Case Report

A Surgical Case of Quadruple Lung Cancer

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The patient was a 50-year-old male psychiatrist with a history of smoking 3 packs of cigarettes per day for 30 years. Chest computed tomography (CT) showed a nodular shadow in the left S6 segment in April 2002, for which thoracoscopic partial resection of the lung was performed. Because adenocarcinoma was diagnosed by intraoperative frozen sectioning, a left lower lobectomy and lymph node dissection were performed. The pathological diagnosis was adenocarcinoma with mixed subtypes (AMS, pT1N0M0). Cytologically, the tumor cells exhibited tall columnar eosinophilic cytoplasm. In March 2005, chest CT showed a nodular shadow in the right S3 segment, and thoracoscopic partial resection of the lung was performed. Histopathological examination revealed AMS (pT1N0M0). Cytologically, cancer cells showed cuboidal cytoplasm. In November 2007, a nodular shadow appeared in the right S4 segment on chest CT, and thoracoscopic partial resection of the middle lobe and the portion of the upper lobe that had adhered to the middle lobe was performed. Histologically, the middle-lobe tumor was solid adenocarcinoma with mucin (pT1N0M0). Although no gross tumor could be identified in the upper lobe, histological examination revealed nonmucinous bronchioloalveolar carcinoma (pT1N0M0). The patient is currently following a favorable course. Herein, we report a surgical case of quadruple lung cancer. (Ann Thorac Cardiovasc Surg 2010; 16: 345–350)

Key words: quadruple lung cancer, adenocarcinoma, surgery

Introduction

Although cases of multiple (often up to triple) lung cancer have been reported, those of quadruple lung cancer are very rare.[1)] We recently encountered a patient who had developed four lung cancers, all of which were surgically resected. The differentiation between primary and metastatic cancers is often problematic in patients with multiple lung cancer. In this patient, each lung cancer was pathologically considered to be primary. We herein report a surgical case of quadruple lung cancer.

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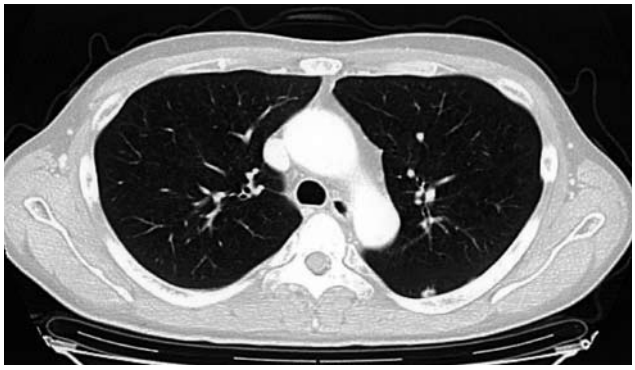
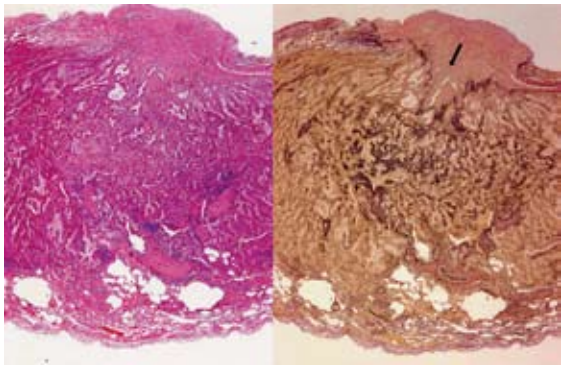
Case Report

The patient was a 50-year-old male psychiatrist who had been found to have a nodular shadow in the left S6 segment on a computed tomography (CT) scan during a health checkup, and he had visited our department in April 2002. He had smoked 3 packs of cigarettes per day for 30 years. He had no history of exposure to asbestos or radiation. His past medical history was unremarkable. He was 176 cm tall and weighed 59.8 kg. Superficial lymph nodes were not palpable, and he was in good health except for the chief complaint.

Because chest CT performed in April 2002 showed a small nodular shadow in the left S6 segment, the patient underwent thoracoscopic partial resection of the lung (Fig. 1A). The tumor was diagnosed as a microinvasive adenocarcinoma by intraoperative frozen sectioning, and left lower lobectomy and lymph node dissection were performed. The tumor was a $10 \times 5 \times 3$ mm grayish-white, well-circumscribed nodule. The postoperative pathological





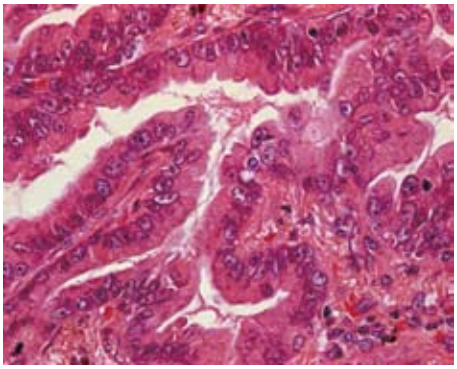


Fig. 1.

