

Adenocarcinoma of Lung and Bronchial Carcinoid Presenting as Double Synchronous Primary Lung Cancer: A Case Report and Review of Literature

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Abstract

Recent advances in imaging techniques led to an increase in the incidence of synchronous and metachronous primary lung cancers due to early detection. Management of these patients is challenging and prognosis depends on the stage of the tumor at initial diagnosis and histological type. A 68-year-old African American male patient with medical history of hypertension and diabetes mellitus presented to our emergency department with right sided chest pain, worsening dyspnea and dry cough of 2-week duration. He also reported significant weight loss and was a smoker with 25 pack-years smoking history. Chest radiology showed a large right pleural effusion. Subsequent thoracentesis and fluid analysis revealed a lymphocytic exudate. Patient underwent bronchoscopy with findings of an endobronchial lesion in the left lower bronchus. Microscopic analysis of the biopsy specimen showed a well differentiated carcinoid. It was decided to proceed with VATS and pleural biopsy as part of workup for unexplained exudative pleural effusion. Multiple pleural nodules were detected during the procedure and biopsy of these nodules revealed adenocarcinoma of lung. He was evaluated by Oncology and underwent palliative chemotherapy. The association of carcinoid with adenocarcinoma of lung was infrequently reported in the past. This case also highlights the importance of additional diagnostic workup for primary when the diagnosed malignancy does not explain the clinical presentation.

Keywords: Pleural effusion; Smoking; Bronchoscopy; Dyspnea; Neuroendocrine tumor

Introduction

Despite advances in technology, the incidence of lung cancer

is increasing and remains the most common cause of cancer-related deaths. Multiple primary lung cancers are rare and can be synchronous or metachronous. When different primary lung cancers are simultaneously detected in a patient, they are referred to as synchronous primary lung cancers. Metachronous cancers are tumors that occur at different times in the same patient. If the tumors are histologically identical, a tumor-free period of at least 2 years is required for diagnosis. Diagnosis of these cancers remains a challenge as multiple lesions on imaging can be mistaken for a metastatic tumor. The distinction between the two has great therapeutic and prognostic implications. We report a case of a 68-year-old man who presented to our hospital with a massive right pleural effusion. He was diagnosed with synchronous carcinoid and adenocarcinoma of the lung with pleural metastasis. We also present a detailed discussion on literature published in the past and optimal management of these patients.

Case Report

A 68-year-old man presented to the emergency room with right sided chest pain, worsening dyspnea and dry cough of 2-week duration. He also reported weight loss of 40 pounds in 2 months without fever or night sweats. His medical history was significant for hypertension and diabetes mellitus. He had a left below knee amputation in 2010. He had no family history of lung disease or cancers. He was a smoker with 25 pack-years smoking history and admitted using marijuana occasionally. He was from Jamaica and immigrated to the United States in 1982.

Physical examination revealed a thin, cachectic man with digital clubbing, a systolic murmur along left sternal border and decreased air entry on the right side. There was no palpable lymphadenopathy. He had a chest X-ray on arrival which showed massive right pleural effusion with compression of the heart and had emergent chest tube placement (Fig. 1). Pleural fluid was serosanguinous and analysis was consistent with a lymphocytic exudate, cultures remained negative and fluid cytology was negative for malignant cells. CT scan of the chest revealed a loculated right pleural effusion and mediastinal adenopathy (Fig. 2). He underwent a repeat thoracentesis and fluid cytology was positive for atypical cells. Laboratory parameters are shown in Table 1.

Fiberoptic bronchoscopy and EBUS guided transbronchial needle aspiration of subcarinal and right lower paratracheal lymph nodes were performed. There was an endobronchial lesion in the left lower bronchus, pathology revealed neuroendocrine tu-

Manuscript submitted June 13, 2018, accepted June 26, 2018

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doi: <https://doi.org/10.14740/wjon1129w>

