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CASE REPORT

Metachronous and Synchronous Triple Primary Lung Cancers in a Chronic Smoker

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Abstract

Multiple primary lung cancers (MPLCs), characterized by the presence of more than one distinct primary lung tumors, may develop either synchronously (simultaneously) or metachronously (after initial cancer treatment). This case describes a rare occurrence of three primary lung cancers in a chronic smoker. After a lobectomy for right middle lobe adenocarcinoma (ADC), the patient was diagnosed with synchronous small cell carcinoma (SCLC) in the right upper lobe and squamous cell carcinoma (SCC) in the right lower lobe. Notably, the ADC and subsequent lung cancers were metachronous. Due to her unsuitability for surgery, the patient pursued a treatment regimen involving radiation therapy, chemotherapy, and immunotherapy. This case underscores the need for vigilant identification and comprehensive management of MPLCs, particularly in high-risk patients, to improve outcomes and reduce the burden of this rare condition.

Keywords: Multiple primary lung cancers, Synchronous and metachronous lung cancers, Smoking

1. Case presentation

A woman in her late 60s, with a complex medical history and a significant smoking background of 50 pack-years, visited following a lung cancer screening CT scan that revealed a 1.9 cm tumor in the right middle lobe. Notably she was asymptomatic at the time, negating any cough, weight loss, hemoptysis, chest pain, or shortness of breath. A CT-guided biopsy confirmed adenocarcinoma, leading to a right middle lobectomy and lymph node dissection. The pathologic report revealed a well-differentiated adenocarcinoma (ADC) without lymph node or pleural involvement, staged as a pathologic T1b lesion, consistent with stage I lung cancer.

Her medical history included chronic obstructive pulmonary disease (COPD), coronary artery disease, heart failure, anxiety, depression and prior non-Hodgkin's lymphoma treated with CHOP, radiation therapy, and stem cell rescue, resulting in long-term remission. She had a family history of breast and lung cancers, was a chronic smoker, and had occupational exposure to sandblasting and grinding dusts due to her previous job as a dental technician.

Despite smoking cessation efforts, the patient struggled to quit. After five years, a follow-up CT scan revealed a new 1.6 cm subpleural nodule in the right upper lobe (RUL) (Fig. 1). Further investigations using positron emission tomography (PET) imaging showed hypermetabolic activity in the RUL lesion and right hilar node (Fig. 2). Navigational bronchoscopy and endobronchial ultrasound (EBUS) revealed two tumors: the RUL lesion and an incidental finding of endobronchial tissue obscuring the right lower lobe (RLL) superior subsegment (Fig. 3). Pathology confirmed a poorly-differentiated small cell carcinoma (SCLC) in the RUL, as well as a moderately-differentiated squamous cell carcinoma (SCC) in the RLL lesion with metastasis to the right hilar lymph node. Her two new tumors were consistent with limited stage small

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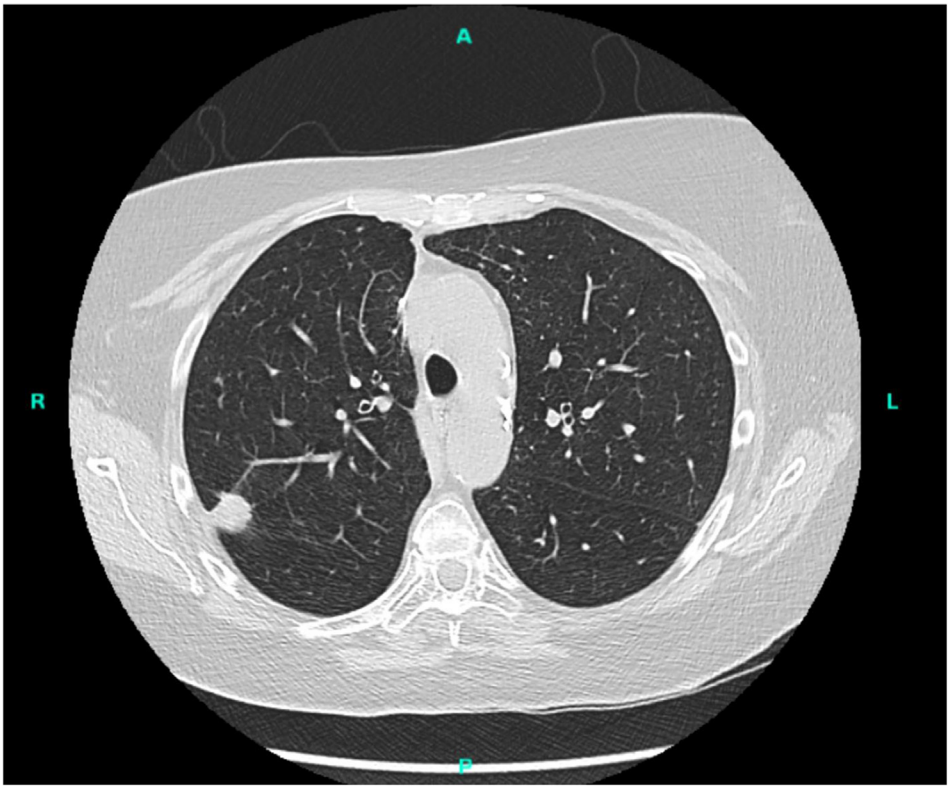

