

## CASE REPORT

# Bilateral synchronous double primary lung cancer: A case report

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**Key Clinical Message**

Bilateral synchronous double primary lung cancer (sDPLC) is a rare disease in clinics. This study analyzed the clinical data of a patient with bilateral sDPLC, aiming to improve medical workers' understanding of the disease and avoid missed diagnosis and misdiagnosis.

**Abstract**

A 68-year-old male was admitted to the hospital with “intermittent cough and expectoration for two months.” Enhanced chest computed tomography (CT) showed that the upper lobe of the left lung had a mass of high-density shadow, bronchial opening of the left lobe was thickened, lumen was narrow, and middle lobe of the right lung had a mass of high-density shadow. Bronchoscopy was performed to observe the microscopic characteristics of the lesions in the upper lobe of the left lung, and abnormal mucosa was biopsied. The pathological and immunohistochemical results confirmed that it was small cell lung cancer (SCLC) in the upper lobe of the left lung. Considering the occupation of the middle lobe of the right lung, CT-guided lung biopsy was performed, and the pathological and immunohistochemical results confirmed that it was moderately differentiated squamous cell carcinoma (SCC) in the middle lobe of the right lung. Clinicians should strengthen their understanding of sDPLC and focus on the imaging characteristics of chest CT and performance under bronchoscopy. Additionally, it is necessary to perform both CT-guided lung biopsy and bronchoscopy to obtain histopathological findings for the diagnosis.

**KEYWORDS**

case report, simultaneous double primary lung cancer, small cell lung cancer, squamous cell carcinoma

## 1 | INTRODUCTION

Primary bronchogenic carcinoma (abbreviated as lung cancer) is one of the most common malignant tumors in

China and worldwide, and its mortality ranks first among malignant tumors,<sup>1,2</sup> while multiple primary lung cancer (MPLC) is relatively rare in clinics, among which double primary lung cancer (DPLC) is the most common. DPLC

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refers to the occurrence of two primary lung cancers with different origins in one or both lungs of the same patient, with the same or different tissue types. The diagnosis interval is 6 months, which can be divided into synchronous DPLC (sDPLC, <6 months) and metachronous DPLC (mDPLC,  $\geq$ 6 months).<sup>3–5</sup> In recent years, with the improvement of medical diagnosis and treatment level and the aggravation of population aging, the incidence and detection rate of DPLC have increased year by year. However, bilateral sDPLC is very rare in clinical practice, and clinicians often underestimate the understanding of sDPLC. Therefore, a case of bilateral sDPLC diagnosed in The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture is reported as follows, in order to improve the medical workers' understanding of the disease and avoid missed diagnosis and misdiagnosis.

## 2 | CASE PRESENTATION

The patient, a 68-year-old male, was admitted to The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture on February 22, 2023 for “intermittent cough and expectoration for 2 months.” Two months previously, the patient had no obvious induction of intermittent cough accompanied by yellow viscous sputum. Smoked for more than 50 years, with an average of 20 cigarettes per day. Respiratory sounds in the left upper lung were weakened, and dry and wet rales were not heard in both lungs. Upon admission, the whole set of tumor markers showed that CYFRA21-1 4.67 ng/mL increased, and the rest NSE, AFP, PSA, CEA, CA12-5, CA19-9, CA15-3, and ferritin were normal.

On February 23, 2023, enhanced chest computed tomography (CT) revealed that the upper lobe of the left lung had a massive high-density shadow with multiple bands around it, and the central density was dense. The wall of the bronchial opening of the left lobe was thickened and

the lumen was narrow. The middle lobe of the right lung had a massive high-density shadow, the size was about 3.2 cm  $\times$  2.8 cm, and lobulation and burr could be seen (Figure 1). The CT results suggested that the bronchus of the upper left lobe is narrow with obstructive pneumonia. There was a mass in the middle lobe of the right lung, and tumor lesions were considered.