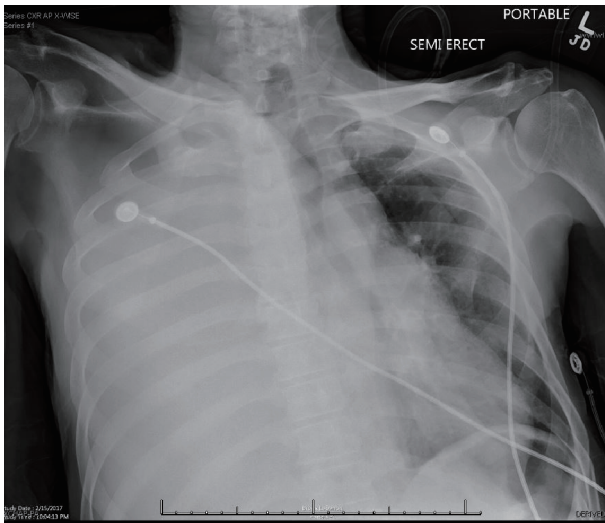


Figure 1. Chest X-ray showing complete right hemithorax opacification with mediastinal shift to the left.

mor consistent with well differentiated carcinoid (Fig. 3). Immunohistochemistry was positive for TTF-1, synaptophysin, chromogranin, CD56 and negative for CK-7, CD20 and LCA (Fig. 4). Mediastinal node sampling was negative for malignancy. Patient underwent right sided VATS for pleural effusion of unknown etiology and was found to have multiple pleural nodules. The biopsy of these nodules was consistent with lung adenocarcinoma. Immunohistochemistry was positive for CK-7, TTF-1, CDX-2 and negative for synaptophysin, chromogranin, napsin-A, CK-20 (Fig. 5). The tumor was negative for EGFR, KRAS mutations, ALK rearrangement and PD-L1 expression. He had a Pleurex catheter placed for long-term drainage of effusion.

There was no evidence of metastasis to brain and bone. He was evaluated by Oncology and discharged to a rehabilitation facility with a plan for palliative chemotherapy considering metastasis to pleura.

Discussion

The first case of multiple primary lung malignancies was re-

ported in 1924 by Beyreuther in post mortem studies, which was a well differentiated squamous cell carcinoma in right lung and adenocarcinoma in left lung [1]. Since then, there have been many case reports and studies describing multiple primary lung cancers with association of squamous cell with squamous cell cancer being the most common followed by squamous cell and small cell carcinoma [2]. The incidence of these cancers, as reported in previous studies, is variable ranging from less than 1% to as high as 16%. Synchronous lung cancers are significantly rarer than metachronous cancers with an average incidence of 0.5% of all lung cancers [3].

Warren and Gates published the original criteria for multiple lung cancers in 1932 [4]. Martini and Melamed in 1975 suggested that to diagnose multiple synchronous primary lung tumors, each tumor should be physically distinct from the other and should be malignant with a different histology. If histology is same, tumor should be located in a different segment, lobe or lung; with absence of carcinoma in common lymphatics and exclusion of extrapulmonary metastasis [5]. In 1995, Antakli et al added DNA ploidy to the diagnostic criteria of tumors with identical histology [6]. The criteria were further modified by the American College of Chest Physicians in 2007 and the update suggests a possibility of metastasis rather than a second primary lung cancer in patients with either a synchronous or a metachronous presentation with an interval of less than 4 years between tumors. The outcomes are variable and generally poor after resection in such patients [7].

Smoking related carcinogenic insults, leading to cellular atypia and allele-specific imbalance in different areas of bronchial mucosa, has been implicated as the cause of multifocality of these lung tumors in several studies [8, 9]. The association of lung adenocarcinoma and bronchial carcinoid is extremely rare and one such report was published in 1966 by Roberts and Cumming [10]. In 1980, Ranchod and Levine published a series of 35 patients with spindle cell carcinoid tumor of which one patient had evidence of adenosquamous carcinoma in the resected specimen [11].

