

Lymph Node Metastasis after Spontaneous Regression of Non-Small Cell Lung Cancer

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Spontaneous regression of lung cancer is a very rare and poorly understood phenomenon. A 64-year-old man presented to Dong-A University Hospital with a shrunken nodule in the right lower lobe. Although the nodule showed a high likelihood of malignancy on needle aspiration biopsy, the patient refused surgery. The nodule spontaneously regressed completely in the next 17 months. However, the subcarinal lymph node was found to be enlarged 16 months after complete regression was observed. We pathologically confirmed metastasis of squamous cell carcinoma and performed neoadjuvant chemotherapy, surgery, and adjuvant chemoradiation. Regardless of tumor size reduction, it is preferable to perform surgery aggressively in cases of operable lung cancer.

Key words: 1. Lung neoplasms
2. Spontaneous neoplasm regression
3. Lymphatic metastasis
4. Surgery

Case report

A 64-year-old man visited another hospital with hemoptysis in March 2015 (Fig. 1). He had a 35-pack-year history of smoking, and hypertension was the only notable aspect of his medical history. His medications included losartan, nizatidine, and levosulpiride, and he did not take any herbal medications or nutritional supplements. An initial chest computed tomography (CT) scan showed an endobronchial nodule measuring 0.8 cm (1.3 cm in the coronal view) in the posterior basal segment of the right lower lobe (Fig. 2A). The nodule exhibited homogeneous contrast enhancement along the segmental bronchus. The mean CT density of the nodule was

50 Hounsfield units (HU) before contrast enhancement and 83 HU after contrast enhancement. Bronchoscopy showed no endobronchial lesion in the observable area. Bronchial washing cytology revealed no malignancy. The patient had no clinical symptoms related to malignancy, and the serum levels of carcinoembryonic antigen and cytokeratin 19 fragment, as tumor markers, were within the normal range. Therefore, the nodule was clinically suspected to be a benign disease, such as an endobronchial hamartoma, rather than cancer at the first hospital that the patient visited. There were no other events of hemoptysis; thus, the clinician at the first hospital decided to conduct regular follow-up. On a follow-up chest CT scan taken 3 months later, the clinician

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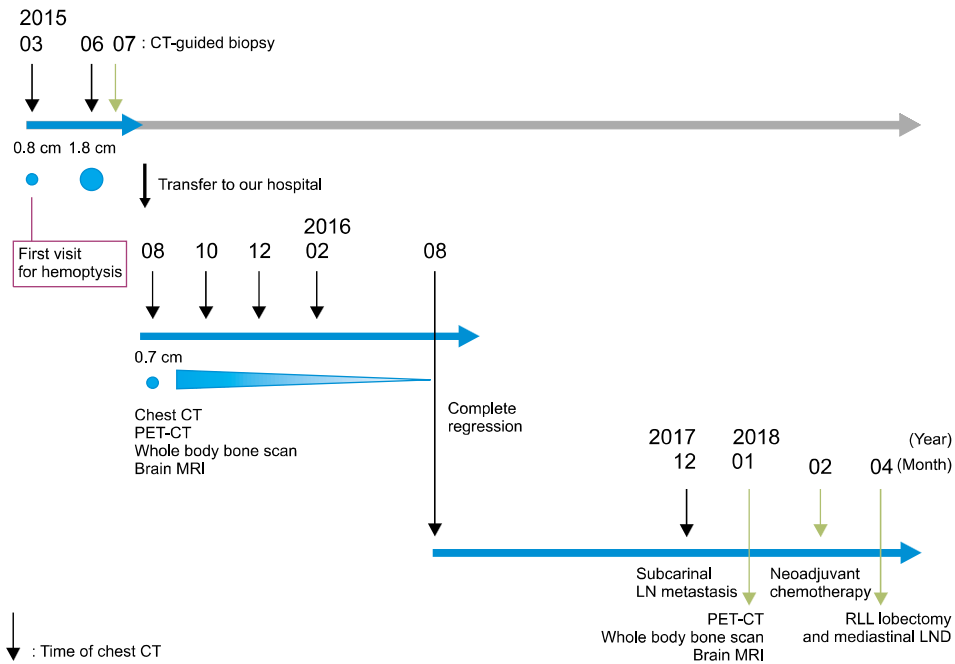


Fig. 1. Flowchart showing the patient's regression course and follow-up chest computed tomography. CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; LN, lymph node; RLL, right lower lobe; LND, lymph node dissection.