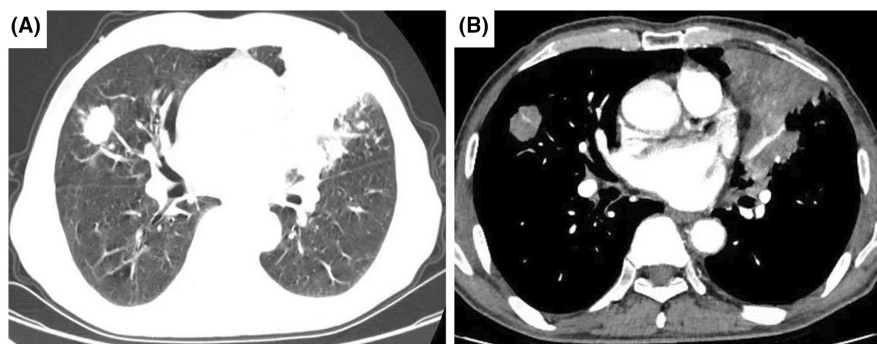
On February 24, 2023, further bronchoscopy showed that the mucosa of the left upper lobe bronchus was abnormal hyperplasia and bulge, and the wall of the bronchus was thickened and hard, and the lumen was narrow (Figure 2).

At the same time, the left upper lobe bronchus was biopsied, and the postoperative pathological examination indicated that the lesion of the left upper lobe bronchus was consistent with small cell lung cancer (SCLC) (Figure 3A). Immunohistochemical results showed that CK, CK7, CD56, Villin, CgA, and Syn were positive, and TTF-1 and CD117 were partially positive, while CK20, NapsinA, P40 and P63 were negative, and the number of Ki-67 positive cells was about 80% (Figure 4A–C).

On February 28, 2023, CT-guided puncture biopsy of the middle lobe of the right lung indicated that the lesion in the middle lobe of the right lung was moderately differentiated squamous cell carcinoma (SCC) (Figure 3B). Immunohistochemical results showed that CK, CK5/6, P40, and P63 were positive, while CK7, TTF-1 and NapsinA were negative, and the number of Ki-67 positive cells was about 20% (Figure 4D–F).

## 3 | METHODS

Based on the imaging characteristics of the patient's bilateral lung lesions, it was necessary to differentiate them from diseases such as metastatic lung cancer, pulmonary tuberculosis, inflammatory pseudotumor, lymphoma, and organizing pneumonia. After being diagnosed with lung

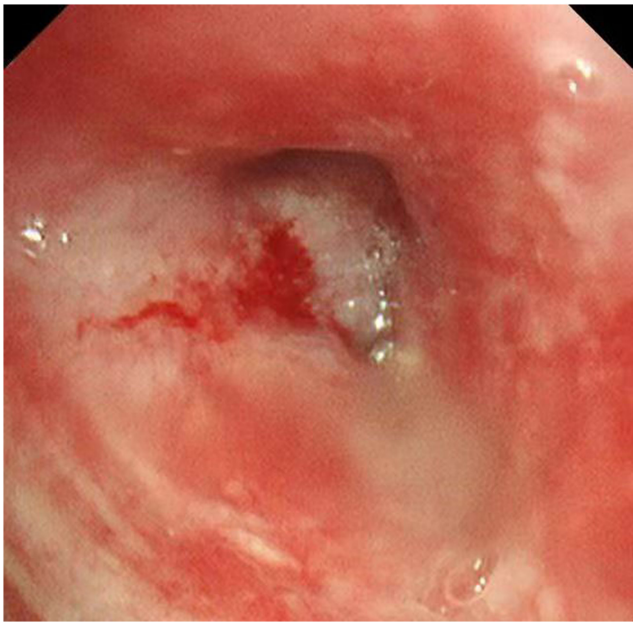


**FIGURE 1** Enhanced chest computed tomography (CT) of the patient showed that the upper lobe of the left lung had a mass of high-density shadow, bronchial opening of the left lobe was thickened, lumen was narrow, and middle lobe of the right lung had a mass of high-density shadow. (A) Lung windows. (B) Mediastinal windows.

cancer through pathology, the patient received symptomatic treatment such as anti-infection, cough relief, and phlegm resolving during hospitalization in our department. After the symptoms improved, the patient was recommended to receive further treatment in the oncology department.

