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Case Report

Metachronous Primary Lung Cancer Occurring during the Spontaneous Regression of Locally Advanced Lung Cancer: A Rare Case Report

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A 71-year-old man was diagnosed as having right primary lung squamous cell carcinoma, clinical stage IIIA, but he refused treatment. However, the right upper lobe nodule and lymph node (LN) #4R showed gradual shrinking without treatment. Four years after the diagnosis, a new nodule was detected in the left lung field. We considered that this new nodule might be metachronous primary lung cancer, and hence resected it for diagnosis and treatment. The tumor in the left lung was diagnosed as basaloid squamous cell carcinoma, and that in LN #4R was diagnosed as squamous cell carcinoma with keratinization. Therefore, the patient was diagnosed as having metachronous primary lung cancer that developed during the spontaneous regression of locally advanced lung cancer.

Keywords: spontaneous regression, metachronous, lung cancer

Introduction

Spontaneous regression of cancer was defined in 1956 as "partial or complete disappearance of a malignant tumor in absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease" by Everson and Cole.[1)] However, this definition resulted in ambiguity regarding the interpretation of "inadequate therapy," and spontaneous regression was redefined by Kumar et al. in 2010 as the "modified Everson and Cole criterion," as follows: 1) the partial or complete disappearance of a tumor in the absence of all systemic or local treatment of the primary or metastatic lesion, 2) occurring in patients who have not received any systemic therapy (chemotherapy, radioablative techniques, and chemoembolization), and 3) the primary malignancy was histologically diagnosed or if biopsy was not performed to evaluate metastatic spread, the thoracic lesion appeared metastatic radiographically and in a clinical context.[2)] The incidence of spontaneous regression is estimated to be about 1 in 60000 to 100000 cancer patients, and is often reported in malignant melanoma, non-Hodgkin's lymphoma, renal cell carcinoma, neuroblastoma, and choriocarcinoma.[1)] However, spontaneous regression of lung cancer is rare. Jeong et al. reported that most patients showing spontaneous regression of non-small cell lung cancers have a prognosis of less than 3 years, and there are limited reports of their long-term survival and tumor recurrence.[3)] To our knowledge, there have been no reports to date of metachronous second primary lung cancer occurring during the spontaneous regression of the initial lung cancer.

Here, we present a case of a patient in which metachronous second primary lung cancer was detected

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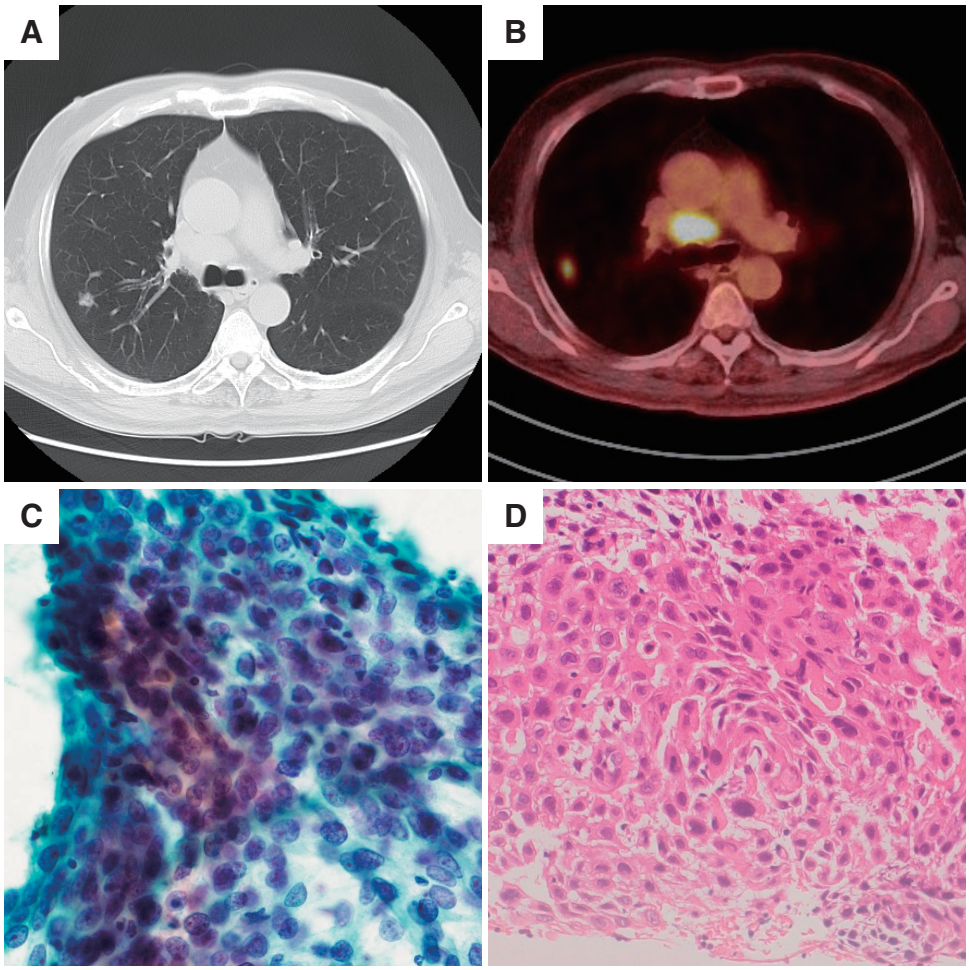

