Clinical Case Report

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Different histological types of triple metachronous primary lung carcinomas in 1 patient

Case report

Jee Hyuk Kim, MD[a], Seung Yong Park, MD, PhD[a], Seoung Ju Park, MD, PhD[a], Myoung Ja Chung, MD, PhD[b], Heung Bum Lee, MD, PhD[a,*]

Abstract

Introduction: The documented incidence of multiple primary lung cancer has increased as a result of the widespread use of early detection tools. We report the successful surgical treatment of a case who had consecutive metachronous adenocarcinoma and squamous cell carcinoma of the lung after successful treatment for small cell carcinoma of the lung.

A 73-year-old man underwent a routine health check-up. Computed tomography showed ground-glass opacity in the upper lobe of the right lung, which was diagnosed as small cell carcinoma. Twenty-nine months after concurrent chemoradiotherapy for the carcinoma, which was in complete remission, a nodule was detected in the apical segment of the right upper lobe. Histopathologically, the tumor was diagnosed as poorly differentiated adenocarcinoma. The second metachronous adenocarcinoma was completely removed by right upper lobectomy with lymph node dissection. Seventeen months later, the patient underwent left upper lobectomy with lymph node dissection and received 4 cycles of adjuvant chemotherapy for another moderately differentiated squamous cell carcinoma.

Conclusion: This case highlights the need for continuous screening for metachronous lung cancer following the successful treatment of primary lung cancer, even small cell carcinoma, to identify patients who could benefit from curative surgery.

Abbreviations: CT = computed tomography, FDG = fludeoxyglucose, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MPLC = multiple primary lung cancer, PET-CT = positron emission tomography-computed tomography.

Keywords: carcinoma, lung, metachronous

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Approximately 8% of all newly diagnosed cancers occur in patients with a prior history of primary cancer.[1] The incidence of multiple primary lung cancer (MPLC) has increased as a result of the widespread use of tools such as spiral computed tomography (CT), [^{18}F] fludeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), and endoscopy,[2] all of which aid in early detection.

In 1975, Martini and Melamed [3] outlined the criteria for MPLC and proposed that tumors are "synchronous" when they are detected or resected simultaneously and "metachronous" when a second tumor is detected sometime after the first. The probability of detecting MPLC that fulfill these criteria ranges from 1% to 15% per patient per year.[4] Nonetheless, there are no guidelines or detailed recommendations for the selection and treatment of patients with synchronous or metachronous MPLC.

Herein, we describe the successful surgical treatment of consecutive metachronous adenocarcinoma and squamous cell carcinoma of the lung after successful treatment for small cell carcinoma of the lung in a 73-year-old man.

2. Case presentation

A 73-year-old man, who was a current smoker (50 packs per year), underwent a health check-up. His medical history included hypertension, transient ischemic attack, and a herniated lumbar disc.

Chest radiography showed a linear nodular opacity in the right upper lobe (Fig. 1), and spiral CT of the chest demonstrated heterogeneously enhanced ground-glass opacity in the right upper bronchus (Fig. 2A). Bronchoscopy showed a hypervascular endobronchial mass at the opening of the right upper bronchial division (Fig. 2C). Hematoxylin and eosin staining showed typical small cell carcinoma features and tumor cells demonstrated positive staining for chromogranin A, synaptophysin, and

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[a] Department of Internal Medicine, Research Center for Pulmonary Disorders, [b] Department of Pathology, Chonbuk National University Medical School, Jeonju, South Korea.

[*] Correspondence: Heung Bum Lee, Department of Internal Medicine, Chonbuk National University Medical School, Deokjin-gu, Jeonju, Republic of Korea (e-mail: lhbmd@jbnu.ac.kr).

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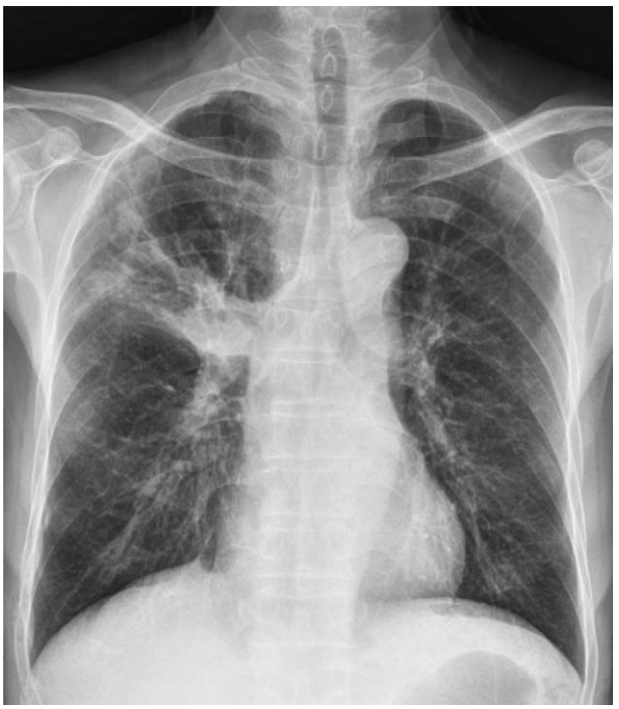