Fig. 1. Computed tomography (CT) scan of the chest. There is a new, mildly lobulated subpleural nodule in the right upper lobe measuring 1.6 x 1.6 cm.

cell carcinoma in RUL and stage II (T2, N1, M0) squamous cell carcinoma in RLL.[1]

Given the complexities and her high surgical risk, a multidisciplinary tumor board recommended a combined treatment approach with radiation therapy and chemotherapy. However, during the simulation session for radiation therapy, new bilateral lung nodules were discovered, raising concerns about extensive stage malignancy from the small cell carcinoma. Consequently, immunotherapy with atezolizumab was integrated into her chemotherapy regimen of carboplatin and etoposide.

After six months of treatment, the patient is maintained on immunotherapy with atezolizumab. The RUL nodule decreased in size to 1.4 cm, with stable bilateral pulmonary nodules. Magnetic resonance imaging (MRI) of the brain and bone scan showed no signs of metastasis. The patient continues to experience chronic symptoms, including cough, exertional dyspnea, and fatigue, attributed to her medical conditions. Smoking cessation remains challenging due to her illness, anxiety, and depression. She's actively participating in a nicotine dependence treatment program and has reduced her daily cigarette consumption to fewer than eight.

2. Discussion

Multiple primary lung cancer (MPLC) is defined as the occurrence of more than one lung cancer, and it is relatively uncommon compared to a single lung cancer. Triple primary lung cancer is even more exceptionally rare within the MPLC category, and, to our knowledge, this is the second documented case reporting triple primary lung cancer with three distinct histologic types.[2] There are currently three main diagnostic criteria for MPLCs: Martini Melamed criteria, ACCP guidelines, and the TNM staging system due to the absence of globally recognized guidelines and diagnostic challenges.[3] In general, MPLC is categorized as synchronous or metachronous. Synchronous MPLC involves new cancer developing concurrently, with either a different histology or the same histology but distinct molecular genetics or locations without mediastinal node involvement or systemic metastases.[4] On the other hand, metachronous MPLC refers to a new cancer with either distinct histology or the same histology appearing after a tumor-free interval of 4 years or more.[4] To define either synchronous or metachronous MPLCs, it is crucial to rule out metastases from other lung lesions, benign nodules,

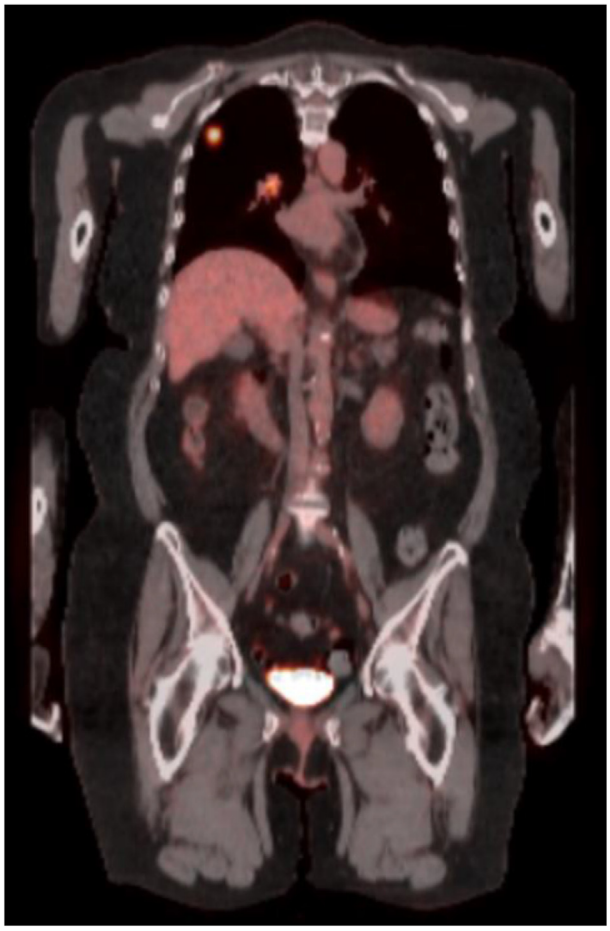

Fig. 2. Positron emission tomography (PET) scan. There are a 1.6 cm right upper lobe mass measuring with a maximum standardized uptake value (SUV) of 11.4 and a hypermetabolic right hilar node with maximum SUV of 8.2.

infectious processes, or extrapulmonary metastasis. Diagnosis can be challenging when the new tumor shares the same histology as a known tumor. In this scenario, molecular genetic analysis plays a crucial role in helping to differentiate MPLCs from intrapulmonary metastasis. In this case, the patient had three primary lung cancers in different sites of the right lung: ADC in RML, SCLC in RUL, and SCC in RLL with right hilar node involvement. The ADC and subsequent lung cancers were metachronous, with a tumor-free period of over 4 years, while the SCLC and SCC were synchronous, discovered simultaneously. The classification of this patient's MPLC types was straightforward given the distinct histologies and locations of these tumors.