#### 4 | CONCLUSION AND RESULTS

In summary, the diagnosis was bilateral sDPLC, that is, SCLC in the upper lobe of the left lung and moderately differentiated SCC in the middle lobe of the right lung. After a clear diagnosis was made in our hospital, the patient went to a higher hospital for further diagnosis and treatment. Through follow-up, we learned that the doctors in the higher hospital suggested the patient to undergo radiotherapy or chemotherapy for SCLC in the left lung and



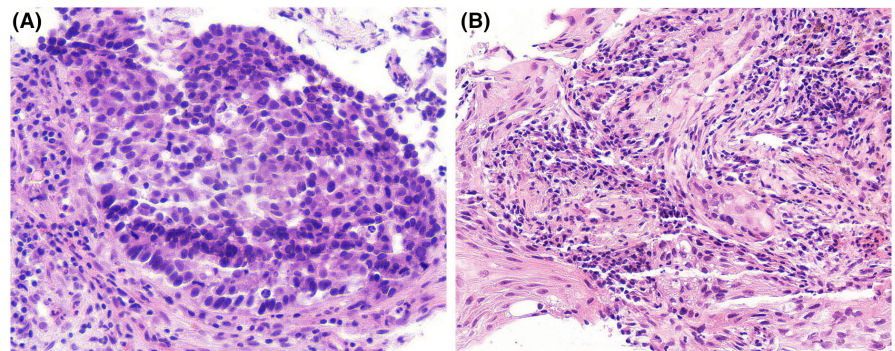
**FIGURE 2** Bronchoscopic view of the left upper lobe bronchus showed that the mucosa was abnormal hyperplasia and bulge, and the wall of the bronchus was thickened and hard, and the lumen was narrow.

surgery for SCC in the right lung, but the patient gave up the treatment due to the high treatment costs and family factors. Unfortunately, when the patient was followed up 10 months after discharge from the hospital, he had not undergone any intervention for lung cancer.

