



Case report

Organizing pneumonia secondary to lung cancer of unknown primary site

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ABSTRACT

Background: Secondary organizing pneumonia (OP) is associated with other pathological conditions, such as infections, drugs, cancers and radiotherapy. Lung cancer-associated secondary OP has rarely been reported.**Case review:** In this study, we reported on a case of secondary OP caused by lung cancer. The patient was initially diagnosed with community-acquired pneumonia and then cryptogenic organizing pneumonia by CT scan-guided and transbronchial lung biopsy. Poor response to anti-infection or corticosteroid therapy prompted us to search for underlying disease. A TBNA biopsy of the 4R mediastinal lymph node revealed the diagnosis of lung cancer.**Conclusion:** OP secondary to lung cancer of unknown primary site are rare. When OP patients have lymphadenopathy or poor response to glucocorticoid, a more differential diagnosis should be considered, especially for avoiding the misdiagnosis of a malignancy.

1. Introduction

Organizing pneumonia (OP) is a pulmonary clinicopathological syndrome that reacts to noxious environmental or endogenous factors. It is seldom observed in patients with lung cancer. Most lung cancer-associated OP was caused by chemotherapy or radiotherapy. In resected specimens, OP is usually adjacent to lung cancer and is not the major pathological change. Here, we report on a patient with OP secondary to lung cancer of unknown primary site.

1.1. Case report

The patient was a 63-year-old male smoker (40 pack-years). He presented with symptoms of cough, hemoptysis, fever, and weight loss for 2 months. The patient was admitted to the local hospital in 2016-03-21. The chest CT scan showed a soft tissue shadow of 2.8*3.5 cm with large patchy shadows around the upper lobe of the right lung (Fig. 1 A). A PET-CT scan revealed a mass of 2.5*3.5 cm near the right hilar and a patchy shadow of 4.9*3.3 cm in the upper lobe of the right lung. The mean FDG metabolism of the mass near the right hilar was 4.9 (the highest was 9.6). The mean FDG metabolism of the patchy shadow was 4.7 (the highest was 6.0). The CT scan-guided percutaneous biopsy in

the right pulmonary apex and right upper lobe (area indicated by the white arrow in Fig. 1 A) was performed twice in 2016-03-25 and 2016-03-30, and pathology results showed chronic pneumonia and OP with local necrosis. The TBLB pathobiology in 2016-04-05 showed chronic inflammation of some bronchial mucosa in the right upper lobe. Community-acquired pneumonia was diagnosed. Cefotiam and Clindamycin were given as anti-infection therapies, and his body temperature dropped to normal, but cough and bloody sputum had not been well improved. A chest CT scan in 2016-04-11 showed that lesions in the upper lobe of the right lung had shrunk, but other lesions enlarged, and the lymph nodes in the right hilum and mediastinum were still swollen (Fig. 1 B).

The patient was admitted to Zhongshan Hospital, Fudan University in 2016-05-10 for further diagnosis and treatment. Physical examination showed that he was well developed and nourished. The sounds in both lungs are clear and regular, with no abnormal changes in the heart or abdomen. Bilateral supraclavicular and cervical lymph nodes were not enlarged. Blood routine and blood biochemistry showed the following: white cell count $10.81 \times 10^9/l$ with 65.6% granulocytes and 16.4% lymphocytes, hemoglobin 119 g/l, platelet count $246 \times 10^9/l$, erythrocyte sedimentation rate 73 mm/H and C reactive protein 52.2 mg/l. T-spot test: antigen-A 1, antigen-B 0. Arterial blood gas analysis

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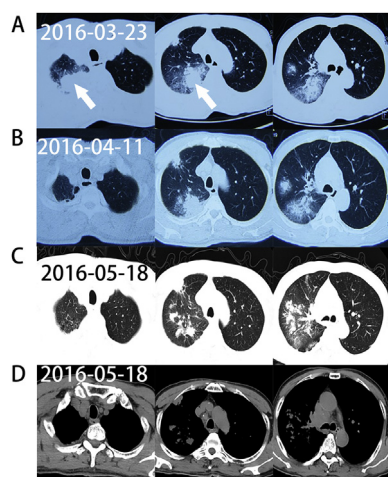


Fig. 1. Series of chest computerized tomography (CT) images from March 2016 to May 2016. The images show that lesions in the puncture site of the right lung were significantly reduced, and the lymph nodes in the right hilum and mediastinum were still swollen. Two CT scan-guided percutaneous biopsies were performed in the area indicated by the white arrow in A.

showed PO_2 69.0 mmHg and PCO_2 40 mmHg. Tumor marker: CA125 68.3 U/ml and Cyfra211 3.7 ng/ml were slightly elevated, and other markers, such as CEA, CA199, NSE, SCC and proGRP, were all normal. Antinuclear antibody (cytoplasmic pattern) 1:100 and other autoantibody or rheumatoid factors were all negative. The pathological sections from the local hospital were rechecked by our pathology department, considering OP with eosinophil infiltration and scattered hemosiderin deposition (Fig. 2 A).

