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Repeated Occurrence of Second Primary Lung Cancer at Different Sites in Trachea

A Case Report

Yong Chul Lee, MD, PhD, Yun Ji Park, MD, Su Jin Gang, DVM, Myung Ja Chung, MD, PhD, and So Ri Kim, MD, PhD

Abstract: Multiple or second primary lung cancers can develop at any sites in the lung with same or different histologic types, synchronously and/or metachronously. In case of metachronous occurrence of the second primary lung cancer, it is easy to confuse with the primary lung cancer as a recurrence of precedent lung malignancy treated successfully or metastasis. Previous reports have demonstrated that majority of the second primary lung malignancies have same histologic types regardless of their developing time and location. However, the repeated occurrence of the second primary lung malignancy, in particular with the different histologic features, is a very rare condition.

A 62-year-old male who had past history of squamous cell carcinoma treated with surgery and adjuvant chemotherapy and the recurrence of lung malignancy on the trachea, which was also resected successfully visited our hospital due to blood tinged sputum. Evaluation using bronchoscopy and chest computed tomography revealed the tracheal mass looked similar grossly to the previous recurred tracheal mass that was resected surgically. Unexpectedly, the newly developed tracheal mass was confirmed as small cell lung cancer, the different histologic type from previous ones.

In this report, we describe an interesting case of subsequent occurrence of second primary lung cancers showing histologic shifting at different sites in trachea, suggesting that it is important for physician to make an effort to identify the histologic characteristics of second primary lung cancers for the correct and adequate treatment no matter what they exhibit similar gross morphology.

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From the Department of Internal Medicine and Research Center for Pulmonary Disorders (YCL, YJP, SJG, SRK); Department of Pathology, Chonbuk National University Medical School (MJC); and Research Institute of Clinical Medicine of Chonbuk National University–Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, South Korea (YCL, MJC, SRK).
Correspondence: So Ri Kim and Yong Chul Lee, Department of Internal Medicine, Chonbuk National University Medical School, San 2-20, Geumam-dong, Deokjin-gu, Jeonju, Jeonbuk 561-180, South Korea (e-mail: sori@jbnu.ac.kr (SRK), leeyc@jbnu.ac.kr (YCL)).
So Ri Kim and Yong Chul Lee contributed equally to this work.
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Abbreviations: 18-FDG = 18-fluorodeoxyglucose, CT = computed tomography, PET = positron emission tomography, PET/CT = positron emission tomography/computed tomography.

INTRODUCTION

Second or multiple primary lung cancer is defined as 2 or more pulmonary tumors developing independently of each other in location and/or time.[1] Second primary lung cancers are divided into 2 subgroups, synchronous and metachronous lung cancer, according to its simultaneity.[1] The incidence of second primary lung cancers is relatively low, showing approximately 16% of patients who were treated for initial lung cancer.[2] In recent years, the incidence of second primary lung cancers seems to have increased as the result of longer survival after resection of primary cancers[3] and the use of early detection tools such as multislice spiral computed tomography (CT) and positron emission tomography (PET). However, the development of second primary lung cancer with different histologic types is a very rare pathologic condition, especially occurrence of small cell lung cancer, following non-small cell lung cancer. Moreover, up to date, there are little reports on the subsequent occurrence of second primary lung cancer in a patient treated with surgical resection for the initial lung cancer, especially in tracheal region.

Herein, we introduce our interesting experience of subsequent occurrence of second primary lung cancer with different histologic types, at one time as squamous cell carcinoma and the other time as small cell lung carcinoma, limited to only trachea in a patient treated with surgical resection for the squamous cell carcinoma initially.