A

B | C

A: Chest CT scan demonstrating a well-defined, small nodule in the left S6 segment.

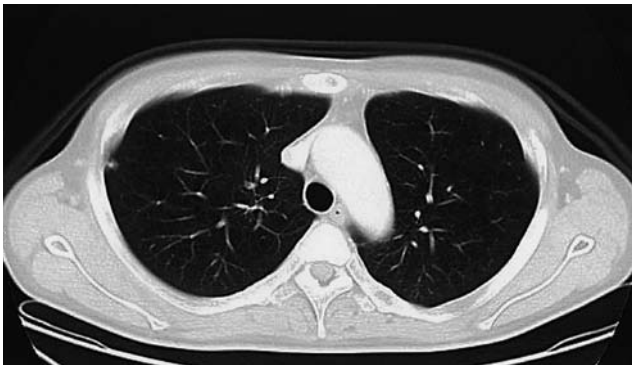
B: The tumor was diagnosed by hematoxylin-eosin staining as adenocarcinoma with mixed subtypes, predominantly bronchioloalveolar growth with foci of invasive acinar and papillary components. With the Elastica–van Gieson stain, elastic fibers are stained dark brown and collagen fibers pink. Most of the alveolar elastic fibers were preserved, but a few tumor glands invaded visceral pleura beyond the elastic lamina (arrow).

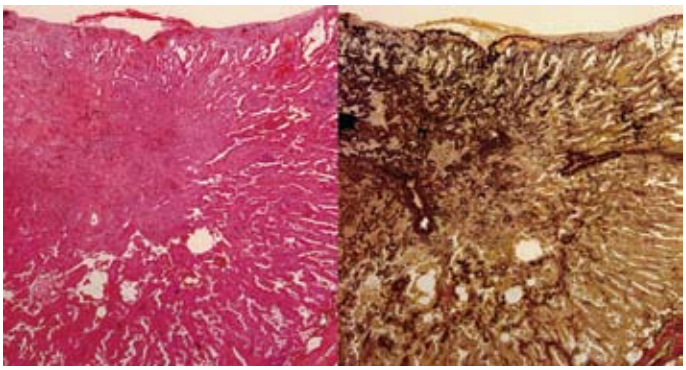
C: Cytologically, the tumor cells had tall columnar eosinophilic cytoplasm resembling bronchial lining epithelial cells.

diagnosis was adenocarcinoma with mixed subtypes (AMS) (pT1N0M0) (Fig. 1B). Because the tumor had invaded beyond the elastic lamina of the visceral pleura, it was diagnosed as p1 (bronchioloalveolar growth [BAG] >> acinar pattern [Aci], papillary pattern [Pap]). Cytologically, the tumor cells exhibited tall columnar eosinophilic cytoplasm and the morphological appearance of bronchial lining epithelial cells (Fig. 1C).

During postoperative follow-up, chest CT showed a small nodular shadow in the right S3 segment in March 2005 (Fig. 2A), and thoracoscopic partial resection of the lung was performed. On gross examination, a 0.7 × 0.5 cm, grayish tumor that was well demarcated from the surrounding lung was observed. Histopathological examination revealed AMS (pT1N0M0) (Fig. 2B). The tumor had an elastic scar in the central area. Tumor cells showed a predominantly bronchioloalveolar growth pattern with focal acinar and papillary invasive components in the area of periphery of a central scar (Fig. 2B). These findings indicated that this tumor was a minimally invasive adenocarcinoma (BAG >> Aci, Pap).[2] Cytologically, the cancer cells showed peg-shaped or cuboidal cytoplasm and had the morphological appearance of Clara cells or type II pneumocytes (Fig. 2C). Since this cancer was different in cell morphology from the left lower-lobe lung cancer resected in 2002, it was not regarded as metastasis from the previous lung cancer, but as a second primary lung cancer, and chemotherapy was not performed. Thereafter the patient was closely monitored.

During postoperative follow-up, a small nodular shadow appeared in the right S4 segment on chest CT in November 2007 and tended to enlarge over time (Fig. 3A). Because PET showed abnormal fluorodeoxyglucose-uptake (SUV_{max}=7.1) in the same lesion, thoracoscopic partial resection of the





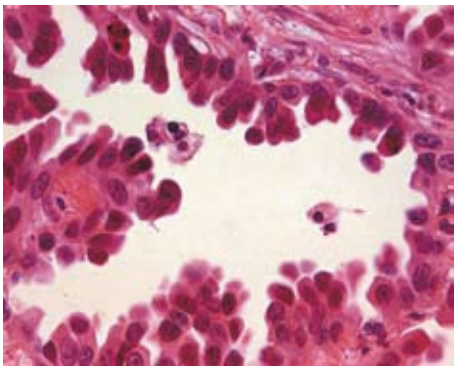


Fig. 2.