Initial diagnosis of OP was made, and intravenous corticosteroid therapy was started for 2 weeks. Most symptoms disappeared, except for occasional hemoptysis. However, the follow-up chest CT scan in 2016-05-18 showed that lesions in the puncture site of the right lung were significantly reduced, but other lesions expanded, and the lymph nodes remained swollen (Fig. 1 C, D). We persuaded the patient to receive EBUS in 2016-05-20, and the examination showed slightly swollen mucosa and narrow lumen in the right upper bronchial. The lower segment of the right middle bronchial was external compressive stenosis with congestive mucosa. TBLB was performed under the guidance of ultrasound in the shadow of the posterior segment of the right upper lobe, and pathobiology showed alveolar septal fibrous tissue hyperplasia, with organizing pneumonia lesions in some areas (Fig. 2 B). TBNA from 4R mediastinal lymph nodes showed atypical cells (Fig. 2 C). The immunohistochemical results were CD1a(-), CD21(-), CD23(-), CD30(-), CD33(-), CD68(+), CKpan(++), D2-40(-), EMA(+++), Langerin(-), S-100(+), Vim(+++), CD10(+), CD15(+), CD79a(+), ALK-1(-), PAX-5(-), P63(-), SPA(-), NapsinA(+), TTF-1(+), suggesting poorly differentiated carcinoma

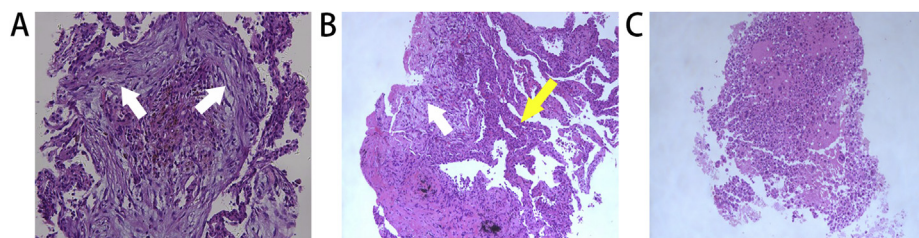


Fig. 2. Pathology of lung and lymph node from March 2016 to May 2016.

(A) Pathology of CT scan-guided percutaneous lung biopsy in the apical segment of the right lung's upper lobe. HE staining of the lung biopsy showed organizing pneumonia lesions (white arrow).

(B) TBLB pathobiology from the posterior segment of the right upper lobe showed alveolar septal fibrous tissue hyperplasia (yellow arrow), with organizing pneumonia lesions (white arrow) in some areas.

(C) TBNA from 4R mediastinal lymph nodes showed atypical cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(sarcomatoid carcinoma is more likely) which arose from the alveolar epithelium. Bronchial aspiration cultures were negative for bacteria, mycobacteria and fungi. The final diagnosis was lung cancer and secondary organizing pneumonia. The patient received one cycle of chemotherapy (gemcitabine 2.0 d1, cisplatin 120 mg d1) and then lost follow-up.

2. Discussion

In this case, with clinical presentation of cough, hemoptysis, lung patchy and mass shadow, hilar and mediastinal lymph node enlargement, differentiation diagnosis included bacterial or viral pneumonia, tuberculosis, lung fungus infection, lung cancer, lymphoma, connective tissue disease, etc. A short period of high fever, white blood cell and CRP elevation indicated an infectious disease. However, an insignificant response to antibiotic treatment and a negative outcome of bronchial aspiration cultures excluded bacterial or viral pneumonia, tuberculosis, and lung fungus infection. Negative autoantibodies excluded connective tissue diseases. Pathological findings from 2 TBLBs and 2 CT-guided percutaneous lung biopsies suggested the possibility of OP; however, COP was not observed due to poor response to corticosteroids. Thanks to TBNA from 4R mediastinal lymph nodes and finding of poorly differentiated carcinoma, secondary OP associated with lung cancer of unknown primary site was determined.

Considering the lesion of OP was located in the right upper lobe, and the 4 lung biopsy pathology results showed that there was no cancer cell infiltrating in the region, we thought OP was not adjacent to lung cancer. However, because the exact location of the lung cancer remained unclear, the CT images of the right upper lung were similar to tumor, and the immunohistochemical results showed that the tumor was arose from the alveolar epithelium, we could not completely rule out the possibility that the tumor was too concealed or too small, so tumor tissue in the right upper lung could not be obtained due to the small amount of specimens collected by aspiration needle puncture. Clear pathological evidence is still needed to prove that there was a tumor in the right upper lung.