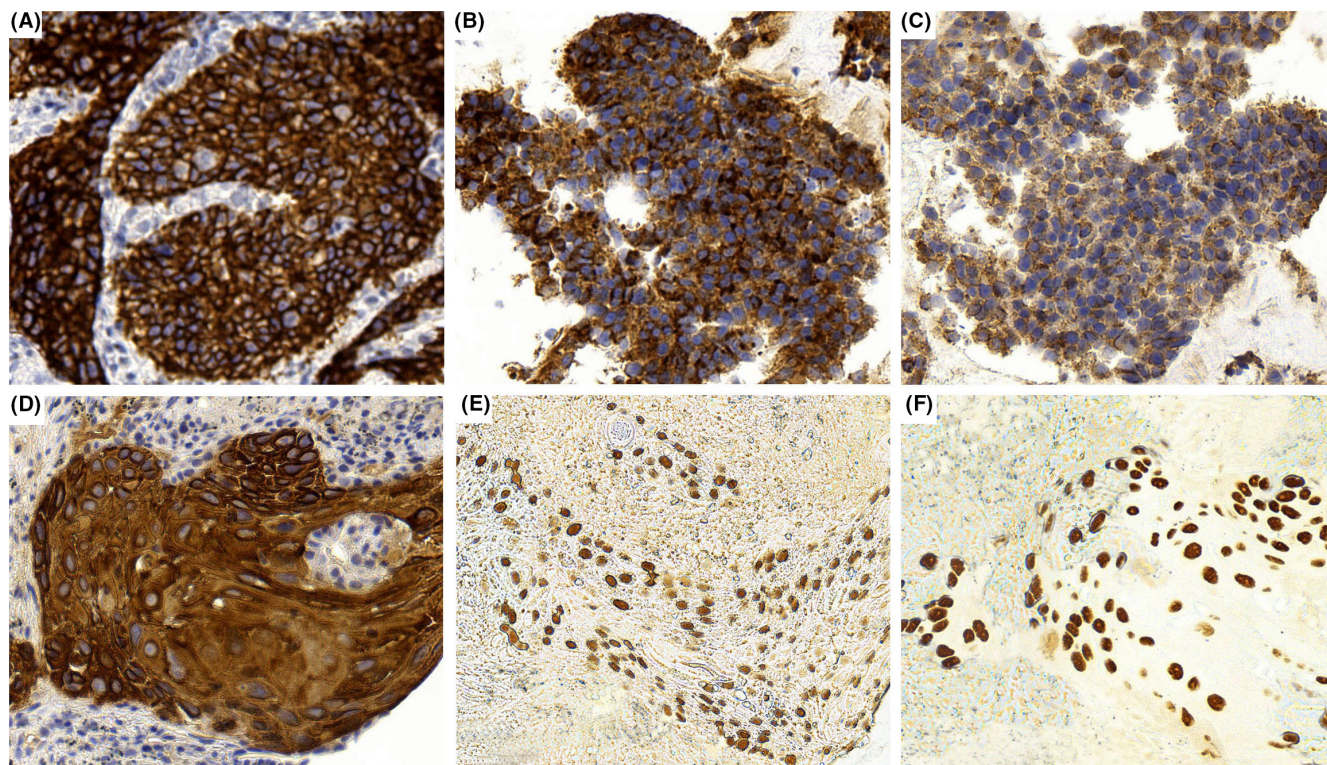
#### 5 | DISCUSSION

MPLC refers to the occurrence of two or more primary lung cancers with different origins at the same time or at different times in different positions of a patient's single lung or both lungs. MPLC is a rare type of lung cancer, while DPLC is the most common type of MPLC. In 1975, the concept of DPLC was first put forward by Martini and Melamed.<sup>3</sup> Based on their diagnostic criteria, the American College of Chest Physicians (ACCP) updated the diagnostic criteria of DPLC in 2003.<sup>6</sup> (1) The cancer focus is located in bilateral or ipsilateral lobes, and the tissue types can be different and the same; (2) Except for the metastasis of cancer; (3) If the histology is the same, the tumors are located in different parts, and the tumors are separated by a certain distance. In addition, DPLC is divided into sDPLC and mDPLC according to whether the diagnostic time interval between lesions is more than 6 months. This patient has different histological types and different tumor sites. The first primary cancer is SCLC in the upper lobe of the left lung, and the second primary cancer is SCC in the middle lobe of the right lung. According to the diagnostic criteria, the diagnosis of bilateral sDPLC in this patient is established.

In recent years, with the increase of environmental pollution, life pressure and the development of laboratory technology, the incidence of DPLC has been increasing year by year.<sup>7</sup> Previous foreign reports show that the incidence of DPLC is about 0.8%–14.5%,<sup>8,9</sup> while the incidence of sDPLC is about 1%–8%.<sup>10</sup> By analyzing the reasons for the low incidence of sDPLC, it may be that the primary cancer is not well understood or mistaken for metastasis.<sup>11,12</sup> As is known to all, the main metastatic routes of SCLC were blood metastasis, lymphatic



**FIGURE 3** Hematoxylin–eosin (HE) staining of the biopsy specimens. (A) SCLC was found in the upper lobe of the left lung. HE  $\times$  400. (B) SCC was found in the middle lobe of the right lung. HE  $\times$  400.



**FIGURE 4** Immunohistochemistry (IHC) staining. CD56 (A), Syn (B), and CgA (C) were positive in the upper lobe lesion of the left lung. CK5/6 (D), P40 (E), and P63 (F) were positive in the middle lobe lesion of the right lung. IHC  $\times 400$ .

metastasis, or direct spread. The typical CT manifestations of general metastatic lung tumors are multiple nodules or masses of different sizes in both lungs, with uniform density, clear boundaries, and mainly scattered around the periphery. The right middle lobe of the patient is a single lesion with irregular shape, lobulated, burred edges, and CT features of peripheral lung cancer, which is inconsistent with the imaging features of metastatic tumors. We highly suspected that the right middle lobe lesion was not a metastatic tumor, so we conducted CT guided lung biopsy of the right middle lobe lesion. Therefore, in order to improve the detection rate of DPLC, clinicians should strengthen their understanding of sDPLC and pay attention to the imaging characteristics of chest CT and the performance under bronchoscope. In addition, it is necessary to perform both the CT-guided lung biopsy and bronchoscopy as required by the condition. Avoid being satisfied with the discovery of one lesion and ignoring other tiny lesions during bronchoscopy or chest CT examination, and conduct a comprehensive and careful examination of multifocal lung diseases to prevent blindness and one-sidedness in diagnosis. At the same time, careful pathological examination can improve the detection rate of DPLC. In addition, serum tumor markers can be used for auxiliary diagnosis and differential diagnosis of lung cancer. Studies have shown that NSE and proGRP have high

specificity for SCLC, CYFRA21-1 has high specificity for SCC, and proGRP is superior to NSE in differentiating SCLC and NSCLC.<sup>13</sup> In this case, the serum CYFRA21-1 was elevated, but the NSE level was not elevated. The possible reason was that the patient was in the early stage of tumor, the tumor cell differentiation was low, and the serum tumor markers were not sensitive. Since the laboratory department of our hospital did not carry out proGRP detection, the proGRP expression level in serum was not detected.

