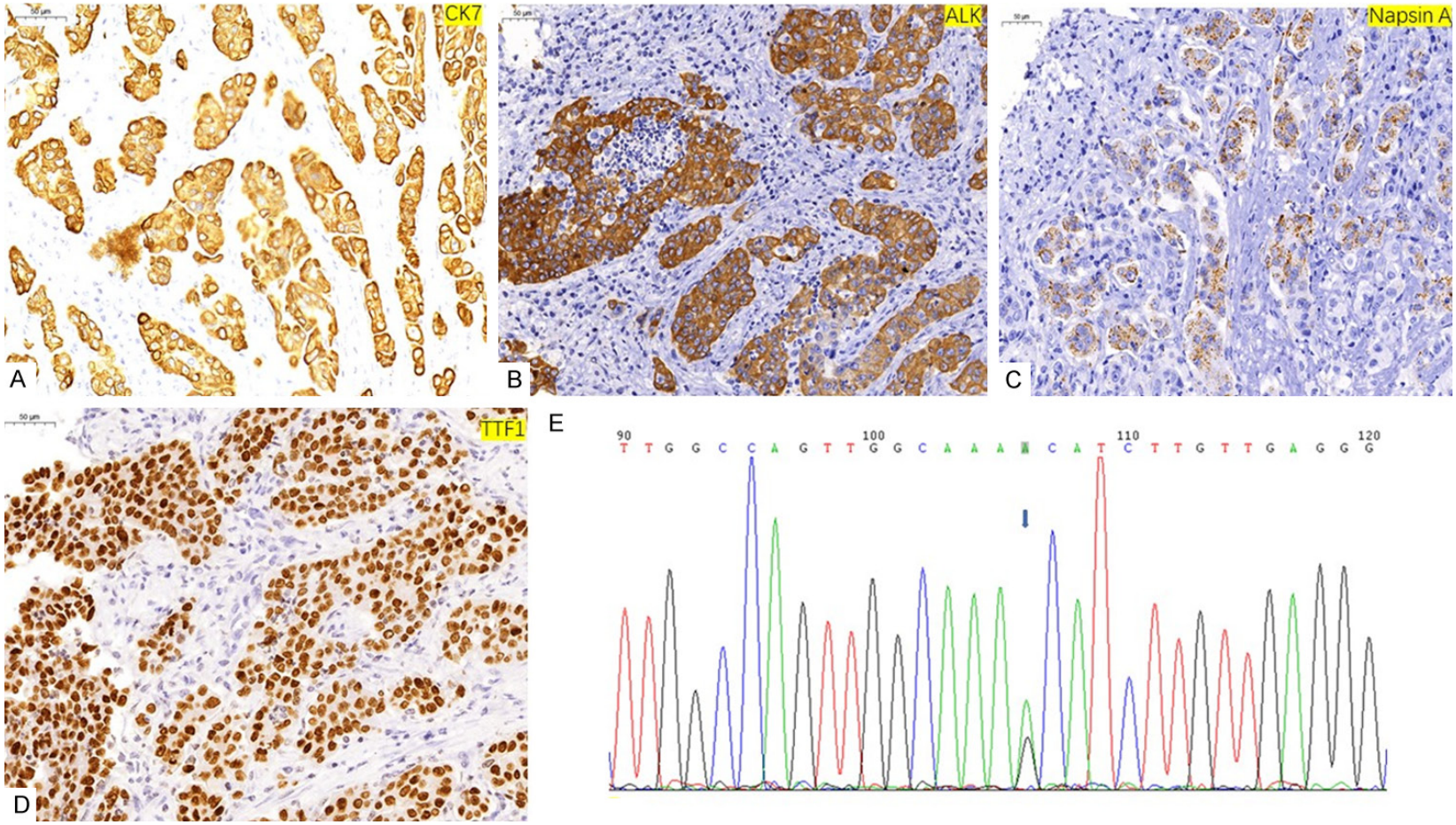

Figure 2. Representative images of immunohistochemistry and molecular pictures. A: Immunohistochemical CK7 expression of the tumor cells; B: ALK expression of the tumor cells; C: Napsin A expression of the tumor cells; D: TTF1 expression of the tumor cells; E: TP53 p.F134L c.400T>C (gene sequencing).

gene 1 (WT-1), Villin, progesterone receptors (PR), Renal Cell Carcinoma Marker (RCC), paired box gene 8 (PAX8), P40, gross cystic disease fluid protein 15 (GCDFP-15), cytokeratin 20 (CK20), caudal-related homeobox 2 (CDX2), estrogen-receptor (ER), GATA Binding Protein 3 (GATA-3), glypican 3 (GPC3), Neural cell adhesion molecule (CD56), mesothelial cell (MC), BRAF V600E, and thyroglobulin (TG). Ki-67 index was 80%. Based on the histopathology and immunohistochemistry results, we reached the diagnosis of micropapillary adenocarcinoma consistent with metastatic lung cancer. Next-generation sequencing test revealed EML4-ALK fusion and P53, exon 5, c400 T>C, p.F134L (**Figure 2E**). The patient was given Pemetrexed plus carboplatin regimen for 5 cycles, and crizotinib 250 mg BID. Her abnormal blood tests dropped into the normal range, and the enlarged lymph nodes became significantly smaller. She had regular follow-ups after that, and in November 2020, there was evidence of enlarged lymph nodes that had recurred in her right neck. The patient was given radiotherapy 30 times outside of our hospital. After her treatment, she had Bevacizumab every 21 days, and Aletinib every 28 days. She remained in good condition and there was no evidence of any primary lung nodule. She died of hemorrhage from tumor invading the right supraclavicular artery 4 years later.