Organizing pneumonia, also referred to as bronchiolitis obliterans organizing pneumonia, is a pulmonary clinicopathological syndrome reacting to noxious environmental or endogenous factors. ATS/ERS [1] suggested naming the cryptogenic one as COP and that related to other diseases was referred to as secondary OP in 2002. According to the literature, approximately 31–44% of OP was associated with other pathological conditions [2], such as infections, connective tissue disorders, drugs, cancers and postthoracic radiotherapy, etc. [3]. Sveinsson OA et al. [4] studied 104 patients, 58 for COP and 46 for secondary OP. After comparing their causes, clinical features, treatment, radiographic features and pathology, they found no major differences in clinical features, radiographic, pathological features and treatment between COP and secondary OP.

Malignant diseases associated OP in solid organ tumors, and hematologic malignancies have been reported [5]. In patients with solid

organ tumors, most are treated by chemical therapy (or other drugs) or radiotherapy [6–8]. In our report, no such treatment was given before OP was defined.

Lung cancer-associated OP has been reported previously. This type of OP is usually adjacent to lung cancer, which is confirmed by pathology. Elżbieta Radzikowska et al. [9] reported one case in which OP foci accompany lung cancer infiltrations. The patient's pathological specimen revealed only small infiltration of carcinoma cells in the wall of the bronchi and large confluent areas of OP. Romero et al. [10] analyzed the curative lung removal specimens of 89 patients with lung cancer and found OP foci in 33 patients; however, OP was not a major change. The results indicate that a pattern of OP adjacent to lung cancer is a common pathological finding.

A few studies have reported [5,11,12] OP and lung cancer in separate parts of the lungs, and whether there is any causal relationship between the two diseases still needs to be discussed. In our case, CT-guided/transbronchial lung biopsy confirmed that there was no cancer cell infiltrating in the OP region. Moreover, bronchoscopy did not find sub-segmental bronchial obstruction. It is difficult for us to find the primary site and accurately determine the T stage of lung cancer.

The mechanism by which cancer related OP forms is not apparent, mechanisms that would elicit a fibrotic response all are possible, such as bronchial obstruction, specific tumor factors, and a local host response to the tumor mediated by the immune system [10]. Tumor cells themselves produce cytokines that attract neutrophils, macrophages, lymphocytes and dendritic cells all attributing to tumorigenic growth and metastatic potential. These cells are closely related to immune and inflammatory response. Kinds of inflammatory factors exist in the tumor microenvironment, such as TNF- α , TGF- β , cytotoxic mediators, proteases, MMPs, interleukins and interferons, which produce potent lymphangiogenic and angiogenic growth factors allowing tumor growth and metastatic spread to the lymph nodes [13]. These factors are likely to cause damage to the lung epithelium, leading to OP.

The patient's diagnosis was delayed for 2 months. To avoid misdiagnosis of secondary OP, especially malignant diseases associated with OP, we have learned two lessons from this case. First, COP seldom presents with swollen hilar and mediastinal lymph nodes. The current literature showed that there were only two cases of patients with organizing pneumonia associated with hilar and mediastinal lymph nodes [14,15]. Second, most COP patients respond to glucocorticoid therapy well. Therefore, when patients have lymphadenopathy and poor response to glucocorticoid therapy, further differentiation diagnosis should be considered.

In this case, the treatment for OP and cancer are all important, and concrete therapy for lung cancer could be changed depending on the patient's condition. Arrabal SR [11] and Enomoto N [12] all chose surgical therapy for patients coexisting with OP and carcinoma in different parts of the lungs. In our case, considering that the patient had lymph node metastasis, chemotherapy was chosen afterwards.

In conclusion, the clinical features and radiographic findings of OP are non-specific, and sometimes it is difficult to differentiate with other diseases. As far as we know, patients with OP and lung cancer of unknown primary site are rare, their mechanism and relationships have not yet been elucidated. When OP patients have lymphadenopathy or poor therapeutic effect to glucocorticoid, a more differential diagnosis from lung cancer to other diseases should be taken into consideration. Once diagnosed, appropriate therapy for both OP and lung cancer could start.

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Availability of data and materials

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List of suggested repositories

Not applicable.

Authors' contributions

Ruolin Mao and Lianpeng Zhang consulted literature and wrote the paper, Jun Hou and Yining Zou provided and analyzed the pathological data, Lei Zhu and Zhihong Chen consulted literature.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient had signed an informed consent for case report.

Conflicts of interest

No conflicts of interest.

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