CASE REPORT

A 62-year-old-man visited our hospital with presenting the blood tinged sputum, who was looked relatively well except inspiratory wheezing on bilateral lung field through physical examination. On his past history, 3 years ago, he was diagnosed as non-small cell lung cancer, squamous cell carcinoma of anatomical stage IIB (T2N1M0) by TNM system (Figure 1) presenting as a mass with high-uptake of 18-fluorodeoxyglucose (FDG) on PET/CT scan (Figure 2A and C). Thus, he was treated with surgical resection of left pneumonectomy and adjuvant chemotherapy in which regimen was composed of paclitaxel and carboplatin. At the time of the diagnosis, he was a current smoker with 30 pack-year history. After the completion of chemotherapy, for 17 months, there was no evidence of recurrence of lung malignancy on his health surveillance.

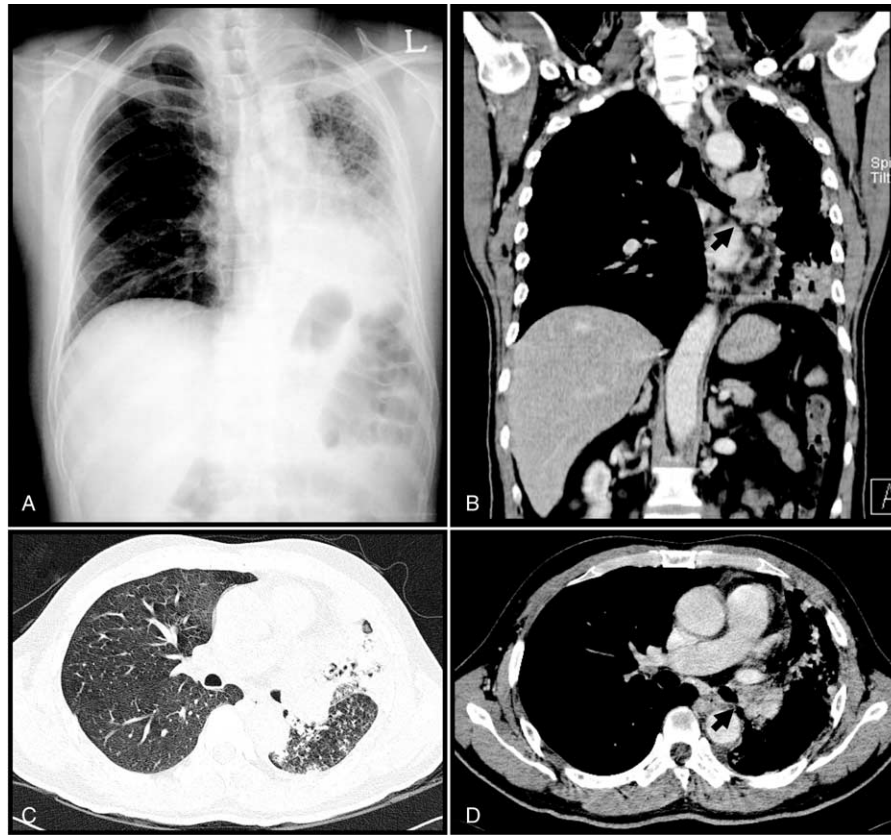

FIGURE 1. Chest radiograph (A) and CT scans (B, coronal view; C, lung setting view; D, mediastinal setting view) of the lung malignancy diagnosed initially 3 years ago. The radiologic images revealed an atelectasis of the left lung with pneumonic consolidation due to the heterogeneously enhanced lung mass on the left main bronchus. CT, computed tomography.