Nagamatsu et al reported a case of cancer-in-cancer and the resected specimen showed a carcinoid component localized within the central fibrous scar of the dominant adenocarcinoma component [12]. A case of five synchronous and metachronous lung cancers in a single patient that developed in a span of 7 years was reported in 2004. The synchronous malignancies were

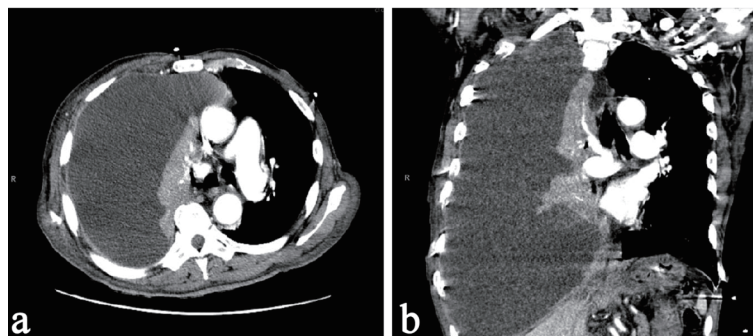


Figure 2. (a) Coronal view CT chest showing massive right pleural effusion with atelectasis of right lung and mediastinal shift to the left. (b) Sagittal view of CT chest showing massive right pleural effusion with atelectasis of right lung and mediastinal shift to the left.

Table 1. Laboratory Parameters

Pleural fluid analysis	
Appearance	Cloudy
WBC count	184 (76% lymphocytes)
RBC count	5,035,000
Lactate dehydrogenase	534
Protein	5.1
Glucose	273
Adenosine deaminase	20
Mycobacterium tuberculosis PCR	Negative
Aerobic culture	Negative
AFB culture	Negative
Sputum AFB × 3	Negative
Connective tissue disease workup	
Antinuclear, anti DNA, anti JO-1, anti GBM, anti CCP, anti Scl-70, anti Sm, anti RNP antibodies, rheumatoid factor, ANCA vasculitides	Negative
HIV antibody	Negative
QuantiFERON-TB	Indeterminate

poorly differentiated squamous cell carcinoma, moderately differentiated adenocarcinoma and a small typical carcinoid [13]. A case of triple synchronous lung cancer with bronchial carcinoid, small cell carcinoma and adenocarcinoma of the lung was reported in 1986 by Jung-Legg et al. This patient also had a rectal carcinoid [14]. Yano and colleagues reported another case of bronchial carcinoid and lung adenocarcinoma in 2002 [15].

The optimal management of patients with multiple primary lung tumors is controversial. If the clinical stage of the tumor and functional status of the patient permit, surgery is the treatment of choice. The two tumors should be staged separately and extensive mediastinal staging and imaging to rule out metastasis is required prior to surgical resection. Stereotactic body radiation

therapy (SBRT) is a novel radiation therapy which has been used in lung cancer management. The 5-year survival in retrospective studies in patients who underwent SBRT was between 51% and 70% [16]. Chang et al reported a 2-year survival rate of 61.5% and 4-year survival rate of 39% with stereotactic ablative radiotherapy (SABR) in early stage multiple synchronous lung cancers with contraindications to surgical resection [17]. An aggressive surgical approach in patients with synchronous lung cancers was shown to have a similar survival benefit when compared to single lung cancer by Finley et al in 2010 [18].

The prognosis of patients with synchronous or early metachronous (< 2 years) was shown to be worse when compared with late metachronous (> 2 years) lung cancers [19]. In a study of 346 post-surgical patients with stage I non-small cell lung cancer, Pairolero et al reported a survival of 51% in patients with a second primary lung tumor at the end of 2 years where as the survival for patients with local recurrence and distant metastasis was 23% and 8% respectively [20]. In 1989, van Bodegom et al demonstrated that patients with multiple primary cancers have a better survival than advanced tumors [21]. Since the year 2000, there were more than 20 reported cases and 20 original studies that mainly analyzed the long-term prognosis of patients with synchronous primary lung cancers. A systemic review and meta-analysis of 1,796 patients with multiple primary lung cancers in 22 studies confirmed a better survival in these patients when compared to intrapulmonary metastasis [22].

Our patient had a rare association of bronchial carcinoid with metastatic adenocarcinoma of lung. As reported in previous studies, smoking could be a contributing factor for the development of synchronous lung cancers in our patient [23]. Although bronchoscopy revealed an endobronchial lesion which later revealed a carcinoid tumor, it was decided to proceed with VATS for further evaluation of his pleural effusion of unknown etiology. It was unfortunate that our patient had

