Case Report

Small cell carcinoma of the lung in a patient with previously treated synchronous adenocarcinoma and squamous cell carcinoma

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ABSTRACT

A 66-year-old Caucasian female with a 40-pack-year history of smoking and chronic obstructive pulmonary disease presented for follow-up of synchronous multiple primary lung cancers: Stage IB left upper lobe adenocarcinoma and Stage IA right middle lobe (RML) squamous cell carcinoma. The patient was treated with left upper lobectomy and RML pulmonary wedge resection 5 years prior. Surveillance chest computed tomography showed an increase in the size of the subcarinal lymph node and right lymph node conglomerate encasing the right upper lobe pulmonary artery, consistent with metastasis. Fine-needle aspiration of level 4R lymph nodes was performed. Histology and immunohistochemical staining confirmed the diagnosis of small cell carcinoma. Consequently, the patient was placed on cisplatin/etoposide combination chemotherapy.

KEY WORDS: Chronic obstructive pulmonary disease, left upper lobe, multiple primary lung cancers, non-small cell lung carcinoma, right middle lobe, small cell lung carcinoma

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INTRODUCTION

Lung cancer is highly aggressive and the most common cause of cancer-related mortality in men and women in the United States of America.[1] Approximately 90% of lung cancers are associated with smoking and tobacco products.[2] Lung cancers are divided into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) based on histology.[3] Multiple primary lung cancers (MPLCs) are a rare occurrence and have two forms – synchronous MPLC (sMPLC) and metachronous MPLC (mMPLC). sMPLC presents relatively at the same time in the patient, while mMPLC occurs later in life. MPLCs can be either physically distinct with different histological subtypes or of a similar subtype. If the MPLC is of a similar subtype, it must be in different lung lobes, originate from carcinoma *in situ*, or not be involved in common lymphatics & extrapulmonary metastase. In addition, mMPLCs must present after a 2-year cancer-free interval.[4] mMPLC is common and typically occurs secondary to the treatment of initial lesions. Tobacco smoke may also create a "field effect" in which multicentric

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lung cancers manifest more frequently.[5] There are no set diagnostic criteria for the diagnosis of MPLCs due to tumor heterogeneity; therefore, the American College of Chest Physicians recommends a multidisciplinary tumor board approach in the diagnosis.[6] Most MPLCs are treated with surgical resection; however, the standard surgical strategies for MPLCs are not well established. Patients with chronic cardiopulmonary conditions who are not surgical candidates may be treated with stereotactic body radiation therapy (SBRT).[4]

CASE REPORT

In August 2015, a 61-year-old White female presented to her primary care provider with concerns regarding a 12-lb weight loss in the past 3 months. Given the patient's social history of 40-pack-year smoking and the patient's family history of lung cancer, a lung cancer screening CT was performed. The CT showed a 3.2 cm × 4.1 cm posterior left upper lobe (LUL) pulmonary mass with extension to the pleural margin as well as a 7 mm right middle lobe (RML) nodule. Subsequently, diagnostic bronchoscopy with LUL and RML video-assisted thoracoscopic surgery (VATS) wedge resection and left and right mediastinal lymph node dissection was conducted. In addition, VATS LUL completion lobectomy was conducted. Histologic examination revealed a Stage IB LUL adenocarcinoma [Figure 1] and a stage IA RML squamous cell carcinoma (SCC) [Figure 2]. From 2016 to 2019, several follow-up CTs were conducted to monitor for possible recurrence. Early follow-up CTs indicated changes that were consistent with expected postsurgical findings. No new pathologically enlarged mediastinal lymph nodes or evidence of metastasis in the chest, abdomen, or pelvis were detected. However, in January 2020, CT findings demonstrated a noticeable interval increase in the size of the subcarinal lymph node and right lymph node conglomerate encasing the RUL pulmonary artery concerning for local metastasis (a).

The patient now presents at our institution for a follow-up on her NSCLC following the concerning CT scan. She presents with dyspnea and cough secondary to chronic obstructive pulmonary disease (COPD) but denies worsening shortness of breath and hemoptysis. The patient continues to smoke daily. Physical examination of the respiratory system demonstrates scattered rhonchi and expiratory wheezing bilaterally without rales or labored respiration. Overall impression suggests pulmonary findings consistent with COPD with imaging concerning for carcinoma recurrence and metastasis. Pulmonology specialists met with the patient and ascertained a history and physical examination consistent with that previously indicated. The CT findings and the need for a lung biopsy to confirm for metastasis were discussed with the patient. Endobronchial ultrasound bronchoscopy was used to sample the mediastinal and hilar lymph nodes. Histological examination revealed clustered cells with nuclear molding, inconspicuous nuclei, and crush artifact. Immunohistochemical findings revealed thyroid transcription factor-1 (TTF-1)-positive, synaptophysin-positive, and P40-negative malignant cells (b and c). The overall findings confirm the diagnosis of small cell carcinoma [Figure 3]. The patient was placed on cisplatin/etoposide combination therapy tentatively. The patient will be followed up to discuss results and finalize care.