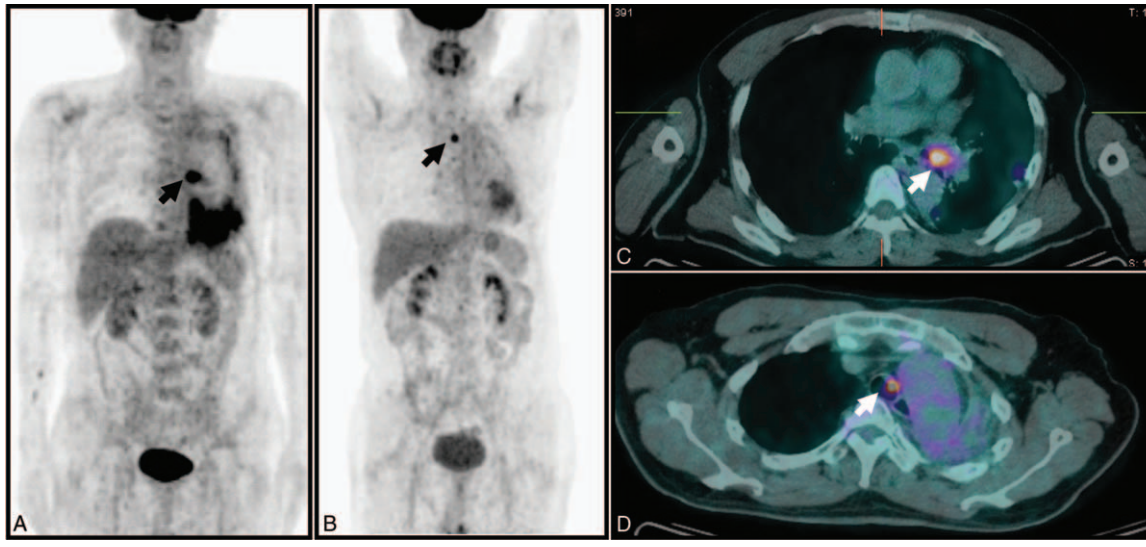

FIGURE 2. PET/CT scans showed the mass with increased 18-FDG uptake in left main bronchus (arrow) at the initial diagnosis of lung malignancy (A, coronal view; C, transverse view). At first occurrence of second primary lung cancer in trachea, the small mass (arrow) was observed and its 18-FDG uptake was significantly high (B, coronal view; D, transverse view). 18-FDG, 18-fluorodeoxyglucose, PET, positron emission tomography, PET/CT, positron emission tomography/computed tomography.

However, at 18 months after the treatment, follow-up PET/CT scan (Figure 2B and D) and spiral chest CT scan (Figure 3A) revealed an isolated mass on the left lateral side of anterior tracheal wall. To evaluate the tracheal mass further, he was underwent bronchoscopy with endotracheal biopsy (Figure 3B), and the histologic type of the mass was confirmed as squamous cell carcinoma with showing typical pathologic features in which tumor cells are arranged in a solid sheet-like pattern and reveal vesicular nuclei with prominent nucleolus, eosinophilic plump cytoplasm, numerous mitoses, and intercellular bridges (Figure 3C). The recurred tracheal mass was treated with stump resection and bronchoplasty, accompanying adjuvant chemotherapy using previous regimen. Until he visited hospital due to blood-tinged sputum, he had shown no sign and symptoms of recurred malignancy for about 10 months.

For evaluation of his blood-tinged sputum, we performed chest roentgenogram, spiral chest CT, and bronchoscopy. Chest roentgenogram did not provide any of specific information related to hemoptysis or pulmonary hemorrhage. Spiral chest CT revealed slightly elevated mucosa in trachea at the level of between 4th and 5th thoracic spine without pulmonary hemorrhage or pneumonic infiltration (Figure 3D). Diagnostic bronchoscopy revealed a sessile type of polypoid mass on the right lateral side of anterior wall in trachea, which was approximately 3 to 4 cm apart from carina (Figure 3E). Unexpectedly, histologic examination of endotracheal mass established small cell lung cancer, in which tumor cells showed round to oval nuclei with scant cytoplasm, finely granular chromatin pattern, and absent nucleoli (Figure 3F). Moreover, the tumor cells also showed positivity for the neuroendocrine markers including CD56, chromogranin, and synaptophysin as well as thyroid transcription factor-1 (TTF-1). This newly developed tracheal mass in the patient was isolated without local invasion and distant metastasis, thus, it was diagnosed as second primary lung cancer, small cell lung carcinoma of limited stage and treated with concurrent chemoradiotherapy; 9 cycles of irinotecan and carboplatin plus definitive radiotherapy. We assured disappearance of endotracheal recurrence without any involvement of other tissues through spiral chest CT, diagnostic bronchoscopy, and PET-CT and then ceased the concurrent chemoradiotherapy. Up to 5-year follow-up, he has shown neither recurrence nor other events involved, and he has maintained the complete remission state (Figure 3G–I).