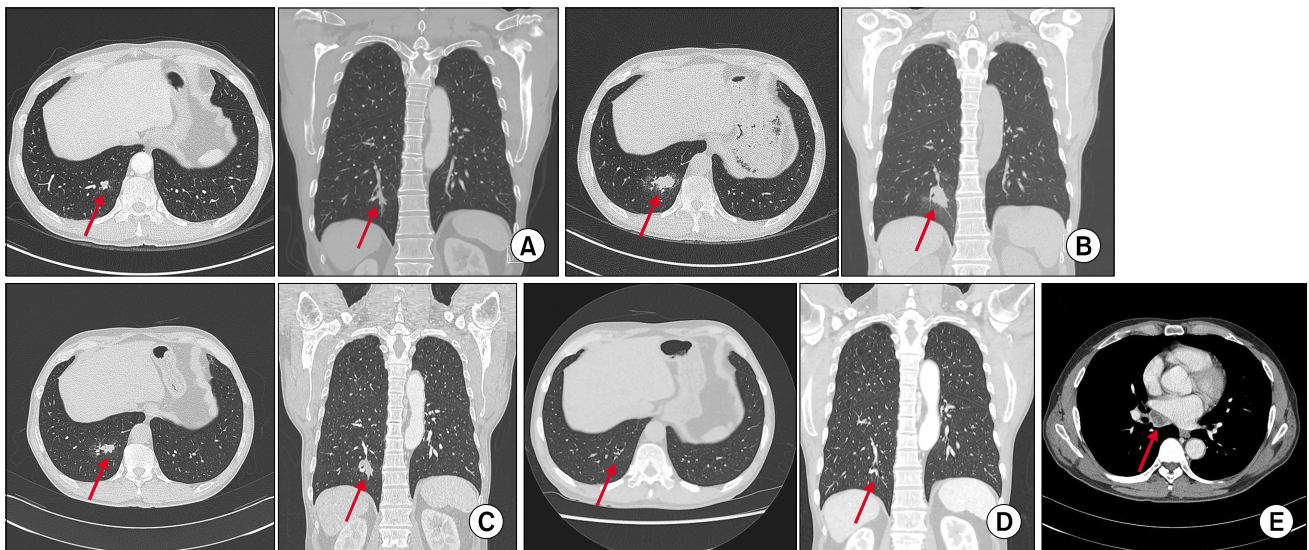


Fig. 2. Serial chest CT. (A) Initial chest CT scan in March 2015 from the first hospital showing the tumor in the right lower lobe in the axial view and coronal view (arrows). (B) In June 2015 (3 months after the initial scan), chest CT scan from the first hospital in the axial view and coronal view (arrows). (C) In August 2015 (after transfer to Dong-A University Hospital), chest CT in the axial view and coronal view (arrows). (D) In August 2016, chest CT showing complete regression in the axial view and coronal view (arrows). (E) Chest CT performed 33 months after the initial chest CT from the first hospital showing enlargement of the subcarinal lymph node (arrow). CT, computed tomography.

found that the size of the endobronchial nodule had increased to 1.8 cm (2.9 cm in the coronal view) (Fig. 2B) and observed a new ground-glass opacity

(GGO) surrounding the nodule. CT-guided needle biopsy for this nodule was performed, and the result was a sheet of atypical cells that were compatible