DISCUSSION

SCLC and NSCLC are known to be linked with tobacco use, thus creating a "field effect" that promotes the

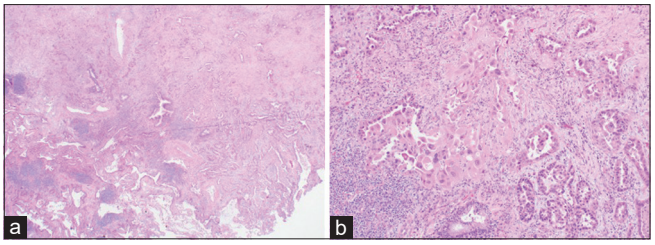

Figure 1: Adenocarcinoma. (a) On low magnification, diffusely infiltrated sheets of solid and acinar tumor clusters in the background of lymphoid aggregate. (b) On high magnification, infiltration of pleomorphic tumor cells in solid and glandular growth pattern with prominent nuclei, conspicuous nucleoli, and abundant cytoplasm

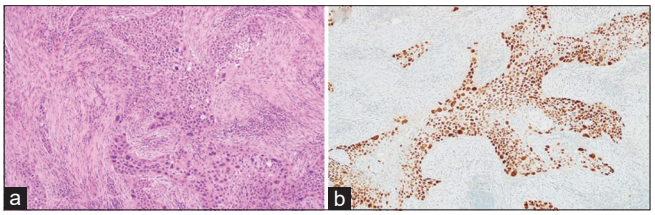

Figure 2: Squamous cell carcinoma. (a) Solid sheets of tumor cells with severe nuclear polymorphism and abundant desmoplastic stroma. (b) P40 stains show strong nuclear positivity in tumor cells

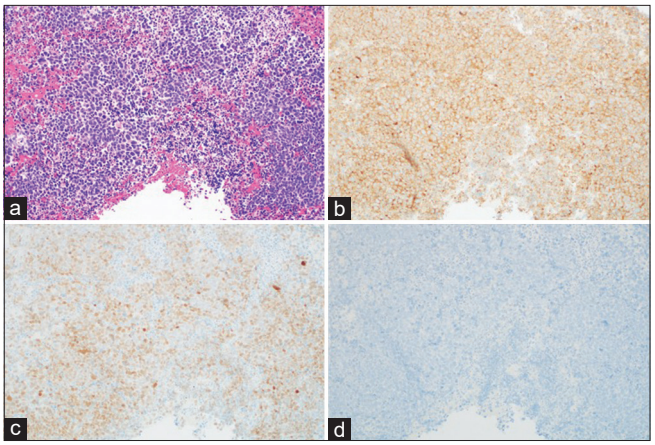

Figure 3: Small cell carcinoma. (a) Sheets of small round blue cells with high nuclear-to-cytoplasmic ratio, nuclear molding, and single cell necrosis. (b) Synaptophysin stain reveals membranous and cytoplasmic staining in tumor cells. (c) Thyroid transcription factor-1 reveals moderate-to-weak nuclear staining of tumor cells. (d) P40, negative in tumor cells

possibility of MPLCs. NSCLCs include adenocarcinoma and SCC. Pathologic diagnosis of SCLC and NSCLCs is based on morphology and pattern of immunohistochemical staining. In our case, the diagnosis of small cell carcinoma was supported by positive TTF-1 and synaptophysin and negative P40. This diagnosis would qualify as mMPLC due to histological differences when compared to the initial tumors and its occurrence more than 4 years after the initial lung cancers.

Stage classification of multiple lesions is critical for surgical treatment because it allows consistent diagnosis of patients; however, the staging guidelines for MPLCs are ambiguous. The diagnosis of MPLCs should be based on a comprehensive review of all available information by a multidisciplinary tumor board.[6] For sMPLC, each tumor should be staged and treated separately and one TNM stage should be given based on a combination of all tumors. For mMPLC, the second tumor should be staged and treated as a primary tumor, independent of prior tumors.[4]

The treatment of mMPLC is often surgical resection; however, feasibility must be assessed based on the pulmonary reserve. Limited resections should be attempted in all cases as segmentectomies have similar outcomes to lobectomies in terms of recurrence-free survival, notably in tumors under 3 cm. Patients with reduced pulmonary reserve associated with an earlier resection may not be suitable candidates for further resection however may benefit from nonsurgical treatment such as SBRT.[4] In the case of adenocarcinoma, genetic profiling should be done to assess for activating EGFR mutations and ALK rearrangements as these are useful targets for treatment with EGFR tyrosine kinase inhibitors or ALK inhibitors.[7] Consideration should be given to the genetic profile of all existing lesions as a lack of these mutations in other lesions may limit the use of the targeted therapies in the management of MPLCs.[4,7] In general, patients with sMPLCs have a poorer prognosis than those with single primary lung cancer. Patients with mMPLC have a similar prognosis in terms of overall survival as compared to those with sMPLCs. In addition, patients with MPLCs have a better prognosis than patients with multifocal lesions designated as intrapulmonary metastasis.[8]

CONCLUSION

In patients with a history of MPLC associated with smoking, physicians should be cognizant of additional malignancies different from the original lesion subtype. Histopathologic examination is the gold standard for diagnosis. Surgery is the standard treatment in MPLC, but clinicians should assess for sufficient pulmonary reserve to ensure viability.

Acknowledgment

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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