Risk factors for MPLCs include smoking, environmental exposures, genetic predisposition, COPD, a previous malignancy (lung, breast, or non-Hodgkin's lymphoma), and a family history of lung cancer, with smoking being the modifiable risk factor.[5,6] Continued smoking increases the risk of developing a second lung cancer more than in non-smokers.[6] Furthermore, patients who underwent a NSCLC resection face a 1–6% per patient-year risk of developing another lung cancer,[6-8] while successfully treated SCLC patients confront a 2–10 % per patient-year risk of additional primary lung cancer.[6] Non-Hodgkin's lymphoma survivors have an increased risk of developing lung cancer, mainly linked to chest radiation exposure, smoking, and female sex.[9] In this case, the patient has multiple risk factors, including smoking, radiation therapy, a history of lung cancer and non-Hodgkin's lymphoma, and a family history of lung cancer, with smoking being the primary modifiable one.

The primary treatment for both synchronous and metachronous MPLCs is surgical resection, as patients are typically diagnosed at an early stage.[4,6-8] It is important to recognize that patients with MPLCs who have previously undergone lung cancer resection may not be suitable candidates for a second lobectomy or pneumonectomy due to their limited pulmonary reserve.[7] In such cases, stereotactic body radiotherapy (SBRT) can be considered as a feasible

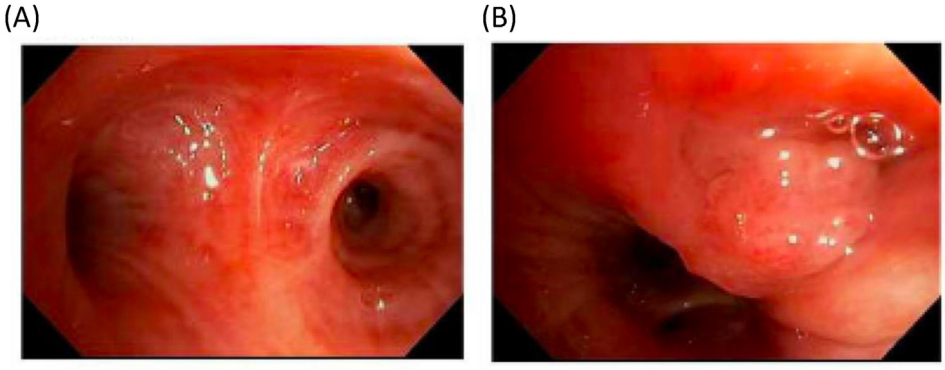

Fig. 3. Navigational bronchoscopy with the right upper lobe (A) and right lower lobe (B) views. The targeted right upper lobe mass was located in the distal part, and the image could not be obtained effectively using the bronchoscopy. The proximal view of the right upper lobe was clear with no mass (A). An incidental finding of endobronchial tissue obstructing the right lower lobe superior subsegment was observed (B).

alternative.[10] In our patient, the presence of two new tumors in the right upper and lower lobes, coupled with her prior right middle lobectomy and moderate COPD, places her at a high risk of respiratory failure, making her an unsuitable surgical candidate.

Adjuvant therapy for MPLCs lacks sufficient study data, necessitating individualized consideration and shared decision-making with patients. In cases of extensive-stage SCLC, combining chemotherapy (carboplatin and etoposide) with the immunotherapy (atezolizumab) has demonstrated synergistic effects, improving survival outcomes.[11] This is followed by maintenance atezolizumab until unacceptable toxicity, disease progression, or no further clinical benefit is observed.[11] For inoperable stage II NSCLC, concurrent chemoradiation is recommended. Preferred chemotherapy options include paclitaxel, carboplatin, cisplatin, and etoposide.[1] Our patient was initially diagnosed with limited-stage SCLC in the RUL, but it was later suspected to be extensive stage due to the appearance of new bilateral lung nodules. Additionally, she was diagnosed with stage II (T2, N1, M0) SCC in the RLL. For her extensive-stage SCLC, we administered a combination of chemotherapy (carboplatin and etoposide) and immunotherapy (atezolizumab), followed by maintenance atezolizumab. Her stage II SCC was treated with concurrent chemoradiation using the same chemotherapy regimen of carboplatin and etoposide that are commonly used for SCLC.

In summary, this case underscores the challenges in diagnosing and managing MPLC, especially in high-risk patients. It also emphasizes the significance of smoking cessation as a modifiable risk factor.

Disclaimers

This is a modified version of a poster presentation that was originally presented at the 2023 Chest Conference in Hawaii on October 9th, 2023.

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Conflict of interest

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