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Case Report

Concurrent Small Cell and Non-Small Cell Lung Cancers: The Diagnostic and Management Challenges of Synchronous Primary Lung Tumors

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INTRODUCTION

Lung cancer patients may present with two distinct primary tumors simultaneously, a condition termed synchronous primary lung cancers (SPLC), or they may develop a second primary lung cancer during or after treatment of the initial tumor, referred to as metachronous primary lung cancer.[1] Advancements in lung cancer screening, surveillance, and management have led to an increase in the incidence of these conditions, posing significant challenges in accurate diagnosis, classification, and management.[1] These challenges arise from the complexities of obtaining tissue samples from multiple intrapulmonary lesions, distinguishing the molecular and histological profiles of different tumors, and addressing the lack of consensus on management strategies, which often depend on the degree of similarity between tumors.[1,2]

Although SPLC is increasingly recognized, it remains uncommon, with a reported prevalence of 0.5% to 5%.[3] SPLC typically is defined as the presence of two or more anatomically distinct cancerous regions within the lungs that are not connected via common lymphatic channels.[3] This scenario raises critical questions about which lesions should be prioritized for biopsy in patients with multiple suspicious lung lesions. Current guidelines highlight the importance of multidisciplinary team (MDT) involvement, including radiologists, oncologists, pathologists, thoracic surgeons, and pulmonologists, to accurately define SPLCs and determine the most appropriate lesions to biopsy within the broader clinical context.[4]

In this report, we describe the case of a woman diagnosed with SPLCs exhibiting two distinct histological types of cancer.

CASE REPORT

The patient was a 67-year-old woman with a medical history of hypertension, dyslipidemia, hypothyroidism, a 50 pack-year smoking history, and chronic obstructive pulmonary disease (COPD). Her family history is significant for cancer, as her father had been diagnosed with both prostate cancer and a brain tumor.

Initial Presentation and Imaging. In March 2022, a chest computed tomography (CT) scan performed to monitor stable, bilateral, sub-centimeter pulmonary nodules revealed:

- Right upper lobe: 5 x 4 mm nodule
- Right lower lobe: 5 mm nodule
- Left costophrenic angle: 5 mm nodule

The nodules remained stable over time. Additionally, a spiculated, irregular mass in the right lower lobe was identified, measuring 2.7 x 2.5 cm, without associated lymphadenopathy. Background emphysematous changes were noted. A CT-guided core needle biopsy of the right lower lobe mass yielded negative results for malignancy.

Loss to Follow-Up and Recurrence. The patient remained asymptomatic and was lost to follow-up until May 2024, when a chest CT was performed following an abnormal chest X-ray. This revealed:

- Enlargement of the right lower lobe mass to 4.9 x 4.5 cm
- A right perihilar lymph node measuring 3 x 2.2 cm, suggestive of nodal metastasis

The previously identified bilateral pulmonary nodules remained stable. A repeat CT-guided biopsy confirmed invasive, moderately differentiated squamous cell carcinoma. The patient was referred to oncology for further evaluation and consideration of chemoradiation.

Advanced Imaging and Biopsy. A positron emission tomography (PET) scan revealed:

- Intense hypermetabolic activity in the right lower lobe mass
- Hypermetabolic metastatic adenopathy in the right hilum and a suspicious right paratracheal lymph node

Endobronchial ultrasound-guided biopsy of the right hilar mass revealed small cell lung cancer (SCLC), distinct from the squamous cell carcinoma (SCC) diagnosed in the right lower lobe.

Diagnosis and Management. The patient's cancer was staged as:

- Non-small cell lung cancer (NSCLC; Squamous Cell Carcinoma): Stage IIA (T2b N0 M0): Tumor > 4 cm but ≤ 5 cm (T2b), with no nodal involvement (N0) and no distant metastasis (M0)
- SCLC: Limited stage, with nodal involvement attributed to the SCLC diagnosis

The patient underwent concurrent chemoradiation, consisting of four cycles of cisplatin and etoposide with radiotherapy starting from the second cycle. Plans were made to initiate adjuvant immunotherapy with durvalumab.

DISCUSSION

SPLCs remain rare.[3] As a result, clinicians often attribute multiple lesions in the same lung, particularly when one lesion is anatomically downstream from another to intrapulmonary spread rather than distinct primary tumors. However, accurate differentiation between multiple primary lung cancers and intrapulmonary spread is critical, as it significantly impacts both management strategies and prognosis. While most synchronous multiple primary lung cancers share similar histologic features, this case illustrates that lesions also can exhibit markedly different histologic characteristics.[1,5]

This case underscores the growing importance of precise histopathologic and molecular characterization for each lung lesion in suspected SPLC. With the rise of personalized cancer treatments, such as targeted therapies and immunotherapy agents tailored to specific molecular mutations, accurate identification of each primary lesion is essential for optimal treatment planning.

The presented case also highlights the diagnostic complexity of SPLC and emphasizes the need for thorough staging, including tissue

biopsy, to avoid misdiagnosis and ensure appropriate management. It also serves as a reminder that SPLCs easily can be overlooked without a high index of suspicion. A multidisciplinary team approach is crucial to navigating these challenging cases and optimizing patient outcomes.

SPLC poses unique management challenges that directly can affect prognosis.[6] Unlike NSCLC, which uses the Tumor, Node, Metastasis staging system, SCLC is primarily staged as limited or extensive disease.[7] Standard treatment for limited-stage SCLC includes four cycles of cisplatin and etoposide with concurrent thoracic radiotherapy.[7] The ADRIATIC trial demonstrated improved progression-free and overall survival with durvalumab as adjuvant therapy for up to two years in patients who show no disease progression after standard chemoradiotherapy, without requiring prior molecular biomarker testing.[8] This treatment strategy aligns with the regimen used for the patient described.

Surgical intervention rarely is indicated for SCLC and is reserved for limited-stage cases without lymph node involvement or other contraindications.[7] Conversely, early-stage NSCLC (Stages I/II) typically is managed with surgical resection or radiotherapy for non-surgical candidates, with adjuvant therapies tailored to specific mutations and clinical indications.[9] The described patient, a non-surgical candidate, is being treated with radiotherapy and platinum-based chemotherapy, an effective approach for NSCLC cases without driver mutations.[9]

There are no established guidelines specifically addressing SPLC, making multidisciplinary collaboration and sound clinical judgment indispensable.[6] Prognosis in SPLC is influenced by factors such as tumor size, histology, and stage. Cases with distinct histologies, like the one presented here, often carry a worse prognosis.[6] This highlights the importance of individualized treatment plans and continued research into SPLC management.

CONCLUSIONS

This case underscores the critical role of multidisciplinary collaboration in the diagnosis and management of SPLCs. A comprehensive approach that includes detailed imaging evaluations and targeted tissue biopsies is essential for distinguishing between multiple primary lung cancers and intrapulmonary metastasis. Accurate differentiation directly guides treatment strategies and significantly influences patient outcomes and prognosis.

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