DISCUSSION

Lung cancer is the leading cause of cancer death in both males and females worldwide, although the incidence of lung cancer decreased in some developed countries.[4] However, the incidence of second primary lung cancers have increased in recent years thank to the introduction of various diagnostic modalities and the development of new therapeutic agents and techniques. Especially, despite the expectation of long-term survival after curable resection in the case of stage I non-small cell lung cancer, the recurrence or new cancers can be emerged in a third of the patients.[5] Therefore, the longer the patients survive from initially presented as early stage of lung cancer, the higher risk for second cancers increases.

The majority of second primary lung cancers have similarity with initially presented lung cancers in histologic type, and the reason proposed is the common genetic background between first primary lung cancers and second primary lung cancers.[6] However, a few cases have been reported on the different histologic types of second primary lung cancers from the primary cancers. It means that second primary lung cancers with different histologic types can be sporadically developed by cancer cell transformation, that is, this issue remains to be clarified. Recently, Rice and colleagues investigated the risk of second primary lung cancers in patients treated with surgical resection for stage I non-small cell lung cancer and revealed that the risk of second primary lung cancers in them is 1.99 per 100 patient-years.[7] In addition, the histologic type of second primary lung cancers is correlated with the first primary lung cancer. The frequently involved sites are both upper lobes. However, the repetitive occurrence of second primary lung cancers has rarely been reported.

In our current case, the patient experienced the repetitive occurrences of second primary lung cancer, in which each second primary lung cancer showed different histologic type, moreover, their locations wandered, possessing similar gross morphology within trachea. Given each histologic type (ie, non-small cell lung cancer versus small cell lung cancer), they should be treated with different therapeutic agents and methods. Moreover, they have very different prognosis, it gives clinicians a lesson that the efforts for identification of the newly developed cancerous lesions histologically are important, even though the lesions look similar each other grossly.

As for pathologic features of both tumors, the characteristics of squamous cell carcinoma include intercellular bridges, individual cell keratinization, and squamous pearl formation.[8] According to the WHO classification, squamous cell carcinoma can be divided into papillary, clear cell, small cell and basaloid subtypes,[9] however, the clinical and prognostic utility is relatively weak. In contrast to non-small cell lung cancer, small cell lung cancer shows the morphologic characteristics as follows; tumor cells are usually smaller than lymphocytes, nucleoli is absent or faint, nuclear chromatin is finely granular or uniform, nuclear-to-cytoplasmic ratio is higher than non-small cell lung cancer, nuclear molding is frequent, necrosis is common and often extensive, cell shape is usually fusiform, and basophilic staining of vessels and stroma are detected occasionally.[10] Despite that the most important stain is a high-quality hematoxylin and eosin (H&E) stain for the pathologic diagnosis of small cell lung cancer, immunohistochemistry, specifically for neuroendocrine markers, is very useful. The most useful neuroendocrine markers include CD56, chromogranin, and synaptophysin.[11,12] TTF-1 expression is present in 70% to 90% of small cell lung cancer, however, it is known that TTF-1 can be positive in 44% to 90% of extrapulmonary small cell carcinoma, indicating that TTF-1 is not useful for defining the primary site of small cell carcinoma.[9,10,13,14] The differentiation of small cell lung cancer from non-small cell lung cancer including squamous cell carcinoma is usually performed based on multiple features of high-quality H&E stained pathologic specimens such as cell size, nuclear-to-cytoplasmic ratio, nuclear chromatin, nucleoli, nuclear molding, cell shape, and hematoxylin vascular staining as described above.[15,16] Distinct immunohistochemical features of small cell lung cancer include the expression of neuroendocrine markers and/or TTF-1 in tumor cells of lung.[11]

Metachronously occurred tumors are detected in relatively early stage to be cured through complete resection. Several surgical series describe 5-year survival rates are ranging from 11% to 52% after operation of metachronous tumor.[17] The patient in this current case underwent the surgical resection for the second primary lung cancer occurred previously, and the second primary lung cancer developed at second time was treated with concurrent chemoradiotherapy according to the standard therapeutic approach for small cell lung cancer.