Fig. 1 Images and pathological findings of the patient 4 years before treatment at our hospital. (**A**) CT images of the nodule in the right upper lobe and swollen LN #4R in the axial view, (**B**) PET scan displaying strong ^{18}F-FDG uptake in the nodule in the right upper lobe (SUV_{max}: 12.0) and LN #4R, (**C**) cytological findings of LN #4R, and (**D**) histological findings of LN #4R. CT: computed tomography; LN: lymph node; PET: positron emission tomography; FDG: fluorodeoxyglucose; SUV: standard uptake value

during the spontaneous regression of locally advanced lung cancer.

Case Presentation

A 71-year-old man, who was a current smoker (smoking index: 2200), was found to have a 1-cm nodule in the upper right lobe, and an enlarged lymph node (LN) #4R with a minor axis of 2.2 cm, on computed tomography (CT) performed by a family doctor 4 years previously for the purpose of routine observation of his emphysema. In addition, positron emission tomography (PET)-CT scan displayed strong ^{18}F-fluorodeoxyglucose (FDG) uptake with a maximal standard uptake value (SUV) of 12.0 in the right upper lobe nodule and LN #4R. Therefore, he visited another hospital for detailed examinations and underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from LN #4R. Cytology revealed atypical cells showing an orangeophilic cytoplasm, nuclear enlargement, and hyperchromasia. Histological analysis demonstrated that the tumor cells were growing in a sheet-like pattern, and intercellular bridges and keratinization were observed in the tumor. Based on the above findings, the patient was diagnosed as having squamous cell carcinoma (**Fig. 1** and **Supplementary Fig. 1**; Supplementary file is available online.). The diagnosis was cT1aN2M0 stage IIIA, and the patient was recommended to undergo chemoradiotherapy. However, he refused treatment and underwent regular follow-up CT scans at a nearby clinic.

Subsequently, the right upper lobe nodule and LN #4R appeared to be gradually shrinking, even without any treatment. Four years after the diagnosis, a new nodule was detected in the left lower lobe, and this time he was positive about undergoing treatment, so he was referred to our hospital for detailed examination and treatment.