Figure 1. Chest radiograph obtained during a health checkup showing a linear nodular opacity in the right upper lobe.

CD56 (Fig. 2D). These findings confirmed that the tumor is a small cell carcinoma.

PET-CT revealed a hypermetabolic nodular lesion obstructing the right upper bronchus and consolidated, uneven FDG uptake in the right hilar area (Fig. 2B). The patient was treated with concurrent chemoradiotherapy for the limited-stage small cell lung carcinoma. Chemotherapy regimens were cisplatin (75 mg/m^2) and etoposide (100 mg/m^2) every 3 weeks, and he was performed CT scans for restaging for progression of the primary cancer every 2 to 3 months. Concomitant 3-dimensional conformal radiation therapy was given by gross tumor volume of 2 Gy daily, 25 fractions as a total dose.

After which the primary carcinoma appeared to be in complete remission. The patient was engaged in a regular follow-up program to undergo screening tests for recurrence of the primary cancer every 6 months during the first 2 years and annually thereafter.

Twenty-nine months after concurrent chemoradiotherapy, a 1.2-cm nodule was detected in the apical segment of the right upper lobe, which was retrospectively determined to have increased in volume over the past 6 months on spiral CT images (Fig. 2E). Bronchoscopy showed a single, round, intraluminal, protruding nodule at the opening of the right upper anterior segment (Fig. 2G). Bronchoscopic cytology demonstrated atypical cells with morphology suggestive of carcinoma. PET-CT, brain MRI, and bone scintigraphy findings confirmed that there was no recurrence of the previous carcinoma and no regional or distant metastasis (Fig. 2F). The results of a pulmonary function test indicated that the patient could tolerate lobectomy: the forced expiratory volume in 1 second (FEV_1) was 2.12 L (104% of the predicted value) and the forced vital capacity (FVC) was 3.04 L (99% of the predicted value). The patient successfully underwent curative right upper lobectomy with lymph node dissection. The histopathology was consistent with adenocarcinoma, acinar predominant type (Fig. 2H), and the pathologic stage was pT1aN0. There was no small cell carcinoma component. Because the pathologic stage was stage IA, he was checked for imaging studies every 6 months for recurrence without any adjuvant treatment.

After 17 months since the right upper lobectomy, CT showed 2 adjacent nodules in the left upper lobe, one measuring 1.3 × 0.7 cm and the other 1.6 × 1.4 cm (Fig. 2I). PET-CT demonstrated a new FDG-avid lesion in the left upper lobe without distant metastasis (Fig. 2J). Brain MRI and bone scintigraphy did not reveal any remarkable findings. Bronchoscopy (Fig. 2K), as well as a transthoracic fine-needle biopsy, revealed squamous cell carcinoma. The patient's cardiopulmonary function was sufficient for a second curative resection: the FEV_1 was 2.32 L (106% of the predicted value) and the FVC was 3.41 L (102% of the predicted value). The patient successfully underwent left upper lobectomy with lymph node dissection. The pathology results were consistent with nonkeratinizing squamous cell carcinoma, pT3N1 (Fig. 2L). Small cell carcinoma or adenocarcinoma components were not observed. The patient then received 4 cycles of adjuvant chemotherapy, in which regimens were paclitaxel (175 mg/m^2) and carboplatin (target area under curve 5 mg/mL/min) every 3 weeks.

The patient was relatively well without recurrence and complications for 28 months after resection of the second metachronous squamous cell carcinoma and for 44 months after resection of the first metachronous adenocarcinoma (Table 1). He is currently on a regular outpatient follow-up every 6 months with imaging studies.