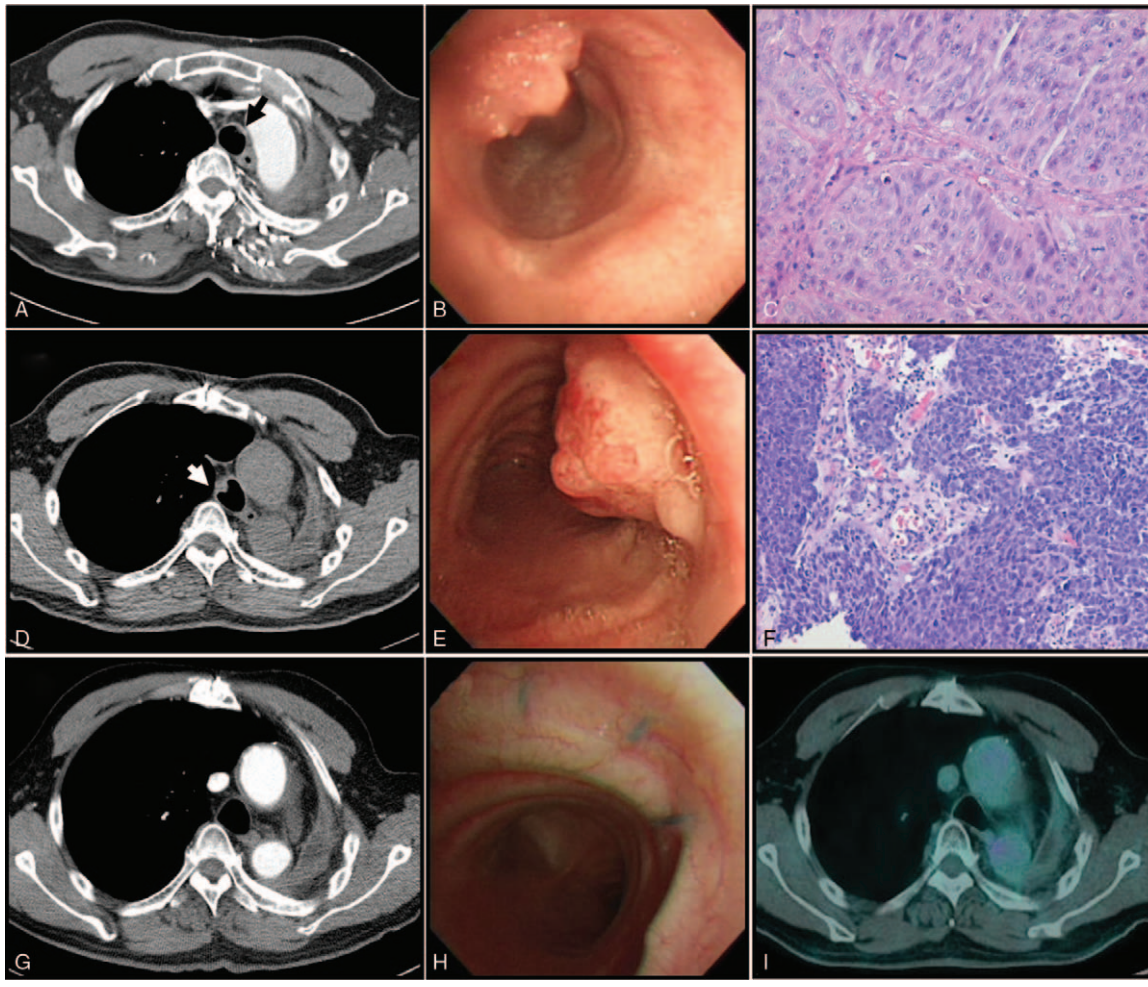

FIGURE 3. (A–C) The second primary lung cancer occurred in trachea firstly. CT scan (A) and bronchoscopic examination (B) revealed that the polypoid mass was located on the left anterolateral wall of trachea. (C) Representative H&E stained section. The tumor cells are arranged in a solid sheet-like pattern and reveal vesicular nuclei with prominent nucleolus, eosinophilic plump cytoplasm, numerous mitoses, and intercellular bridges (400×). (D–F) The second primary lung cancer occurred in trachea repetitively. CT scan (D) and bronchoscopic examination (E) revealed that the tracheal mass with very similar gross morphology to previous one was located on the right anterolateral wall of trachea. (F) Representative H&E stained section. Histologically, tumor cells showed round to oval nuclei with scant cytoplasm, finely granular chromatin pattern, and absent nucleoli (200×). (G–I) Follow-up chest CT scan (G), bronchoscopic finding (H), and PET/CT scan image (I). CT, computed tomography; H&E, hematoxylin and eosin. PET/CT, positron emission tomography/computed tomography.

In summary, we describe a unique and intriguing case of repetitive second primary lung cancer occurred in trachea. They occurred at very close sites with similar gross morphology, however, unexpectedly their histologic types were different each other; non-small cell lung cancer versus small cell lung cancer. Although many physicians will encounter this pathologic situation very scarcely, if any, they should actively attempt to identify the histologic characteristics of second primary lung cancers for the correct and adequate treatment. In addition, the pathophysiology and clinical characteristics including genetic background of the second primary lung cancers with different histologic types should be investigated in the future.

ETHICAL REVIEW AND PATIENT CONSENT

Institutional Review Board 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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REFERENCES

1. Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg.* 1975;70:606–612.

2. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst.* 1998;90:1335–1345.
3. Johnson BE, Cortazar P, Chute JP. Second lung cancers in patients successfully treated for lung cancer. *Semin Oncol.* 1997;24:492–499.
4. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58:71–96.
5. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary lung cancer in resected stage I lung cancer. *J Thorac Cardiovas Surg.* 1995;109:120–129.
6. Wang X, Wang M, MacLennan GT, et al. Evidence for common clonal origin of multifocal lung cancers. *J Natl Cancer Inst.* 2009;101:560–570.
7. Rice D, Kim HW, Sabichi A, et al. The risk of second primary tumors after resection of stage I non small cell lung cancer. *Ann Thoracic Surg.* 2003;76:1001–1007.
8. Kumar V, Abbas A, Aster J. Robbins Basic Pathology. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013.
9. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. WHO/IASLC Classification of Lung and Pleural Tumours. Lyon: IARC Press; 2004.
10. Travis WD. Update on small cell carcinoma and its differentiation from squamous cell carcinoma and other non-small cell carcinomas. *Mod Pathol.* 2012;25:S18–S30.
11. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol.* 2002;26:1184–1197.
12. Maleki Z. Diagnostic issues with cytopathologic interpretation of lung neoplasms displaying high-grade basaloid or neuroendocrine morphology. *Diagn Cytopathol.* 2011;39:159–167.
13. Travis WD. Advances in neuroendocrine lung tumors. *Ann Oncol.* 2010;21:vii65–vii71.
14. Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. *Mod Pathol.* 2000;13:238–242.
15. Vollmer RT. The effect of cell size on the pathologic diagnosis of small and large cell carcinomas of the lung. *Cancer.* 1982;50:1380–1383.
16. Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol.* 1991;15:529–553.
17. Watanabe Y, Shimizu J, Oda M, et al. Second surgical intervention for recurrent and second primary bronchogenic carcinomas. *Scand J Thorac Cardiovasc Surg.* 1992;26:73.