The new nodule was 1.2 cm and in the left lower lobe, and the mediastinal LN #4R was swollen with a minor axis of 1.6 cm. However, the original right upper lobe nodule could not be identified. PET-CT scan displayed strong ^{18}F-FDG uptake in the nodule in the left lower lobe with a maximal SUV of 7.77 and in LN #4R with a maximal SUV of 11.48. Although the swollen LN #4R showed a shrinking tendency, EBUS-TBNA was performed once again at our hospital. Cytology findings were the same as those obtained 4 years previously. Based on the above, the patient was diagnosed as having squamous cell carcinoma, as before (**Fig. 2**). However, as LN #4R showed a shrinking tendency, we thought that the left lower lobe nodule might be metachronous primary lung cancer. Therefore, we decided to resect each lesion for diagnosis and treatment. Considering that the left lower lobe nodule, which was a new lesion, might be more active, we decided to perform surgery from the left side first. However, owing to a preoperative lower lung function (forced expiratory volume $(FEV)_{1.0}$: 1040 mL; $FEV_{1.0}$%: 43.33%), we performed wide wedge resection instead of lobectomy or segmentectomy. The tumor cells formed a mass of small proliferating cells with alveolar structure and peripheral palisading, with fibrosis and necrosis. Immunostaining demonstrated that the tumor was positive for CD56, cytokeratin 5/6, and p40, and therefore, the tumor showed immunohistochemical characteristics of squamous cell carcinoma and was diagnosed as basaloid squamous cell carcinoma (**Figs. 3A–3D**).

Subsequently, we performed dissection of the remaining right-side LN #4R, which was found to be squamous cell carcinoma by preoperative EBUS-TBNA. The nodule in the upper right lobe, which was observed 4 years previously, could not be detected on preoperative CT and was also difficult to palpate during the operation. Therefore, we performed right upper mediastinal dissection without resection of the right upper lobe. The tissue sample of LN #4R demonstrated a sheet-like pattern, with intercellular bridges and keratinization, and therefore the tumor in LN #4R was diagnosed as squamous cell carcinoma (**Fig. 3E**). As the squamous cell carcinoma of LN #4R was histologically different from the basaloid squamous cell carcinoma of the lower left lobe, we diagnosed the patient as having metachronous primary lung cancer.

One year after the surgery, no findings suggesting local recurrence or distant metastasis were found, and the patient is still under follow-up.

Discussion

Spontaneous regression of non-small cell lung cancer is an exceptionally rare phenomenon; however, the underlying mechanisms by which it occurs remain unknown. Immunoregulation after infection or injury, interactions between neuropsychological and immunological systems, hormonal mechanisms, and normalization of cell differentiation are thought to be mechanisms of spontaneous regression.[4] In the present patient, spontaneous regression may have occurred due to an immunological mechanism induced by cell apoptosis or inflammatory necrosis. EBUS-TBNA performed on LN #4R may have triggered the release of cytokines, which may have subsequently induced a T-cell-mediated immune response leading to cell apoptosis and necrosis.[4] Another possible mechanism of spontaneous regression may be interaction between the neuropsychological system and the immunological system. This theory suggests that positive neuropsychological changes enable the immune system to identify and/or eliminate malignant cells more efficiently, but the results of the relevant studies are not conclusive.[5,6] Therefore, it remains unclear as to how spontaneous regression occurred in the present patient.

We believe that the tumor immune microenvironment may be involved in the mechanism of spontaneous regression. Haruki et al. reported that immunohistochemical analysis demonstrated diffuse infiltration of CD8-positive lymphocytes in resected tumor specimens of lung adenocarcinomas undergoing spontaneous regression.[7] Therefore, although the mechanism of spontaneous tumor regression remains unclear, CD8-positive lymphocytes may play an important role. There has been no report to date on programmed death ligand 1 (PD-L1) expression in lung cancers that undergo spontaneous regression, but in our present patient, PD-L1 expression (Dako 22C3 assay) was observed in less than 1% of the tumor cells. Previous reports demonstrated that adenocarcinoma had high PD-L1 expression in pathologically high-grade tumors.[8] It has also been reported that PD-L1 expression is high even in pleomorphic carcinomas with high pathological malignancy.[9] Therefore, the expression of PD-L1 may indicate high