At present, the etiology and pathogenesis of DPLC are still unclear, and comprehensive literature reports may be related to many factors. (1) regional carcinogenesis hypothesis, that is, carcinogens act on mucosal or glandular epithelial cells for a long time, resulting in extensive dysplasia of cells, some of which become cancerous first, and others become cancerous one after another with the extension of time, and the ratio of double primary cancers increases accordingly. (2) Environmental factors, especially smokers, SCC, and SCLC are common. It has also been reported that harmful substances in smoke can mutate P53 gene, which is closely related to the occurrence of DPLC. (3) Iatrogenic factors, such as long-term use of immunosuppressants. (4) Psycho-psychological factors, such as long-term anxiety and depression, decrease autoimmune and increase the probability of illness.<sup>14-16</sup> According to the analysis

of the patient's medical history, this patient has a long history of smoking, and the onset of DPLC may be related to smoking. In addition, the relationship between tumor microenvironment and DPLC has become a hot topic in recent years.<sup>17</sup>

With the development of diagnostic technology, the ACCP updated the diagnostic criteria of sDPLC and added the key points of molecular genetics in 2013.<sup>18</sup> (1) Different histological types, different molecular genetic characteristics or different cancers in situ. (2) When the histological type is the same, the location of the primary focus is different (different lung lobes), and there is no N2, N3 metastasis, and no systemic metastasis. It is proposed to use specific molecular markers or gene point mutation detection to identify the genetic differences between the lesions with the same histological type. Some studies have proven that some molecular markers, such as EGFR and other driver gene mutations, and the expression of cancer-related proteins, such as CLDN2, can be used as a reference to distinguish DPLC from pulmonary metastasis,<sup>19-21</sup> but there is no recognized molecular marker in clinic at present. In this case, the patient's histological type is different, so it is relatively easy to make a definite diagnosis of DPLC. For DPLC with the same histological type, especially sDPLC, it is relatively difficult to make a definite diagnosis, which requires clinicians to carefully identify it with the help of molecular biology methods.

It has been reported that the combination of pathological types of DPLC is adenocarcinoma-adenocarcinoma, followed by adenocarcinoma-SCC, and other combinations are relatively rare,<sup>22</sup> while this patient belongs to the rare SCLC-SCC type.

At present, the treatment methods of lung cancer include surgery, radiotherapy, chemotherapy, molecular targeted drugs, and immunotherapy. However, for MPLC, there are no standard treatment guidelines to date. One study showed that the "Surgery + X" treatment strategy (X including ablation, SBRT, and EGFR-TKIs treatment) showed remarkable efficacy, superiority, and safety in the clinical treatment of early-stage sMPLC.<sup>7</sup> Unfortunately, the patient in this case gave up treatment without any intervention for the lung cancer due to the high treatment costs and family factors.

In short, DPLC is relatively rare clinically, especially bilateral sDPLC is easy to be misdiagnosed or missed. Therefore, in order to improve the early diagnosis of DPLC, doctors should not only improve their understanding of the imaging characteristics of lung cancer and identify the abnormal manifestations under bronchoscope, but also comprehensively consider the risk factors, clinical manifestations, histological types and genetic characteristics of the disease in clinical work. It is hoped that DPLC can be diagnosed and treated early through active and effective

detection methods, so as to improve the survival rate of patients and prognosis.

## AUTHOR CONTRIBUTIONS

**Hai Huang:** Conceptualization; writing – review and editing. **jun li:** Conceptualization; data curation; writing – original draft; writing – review and editing. **bo yin:** Data curation; investigation. **yong liu:** Data curation; investigation.

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All authors have no conflict of interest or financial ties to disclose.

## DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

Written informed consent has been obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy.

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