3. Discussion

The average lifelong incidence of a new primary lung cancer ranges between 1% and 6% per year after radical therapy for nonsmall cell lung cancer and small cell lung cancer, respectively.[2]

In a single institution's 28-year experience with MPLC, the second primary lesions were detected between 5 months and 218 months after the initial curative resection.[5] If a third primary lesion was detected, the interval between the second and third primary lesions was much shorter, ranging between 5.5 and 51 months. The temporal pattern in our patient was consistent with that reported previously. The majority (50.7%) of second primary lesions tend to be histologically similar to the first primary lesion. In our case, the first lesion was small cell carcinoma, but the second and third lesions were nonsmall cell carcinoma.

According to a large institutional study evaluating the development of MPLC after primary surgical resection, second primary tumors developed in 51 patients (5.7%), and the cumulative probability of a cancer-free interval for metachronous tumors seemed to decrease over time: 29% at 3 years, 15% at 5 years, and 2% at 10 years.[6] Hence, a long-term follow-up at 6-month intervals for at least 3 to 5 years could improve the rate of early detection of the second malignancy. In our patient, 3 primary lung cancers developed within 4 years, and surgical resection was performed twice because of early detection of the metachronous tumors via regular follow-up.

Although the management of patients who develop a second primary lung cancer remains a challenge, the 5-year survival rate for all patients with synchronous MPLC who undergo surgical treatment is estimated at 35.3%, and the overall surgical mortality rate is <1.2%.[7] A previous study reported that optimal complete anatomic resection with radical lymphadenectomy was possible in 65.6% of patients, and the 2-year and 5-