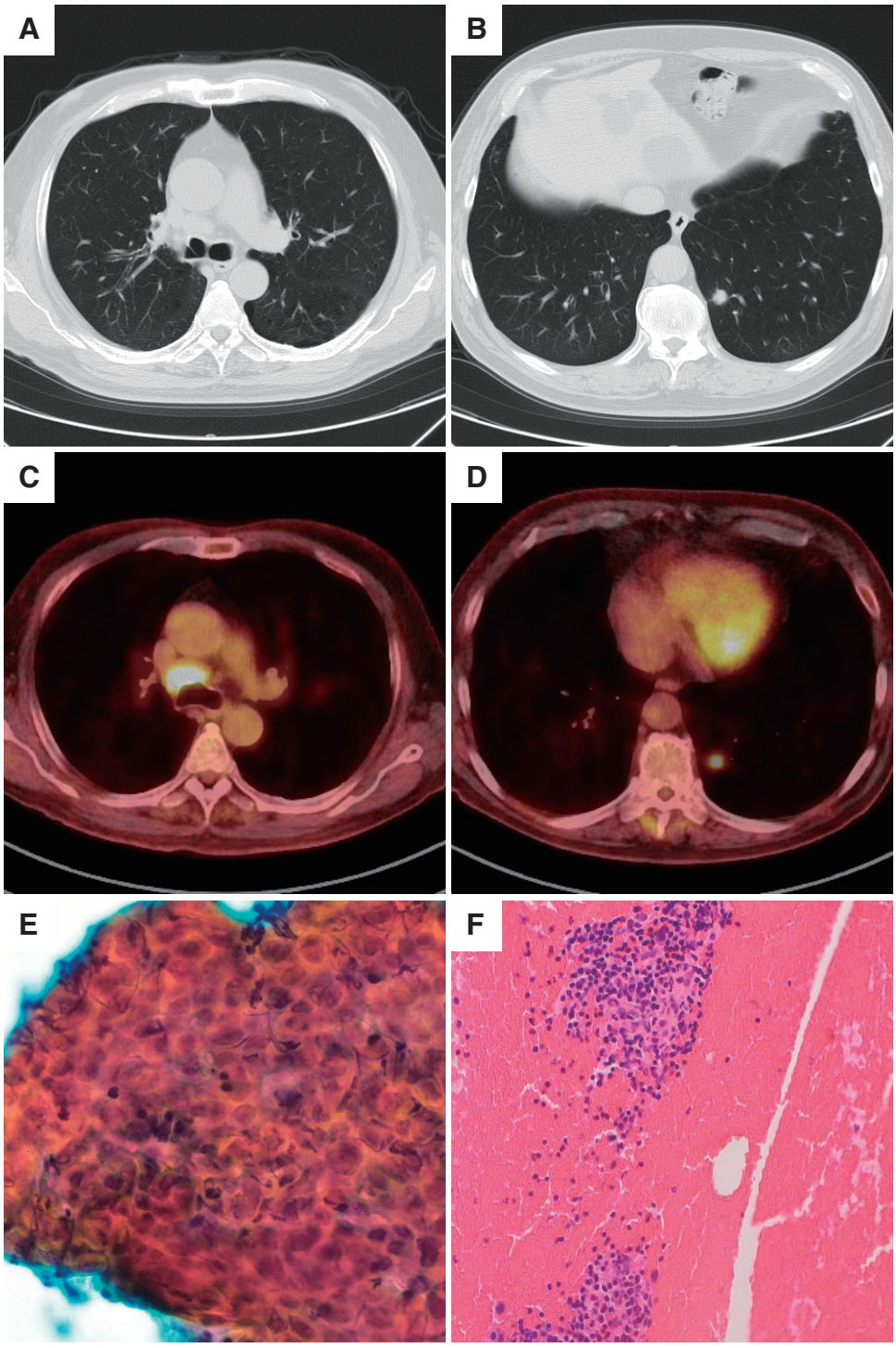

Fig. 2 Preoperative images and pathological findings of the tumors. (**A**) CT images of spontaneous regression of the right upper lobe nodule and LN #4R (remaining swollen) in the axial view, (**B**) CT images of a newly identified nodule in the left lower lobe in the axial view, (**C**) PET scan displaying ^{18}F-FDG uptake in LN #4R (SUV_{max}: 11.48), (**D**) PET scan displaying ^{18}F-FDG uptake in the left lower lobe (SUV_{max}: 7.77), (**E**) cytological findings of LN #4R, and (**F**) histological findings of LN #4R. CT: computed tomography; LN: lymph node; PET: positron emission tomography; FDG: fluorodeoxyglucose; SUV: standard uptake value