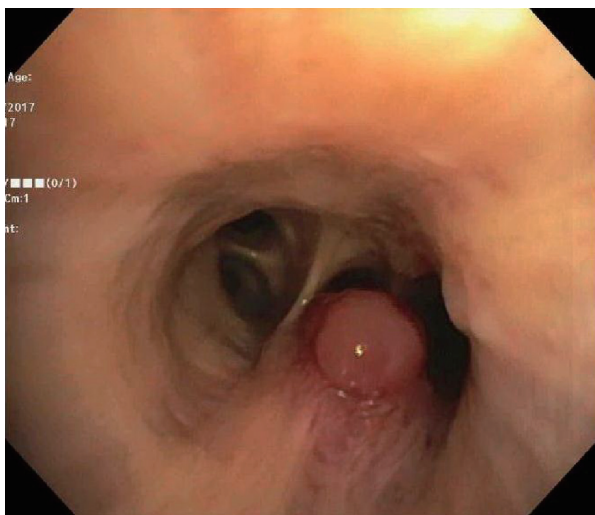


Figure 3. Fiberoptic bronchoscopy revealed an endobronchial lesion in left lower bronchus.

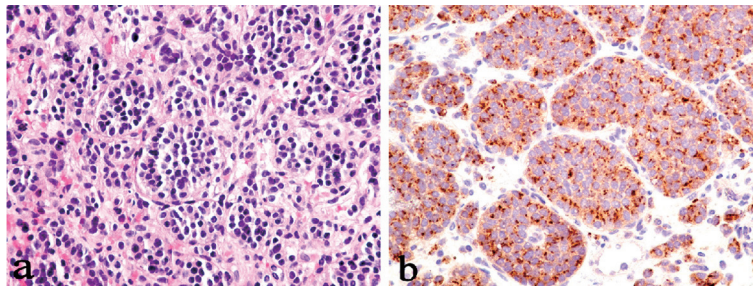


Figure 4. (a) Endobronchial biopsy: carcinoid tumor, high power of organoid pattern with uniform nuclei and no mitosis or necrosis (H&E, magnification $\times 400$). (b) Carcinoid tumor: the tumor cells are immunoreactive to neuroendocrine marker chromogranin (magnification $\times 400$).

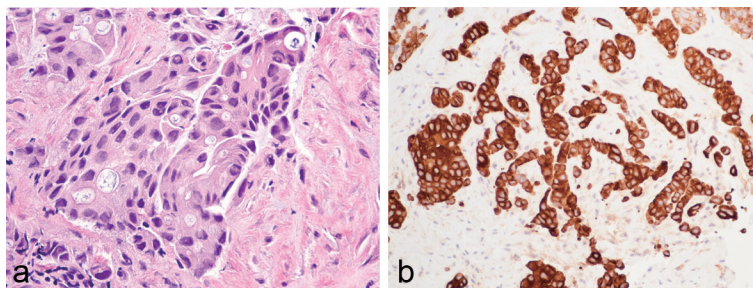


Figure 5. (a) Pleural mass biopsy on high magnification showing acinar pattern of adenocarcinoma composed of glands lined by malignant cells. Some cells show cytoplasmic vacuoles (H&E, magnification $\times 400$). (b) Pleural mass biopsy: the malignant cells are strongly positive for immunomarker cytokeratin -7, which supports the diagnosis of lung primary (magnification $\times 400$).

stage IV adenocarcinoma with pleural metastasis at the time of presentation. Hence, the only treatment that could be offered was palliative chemotherapy.

Conclusions

The frequency of synchronous multiple primary lung cancers has been increasing in the recent years because of the development of early detection techniques and advances in cancer therapy, thus improving patient survival. Nevertheless, the combination of adenocarcinoma with bronchial carcinoid has been described infrequently in the past. A high clinical suspicion for a second malignancy is essential in cases where initial diagnostic workup does not explain underlying clinical presentation. Early diagnosis when tumor is resectable can improve survival in patients with multiple primary lung tumors.

Disclosure

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regard-

ing the publication of this paper.

Abbreviations

ALK: anaplastic lymphoma kinase; CK-7: cytokeratin-7; CK-20: cytokeratin-20; CT: computed tomography; EBUS: endobronchial ultrasound; EGFR: epidermal growth factor receptor; LCA: leukocyte common antigen; PD-L1: programmed death ligand 1; TTF-1: thyroid transcription factor 1; VATS: video assisted thoroscopic surgery; X-ray: roentgenogram

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