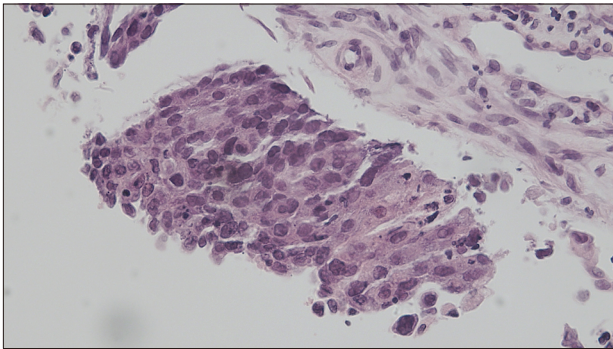


Fig. 3. Tissue obtained via computed tomography-guided biopsy at the first hospital in July 2015 showing large atypical cells with pleomorphic nuclei (H&E stain, $\times 400$).

with squamous cell carcinoma (Fig. 3). The clinician recommended a staging work-up and surgical treatment, but the patient refused.

The patient visited Dong-A University Hospital for surgical treatment in August 2015. We also suspected a malignant tumor based on the previous outside examinations, and performed chest CT, a whole-body bone scan, brain magnetic resonance imaging, and positron emission tomography (PET)-CT as a staging work-up. There was no distant metastasis; however, surprisingly, we found that the size of the nodule had decreased to 0.7 cm (2.1 cm in the coronal view) and that the GGO surrounding the nodule had also become smaller (Fig. 2C). Therefore, for a second opinion, we requested the pathologist in our hospital to review the pathology slide that was obtained by the CT-guided needle aspiration performed at the first hospital that the patient visited. It was difficult to confirm the malignancy of the tumor because the quality of the slide was poor and the amount of the sample was too small. However, atypical cells were still noted, so the possibility of malignancy could not be excluded. We recommended surgery to the patient because the size of the nodule had become too small. However, he refused a further evaluation and wanted to receive follow-up, so we decided upon close observation.

A follow-up chest CT scan was performed every 2 months during the first 6 months. The size of the nodule gradually decreased, and there was no sign of lymph node metastasis. Then, 6 months later (in August 2016), 17 months after the initial chest CT at the first hospital, we performed a further chest CT

scan. It showed that the previous lesion had completely disappeared (Fig. 2D). Thus, we decided to have longer follow-up intervals. In December 2017, 33 months after the initial chest CT at the first hospital, the previous nodular lesion was still not found, but bronchiectasis and fibrotic changes were observed around the site of the previous lesion. Furthermore, the subcarinal lymph node was significantly enlarged and protruded towards the interlobar area (Fig. 2E). Endobronchial ultrasound-guided transbronchial needle aspiration was performed, and it was pathologically confirmed that the patient had lymph node metastasis of squamous cell carcinoma. On a PET-CT scan, the lesion, which had completely regressed in the right lower lobe, had no uptake of fluorodeoxyglucose (FDG), but the subcarinal lymph node had increased FDG uptake. Following a multidisciplinary team discussion, it was decided that surgery would be performed following neoadjuvant chemotherapy.

Following 2 cycles of neoadjuvant chemotherapy using paclitaxel and cisplatin, chest CT showed that the subcarinal lymph node had significantly reduced in size. Thoracoscopic right lower lobectomy and mediastinal lymph node dissection were performed. Intraoperatively, there was no palpable mass at the site of the primary lesion in the right lower lobe. Among the mediastinal lymph nodes, the subcarinal and the right lower paratracheal lymph nodes were enlarged. On pathological exams of the resected specimen, the nodule was not detected at the primary lesion site in the right lower lobe, and the subcarinal lymph node was confirmed as metastasis of squamous cell carcinoma. The patient's final pathological stage was stage IIIA (ypT0N2M0). The patient was discharged on postoperative day 5 without any complications. He underwent adjuvant chemotherapy using paclitaxel and cisplatin and radiation therapy after chemotherapy was completed. He continues to receive follow-up at our hospital and has not yet experienced recurrence.

For the publication, informed consent was obtained from patient.