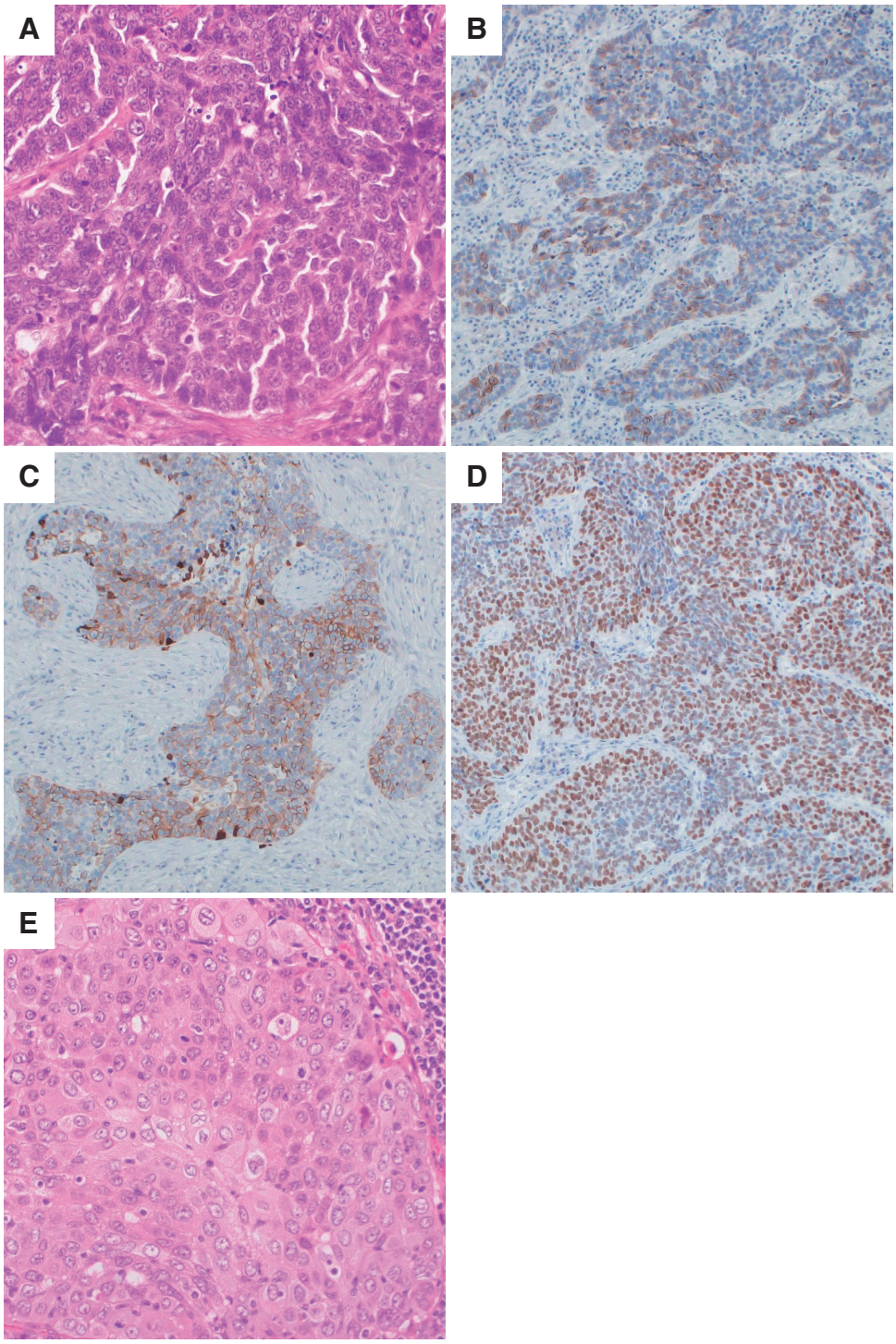

Fig. 3 Histological findings of the resected tumor in the left lower lung and the resected LN #4R. (**A**) Hematoxylin and eosin staining of the left lower lung tumor (magnification: ×200), (**B**) CD56 staining of the left lower lung tumor (magnification: ×100), (**C**) cytokeratin 5/6 staining of the left lower lung tumor (magnification: ×100), (**D**) p40 staining of the left lower lung tumor (magnification: ×100), and (**E**) hematoxylin and eosin staining of the LN #4R (magnification: ×200). LN: lymph node

biological malignancy, suggesting that our patient showing spontaneous regression of squamous cell lung carcinoma may have had a biologically low-malignant tumor. We believe that the unique tumor immune microenvironment of this patient resulted in spontaneous regression. On the other hand, the association between PD-L1 expression level and patient prognosis remains controversial in many types of cancer, and it has been reported that PD-L1 expression in squamous cell carcinoma is not associated with patient prognosis.[10)]

There has also been a report of the recurrence of mediastinal LN metastasis during the spontaneous regression of non-small cell lung cancer, suggesting the possibility of intrapulmonary metastasis and metachronous lung cancer before treatment.[3)] The risk of metachronous primary lung cancer increases as follow-up time extends, with an estimated incidence of 1% to 2% per patient per year.[11)] We considered that our present patient had metachronous primary lung cancer that developed during the spontaneous regression of cancer of the right upper lobe of the lung. On the other hand, if we were not aware of the spontaneous regression of the cancer in the right upper lobe of the lung, we might have diagnosed the patient as having LN #4R metastasis of cancer of the left lower lobe, or synchronous primary lung cancer of the left lower lobe of the lung and mediastinal lung cancer. Also, it cannot be denied that the nodule in the right upper lobe was an inflammatory nodule and the swollen mediastinal LN is a primary unknown cancer. However, CT findings showed irregular margins of the nodule and enlarged mediastinal LNs. Therefore, it was difficult to conclude that the imaging findings from 4 years ago were not lung cancer in the nodule in the right upper lobe. If he had been