To the Editor:

**Endotracheal or Endobronchial Metastasis of Lung Squamous Cell Carcinoma**

**BACKGROUND**

Endotracheal or endobronchial metastasis (EEM) is a rare condition, usually originating from extrapulmonary malignancies such as breast, colon, or kidney cancer. In lung cancer, only a few case reports or case series about EEM have previously been available.

When we encounter a case in which EEM of lung cancer is suspected, several problems remain unclear for us: how we distinguish them from new primary tumors and how we believe the primary tumor metastasized to the airway, whether by local invasion or through lymphatic or hematogenous spread. These questions are important when considering the next treatment strategies.

This case series presents 3 cases which were diagnosed as EEM of lung cancer. We compared genomic profiles of somatic mutations detected from primary and recurrent lesions.

**Case 1**

A 68-year-old man, diagnosed with primary lung squamous cell cancer underwent right lower lobectomy (Fig. 1A). Pathologic stage was IIA and adjuvant chemotherapy was started with cisplatin and vinorelbine but stopped after 2 courses because of severe venous inflammation. One year later, multiple endobronchial nodules were observed by bronchoscopy at the left main broncus, 1 and 3 cm above the main carina at the trachea (Fig. 1B). Transbronchial biopsy (TBB) pathologically revealed squamous cell carcinoma and postoperative metastatic recurrence was suspected. PD-L1 staining was strongly positive for 65% of tumor proportion score, and pembrolizumab was started, showing good response.

**Case 2**

A 77-year-old man was diagnosed with primary lung squamous cell cancer and left lower lobectomy was conducted (Fig. 3A). Postoperative pathologic stage was IIA. Adjuvant chemotherapy was not given. Four years later, multiple endobronchial tumors were observed by bronchoscopy localizing in the left main broncus (Fig. 3B). TBB samples showed squamous cell carcinoma, which we regarded as local recurrence. Left upper lobectomy was attempted but had to be stopped because of solid adhesion. Chemotherapy with carboplatine and paclitaxel combined with concurrent radiotherapy was started.

**Case 3**

A 74-year-old man was diagnosed with primary lung squamous cell cancer and left lower lobectomy was conducted (Fig. 4). Pathologic stage was IA and adjuvant chemotherapy was performed by oral Uracil and Tegafur for 2 years. Two years later, stump recurrence was seen and left complete pneumonectomy with postoperative radiation was conducted. However, only 1 year later, multiple endobronchial tumors were observed in the trachea by bronchoscopy (Fig. 2B). TBB samples also revealed squamous cell carcinoma and diagnosed as postoperative recurrence. Chemotherapy with carboplatine and nabpaclitaxel was started, showing good response.

**Genomic Analysis**

For confirming that these 3 cases should be regarded as postoperative recurrence not as new primary lesions, genome analysis was conducted using samples of primary and recurrent lesions of each cases (Fig. 4). For Case 1, CDKN2A L13P, TP53 N247fs, NFI A1548, and NFE2L2 R34P were identical between primary resected tumor and each of the TBB samples. For case 2, tumor cells obtained by the first lobectomy, the second pneumonectomy, and the third biopsy all had common gene mutation including TP53 R158P and FOXP2 V698L. For
case 3, genomic analysis had shown identical mutations including \textit{TP53}^{Y163C} and \textit{NFE2L2}^{V564A}. These results strongly suggest that the endotracheal and endobronchial tumors represent EEM rather than newly emerged primary carcinoma.

DISCUSSION
Here, we presented 3 cases of EEM genomically identified by detecting gene mutations identical to the past surgical specimens. Previously, many studies have reported that shared mutation profiles were identified between primary tumor and metastases in the lung.\textsuperscript{1–3} In contrast, mutation profiles differed among the individual tumors in 12 patients with multiple primary carcinomas in the lung.\textsuperscript{4} So, it is valid to say that revealing identical mutation profiles strongly suggested the etiology of these cases as EEM rather than new primary.