Discussion

OP (occult primary)-NSCLC is a diagnosis of NSCLC based on mediastinal node biopsies, but no with primary tumor on PET-CT and chest CT within 5 years. OP-NSCLC is very rare and comprises only about 3.5% of stage III cancer [1].

To get a precise treatment for the tumor, a definite pathologic diagnosis must be made first.

A biopsy of the suspected nodules is essential for a definite diagnosis. In practice, most of the time one biopsy is enough. But in our case, clinicians did three biopsies before we found the true carcinoma. Notably, the biopsied tissue showed extensive mucinous changes without any cells within. Possible hypotheses are degenerative changes or metaplastic changes of the tumor. We have not found any similar report. Our case alerted us that sometimes even with US-guided biopsy, an inexplicable tumor in the body would bring unexpected changes. In the end, we needed more biopsies to get a final diagnosis.

The most effective method to identify the primary source was immunohistochemistry. It is the fastest, cheapest, and most broadly available [2]. CK7, TTF1, and Napsin A are the most useful markers in the diagnosis of adenocarcinoma of the lung. In the present case, they were positive and helped us to diagnose the metastatic tumor to be an occult adenocarcinoma of the lung.

Sometimes the conclusion is not so obvious. We should bear in mind that many of these available antibodies have limits and pitfalls. TTF1 may be detected in colon cancer and/or thyroid cancer, and CK7 and Napsin A may both be positive in clear cell carcinoma of the ovary.

Hayashi et al. used microarray analysis to detect expression of genes in 130 patients who had unknown primary cancers. They predicted the possible primary sites were pancreas (21%), stomach (21%), or lymphoma (20%) [3]. Moran et al. studied the tumor DNA methylation profiling and predicted 87% (188/216) of the origin of the metastatic cancers with unknown primary. They found their epigenetic tumor type classifier could be useful in unmasking the original site of the metastatic tumors, and that was a key step towards improving the clinical management of these patients [4]. Santos et al. built the reported largest Reference Database of cancer origin based on 100 different sources and generated a gene-expression classifier using 95 genes. In their validation study, by using a real-time PCR-based assay on 105 metastatic pathologic permanent samples, they got 99.04% specificity and 97.22% reproducibility [5].

However, though these molecular classifiers are promising, there are some drawbacks. They are less widely available, not widely validated, and not affordable. The standard pathology evaluation nowadays is still based on morphology, immunohistochemical assessment, and clinical pictures; such as the 18F-fluorodeoxyglucose-positron emission tomography-CT, which is essential to clarify the primary site and the spread of tumor, increasing the rate of finding the primary by 37.5% [6]. However, in our

case, the PET-CT did not find the origin. On the contrary, it was highly suspected that those high uptake lymph nodes could be lymphoma.

The most common histologic types of metastasis from an unknown primary site are adenocarcinoma and squamous carcinomas [7, 8]. Our case was a micropapillary adenocarcinoma, which is a variant of the invasive lung adenocarcinoma and thought to be more aggressive than other subtypes. For a specific case, it is difficult to predict the prognosis. Our patient was alive for 4 years.

The treatment for these unknown primary site tumors is different according to the probable original sites because some may have a comparably favorable prognosis, while others have unfavorable prognoses. Usually, these patients get tailored therapy such as surgery, radiotherapy, or targeted therapy [1, 2, 7]. However, there is no uniform regime. Our patient got chemotherapy, targeted therapy, and radiotherapy.

Metastatic lesions of unknown primary site usually have a poor prognosis. Hayashi et al. found the patients did not have improvement in survival even the treatments were site-specific [3]. Hemminki et al. found that unknown primary site tumors were associated with a poor prognosis with the 12-month survival rates being 16-17%, and a median survival time of only 3 months [8]. Contrary to our common sense, the OP-NSCLC in the study done by Romesser et al. had found markedly favorable outcomes, because the patients in their study had longer survival time and lower rates of relapse. They thought OP-NSCLC might have a unique underlying biology [1].

One hypothesis about OP-NSCLC is that the primary tumor is too small to be noticed. However, imaging technology nowadays should find the millimeter nodules which argues against this hypothesis. Another hypothesis is that these “metastatic” tumors are not metastatic but arise from epithelial inclusions within the regional lymph nodes. The third one is that the primary tumor might go through spontaneous regression while leaving the metastatic deposits [1]. The origin of these peculiar tumors remains to be revealed.

In conclusion, the OP-NSCLC seems to have a relatively better prognosis as compared with the same stage NSCLC. The diagnostic process may be tortuous but a definite pathologic diagnosis is a basis for therapy. There are many methods that could be chosen to help with the diagnosis, but the widely used and affordable methods are always the primary choice. Treatment for the unknown primary site tumor is personal and comprehensive.

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Disclosure of conflict of interest

None.

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