treated 4 years earlier, we considered that it was not possible to judge it as a primary unknown carcinoma instead of right upper lobe lung cancer. In addition, given the spontaneous shrinkage of both the nodule in the right upper lobe and mediastinal LN, we considered unilaterally this to be primary right upper lobe lung cancer with spontaneous regression.

Jeong et al. reported that it is preferable to aggressively perform surgery for non-small cell lung cancers undergoing spontaneous regression, regardless of the reduction in tumor size, in cases of operable early stage lung cancers.[3)] In our present case, we also considered performing transbronchial lung biopsy, but there was no bronchus reaching the tumor and there was a high possibility that a diagnosis could not be obtained because of the small nodule size. Therefore, surgery was performed in consideration of diagnostic implications and treatment. On the other hand, because of the low lung function of the patient, we performed partial wide wedge resection. Subsequently, we only performed right upper mediastinum LN dissection, including LN #4R, which remained as a lesion, and did not resect the right upper lobe where the primary lesion was previously located. Therefore, there is a possibility that the cancer will recur in the future, and careful follow-up of the patient is hence necessary.

Conclusion

To the best of our knowledge, there have been no reports to date of metachronous lung cancer developing during spontaneous regression of lung cancer, as observed in the present patient. As there is a limited number of cases of patients with lung cancer undergoing spontaneous regression, for which surgical specimens are available, it is necessary to continue the collection of tumor samples from such patients for immunohistological analysis in the future. Size reduction on imaging of early lung cancer that has not been pathologically diagnosed is often considered to be an inflammatory change, but the possibility of the spontaneous regression of lung cancer cannot be ruled out. As recurrence or metachronous lung cancer may occur after the spontaneous regression of lung cancer, regular follow-up of such patients is considered to be necessary.

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Disclosure Statement

None declared.

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