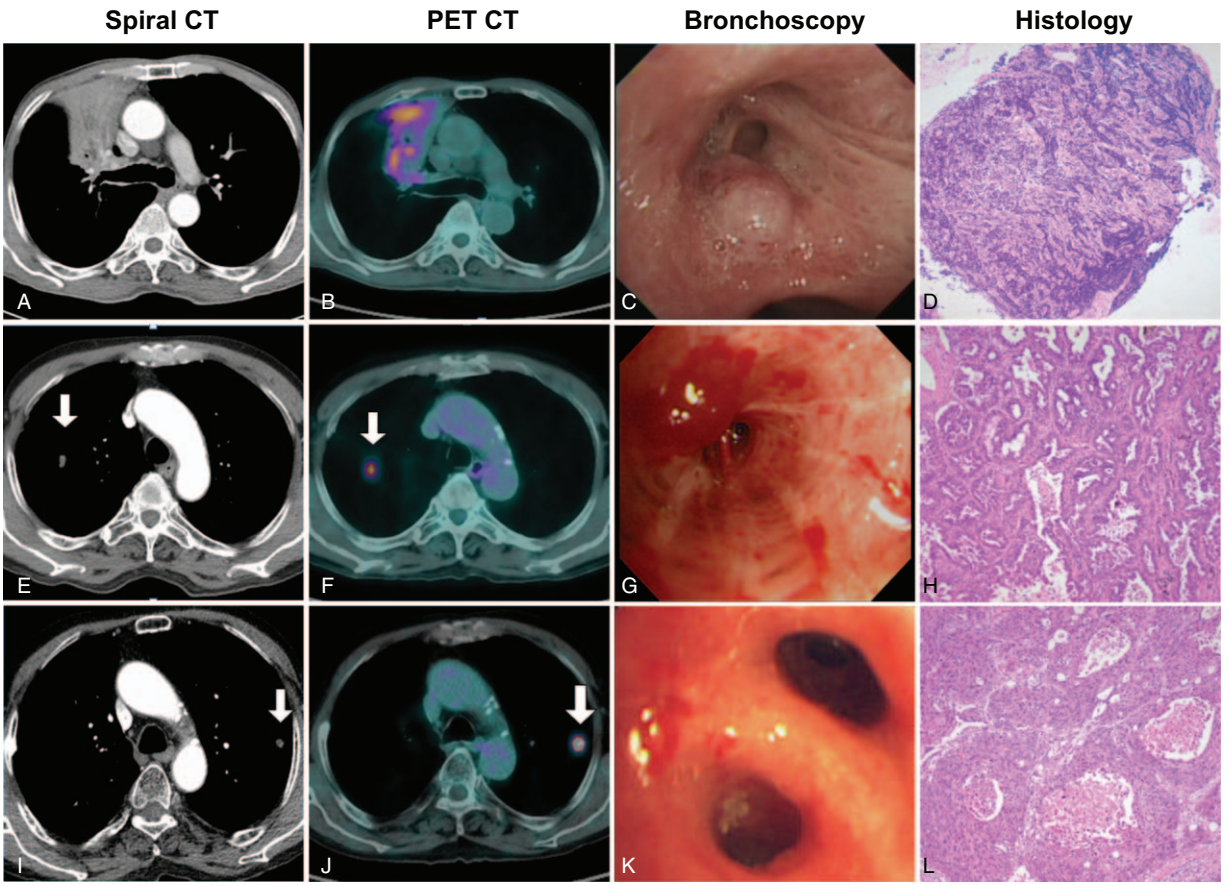

Figure 2. Radiological, bronchoscopic, and histological findings of the primary carcinoma and 2 consecutive metachronous carcinomas of the lungs. (A) Heterogeneously enhanced ground-glass opacity in the right upper lobe, which appears to originate from the distal portion of the right upper lobar bronchus. (B) A hypermetabolic nodular lesion can be seen obstructing the right upper bronchus, as well as consolidated, uneven FDG uptake in the right hilar area. (C) A hypervascular endobronchial mass at the opening of the right upper bronchial division. (D) A photomicrograph showing tumor tissue consisting of cells with small hyperchromatic oval nuclei with scanty cytoplasm and crushing artifact. Tumor cells are positive for CD56 immunostain. Immunostaining and morphology confirmed small cell carcinoma (100×, hematoxylin and eosin). (E) A 1.2-cm linear nodule in the right upper lobe apical segment. (F) Positron emission tomography-computed tomography image showing no recurrence of the previous carcinoma and no regional or distant metastasis. (G) A single round intraluminal nodule protruding at the opening of the right upper anterior segment. (H) Photomicrograph of a pathological specimen obtained from the right upper lobectomy showing clusters and discreet pleomorphic malignant cells with formation of acinar structures, which confirmed adenocarcinoma (100×, hematoxylin and eosin). (I) A newly developed peripheral nodule in the left upper lobe. (J) A new FDG-avid lesion in the left upper lobe without regional or distant metastasis. (K) Whitish intraluminal plaques and edematous mucosa are clearly visible in the left upper lobe apicoposterior segment. (L) Photomicrograph of a pathological specimen obtained from the left upper lobectomy showing that the tumor tissues consist of malignant cells with keratinization and intercellular bridges, which confirmed squamous cell carcinoma (100×, hematoxylin and eosin). FDG = fludeoxyglucose [^{18}F].

year overall survival rates were 61.6% and 34%, respectively, with a median survival duration of 35 months.[8] Those results strongly suggest that aggressive surgical management can be recommended regardless of whether the MPLC is synchronous or metachronous and if the patients have tolerable anatomical staging and physiologic performances. The American College of Chest Physicians recommends surgical treatment after invasive mediastinal staging and extrathoracic imaging as the first choice

Table 1

Clinical courses of the primary small cell carcinoma and 2 consecutive, metachronous, histologically distinct nonsmall cell carcinomas.

Histological type	Small cell carcinoma (1st)	Poorly differentiated adenocarcinoma (2nd)	Moderately differentiated squamous cell carcinoma (3rd)
Time interval		29 months (1st–2nd)	46 months (1st–3rd), 17 months (2nd–3rd)
Location	Right upper lobe bronchial opening	Right upper anterior segment	Left upper apicoposterior segment
Radiological characteristics	Heterogeneous enhancement with ground-glass opacity	Growing simple linear nodule	Newly detected peripheral well-defined nodule
Anatomical staging	Limited disease	Stage IA (T1aN0M0)	Stage IIIA (T3N2M0)
Pathological staging		pT1aN0	pT3N1
Treatment intervention	Concurrent chemoradiotherapy	Right upper lobectomy with lymph node dissection	Left upper lobectomy with lymph node dissection and adjuvant chemotherapy

for patients with 2 primary nonsmall cell lung carcinomas (synchronous or metachronous).[9] Our patient had tolerable physiological performance and anatomical staging following concurrent chemoradiotherapy and right upper lobectomy. Therefore, it was possible to perform subsequent surgical management to provide a survival benefit.

Surgical treatment for metachronous adenocarcinoma and squamous cell carcinoma was successful in a 73-year-old man after successful concurrent chemoradiotherapy for small cell carcinoma. This case highlights the need for continual and careful monitoring and pathological evaluation of patients with lung cancer in remission to distinguish between recurred or metastatic lesions and metachronous primary lesions in order to identify patients eligible for curative surgery.

4. Ethical review and patient consent

Institutional Review Board (IRB) of Chonbuk National University Hospital has stated that it is not necessary to achieve IRB approval for this case report, and this report requires obtaining patient consent because this study is dealt with only the patient's medical record and related images, retrospectively. Written informed consent of this case report and accompanying images was obtained from the patient for the publication.

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