Discussion

Spontaneous regression was defined by Cole and Everson [1] in 1956 as 'partial or complete dis-

appearance 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.' However, this definition led to ambiguity regarding the interpretation of the term 'inadequate therapy,' so Kumar et al. [2] redefined it as the 'modified Everson and Cole criterion' in 2010. This criterion was defined as follows: (1) partial or complete disappearance of the tumor in the absence of all systemic or local treatment of the primary or metastatic lesion, (2) with the exclusion of patients receiving any systemic therapy (chemotherapy, radioablative techniques, chemoembolization), and (3) histological diagnosis of the primary malignancy or, if no biopsy was done to document metastatic spread, the thoracic lesion had to appear metastatic radiographically and in a clinical context [2]. The incidence of spontaneous regression is estimated to be approximately one in 60,000–100,000 people with cancer [1]. Spontaneous regressions has most commonly been reported in malignant melanoma, non-Hodgkin lymphoma, renal cell carcinoma, neuroblastoma, choriocarcinoma, and leukemia; however, spontaneous regression in lung cancer is a rare phenomenon.

Spontaneous regression is explained as an immunological mechanism that is induced by cell apoptosis or inflammatory necrosis [3]. Factors that trigger these responses include injuries due to biopsy or thoracostomy, as well as infections. As cytokines are released, a T cell-mediated immune response is induced. In addition, proteins such as BCL-2 and p53 inhibit or induce cell apoptosis [3]. Another mechanism of spontaneous regression is loss of exposure to exogenous carcinogens during the early stage of carcinogenesis; this leads to the differentiation of tumor cells into a normal phenotype (i.e., the tumor cells recover). This mechanism has been observed in retinoblastoma, neuroblastoma, embryonal carcinoma, or choriocarcinoma [4]. Other mechanisms of spontaneous regression include those induced by hormones and psychoneuroimmunological factors [4].

Although many theories have been proposed to explain the mechanisms by which spontaneous regression occurs in various types of cancers, none has been proven, and this also holds true for spontaneous regression in non-small cell lung cancer. In the present case, it is proposed that new antigens were

released during the aspiration needle biopsy and activated the immune response; however, it is also possible that the feeding artery of the tumor became damaged during the biopsy process, and that this led to tumor necrosis. We observed a gradual decrease in tumor size followed by disappearance of the primary lesion through a series of chest CT scans. The regressed tumor did not show FDG uptake on the PET-CT performed before administering neoadjuvant chemotherapy. In addition, no residual tumor was observed at the primary lesion site in the post-operative pathological results. Therefore, these findings suggest complete regression of the primary tumor in our patient.

Marques et al. [5] reviewed 17 cases of spontaneous regression in lung cancer, 10 of which involved non-small cell lung cancer. Spontaneous regression in non-small cell lung cancer has rarely been reported, with only 3 cases reported in Korean domestic journals. According to the literature that we reviewed, there have been a total of 19 cases of spontaneous regression in non-small cell lung cancer since the 1990s. These cases lacked long-term survival or recurrence outcomes. Only 4 of the 19 reported cases had long-term outcomes that showed a recurrence- or progression-free period of 5 years or more [3,6-8]. The other cases reported a variety of follow-up periods, ranging from 2 months to 31 months. In most cases, the patients had advanced-stage cancer, or had poor pulmonary function even if they had early-stage cancer; thus, surgery was not indicated. Various patterns of complete or partial regression were observed. For instance, the primary lesion disappeared, but the metastatic lesion remained; both the primary and metastatic lesions remained after regression; or the primary lesion remained, but the metastatic lesion disappeared. For these reasons, it is difficult to identify long-term outcomes after spontaneous regression.

A change in tumor size is one of the most important indicators for assessing the malignant potential of a tumor in all lung cancer screening guidelines. The present case shows that a spontaneous gradual decrease in size does not necessary entail the absence of potential malignancy. If other indicators exhibit a high possibility of malignancy, active evaluation and treatment are needed, rather than observation.

We incidentally obtained follow-up results after the spontaneous regression of early non-small cell lung cancer. In addition, this is the first report of recurrence in the mediastinal lymph nodes following complete regression of the primary lesion in early non-small cell lung cancer. This case showed that complete regression is not a 'cure' (i.e., it cannot confirm the disappearance of cancer). Therefore, regardless of tumor size reduction, it is preferable to perform surgery aggressively in cases of operable early-stage lung cancer.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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