To date, EEM from extrapulmonary tumor have often been reported,\textsuperscript{5–9} but those from primary pulmonary tumors are considered to be rare; there have been only 3 case reports and 1 case series including 6 cases of EEM published previously.\textsuperscript{10–13} Among them, 7 cases were EEM of squamous cell carcinoma. Clinically, it is difficult to distinguish them from de novo primary tumor because squamous cell carcinoma is also likely to originate from carcinoma in situ at endobronchial mucosa. More than that, they do not have morphologic variation, which make difficulty of distinguishing between recurrence and de novo primary tumor. However, Chong and colleagues have cast doubt upon the de novo primary tumor hypothesis based on the presentation in their 6 case series that tumor cells were pathologically located in the submucosal layer without involving the epithelium.\textsuperscript{10} Our case series strengthens this conclusion based on the genomic identity between mutations in the primary and metastatic tumors.

Profiles of somatic mutation detected in case 1 were completely identical between primary and metastases, while only partially identical in case 2 or 3. The identical mutations between them were considered to be trunk mutations generated in the early

FIGURE 1. Primary and recurrent lesion of case 1. A, Primary lesion in the right lower lobe for which lobectomy was performed. B, One year after the lobectomy, multiple endobronchial tumors seen at the left main bronchus and 1 and 3 cm above the carina.
FIGURE 2. Primary and recurrent lesions of case 2. A, Primary lesion in the left lower lobe for which lobectomy was performed. B, Multiple endobronchial tumors are seen 3 years after the lobectomy.

FIGURE 3. Primary and recurrent lesions of case 3. A, Primary lesion in the left lower lobe for which lobectomy was performed. B, Multiple endobronchial tumors are seen at the left main bronchus 4 years after the lobectomy.
In conclusion, this case series strongly suggest that multiple endotracheal or endobronchial tumors are metachronous recurrence, which are distinguished from de novo primary.

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intrapulmonary metastases using DNA rearrangements in non-small-cell lung cancer. J Clin Oncol. 2014;32:4050–4058.

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Delayed Presentation of Hemothorax and Mediastinal Hematoma Requiring Surgical Intervention After Linear Endobronchial Ultrasound

To the Editor:

CASE PRESENTATION

A 55-year-old male with coronary artery disease status post drug-eluting stents in 2009, maintained on dual antiplatelet therapy (DAPT) with clopidogrel 75 mg daily and aspirin (ASA) 325 mg daily, and an 80 pack-year history of tobacco dependence was referred for evaluation of a right upper lobe lung nodule. No additional risk factors for bleeding were identified. Computed tomography of the chest showed a 29.0 mm spiculated right upper lobe nodule with right hilar and paratracheal lymphadenopathy. Poor functional status excluded him from possible curative intent surgery by previous thoracic surgery consultation.

The patient underwent staging endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) followed by navigation bronchoscopy with biopsy and fiducial marker placement for potential radiosurgery. Both ASA and clopidogrel were held 6 days before the procedure. One hour before the procedure, ASA 325 mg was administered out of the concern for potential elevated risk of peri-procedural myocardial infarction. Lymph nodes at stations 4L, 7, 4R, and 11R (measuring in the shortest diameter 8, 12, 9, and 11 mm, respectively) were noted by EBUS without significant vascularity. Three passes per lymph node were obtained with a 21-G EBUS-TBNA needle. Rapid on-site cytologic evaluation was negative for malignancy. There was no excessive intraluminal bleeding or hematoma on ultrasound immediately following the procedure. The navigational portion of the procedure was uneventful. The patient was discharged the same afternoon with instructions to resume DAPT. Clopidogrel was restarted ~4 hours after the procedure.

On postprocedure day 4, the patient presented to the emergency department with acute right-sided chest pain associated with progressive dyspnea. Computed tomography revealed a large right pleural effusion with layering internal hyperdensity in apparent communication with a posterior mediastinal fluid collection (Fig. 1). A 14-Fr chest tube was placed, draining 1050 mL of hemorrhagic pleural fluid. The fluid hematocrit was 20% (systemic 32%), confirming the diagnosis of hemothorax. Progressive tachycardia and hypotension developed with 400 mL additional hemorrhagic fluid drained over the next hour. Four units of packed red blood cells were transfused emergently; however, the patient remained hypotensive and tachycardic.

Thoracic surgery performed emergent exploratory thoracotomy, revealing 1 L of thrombus in the right hemithorax and a large posterior mediastinal hematoma. Intraoperative transesophageal echocardiogram revealed left atrial compression with impaired cardiac function (Fig. 2). There was no clear evidence of injury to major cardiac or vascular structures, but hemorrhage appeared to originate in the subcarinal region. After an uneventful recovery, he was discharged on postoperative day 5.

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