A: Chest CT scan showing a small, ground-glass opacity nodule in the right S3 segment.

B: Histopathological examination revealed AMS, predominantly BAG with foci of minimally invasive components. In the central area, Elastica-van Gieson staining showed collapsed elastic scar.

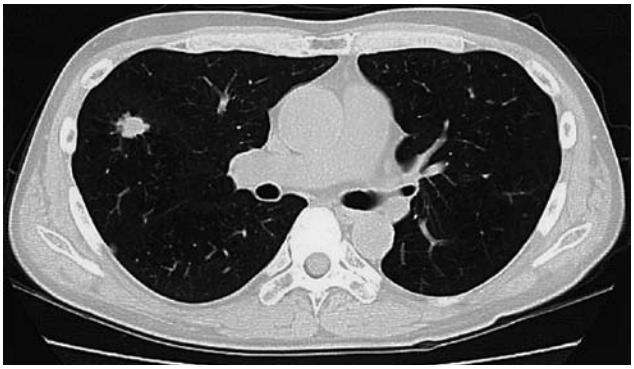
C: Cytologically, the cancer cells had peg-shaped or cuboidal cytoplasm resembling Clara cells or type II pneumocytes.

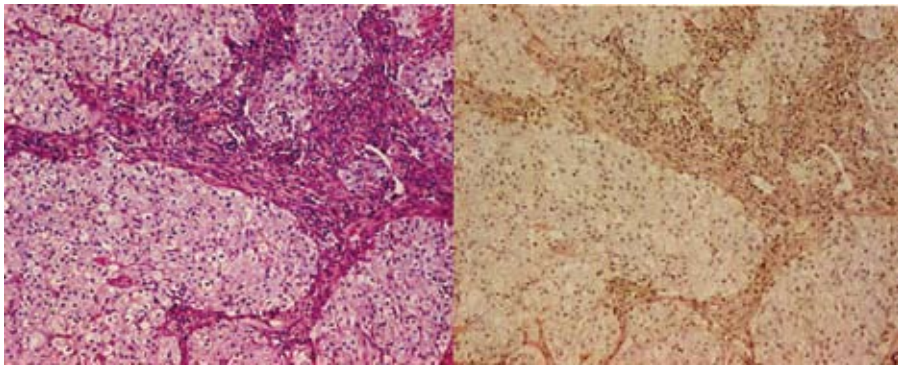
A
B C

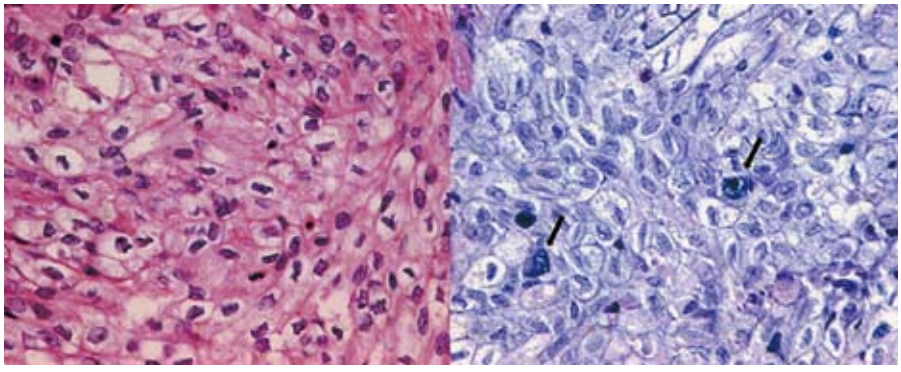
middle lobe was performed in July 2008. And because of adhesion between the middle and upper lobes, partial resection of the upper lobe was also performed. Postoperative pathological examination revealed a 1.7 × 0.6 cm, well-circumscribed, irregularly bordered, white nodule in the middle lobe. Histologically, it was a tumor composed of solid invasive nests (pT1N0M0) (Fig. 3B). Alcian blue-periodic acid-schiff staining identified scattered cytoplasmic mucin droplets, suggesting solid adenocarcinoma with mucin (Sol, solid growth only) (Fig. 3C). Tumor invasion remained in lymphatic vessels, with no apparent invasion into blood vessels. The previous two cancers showed predominantly BAG with focal Aci or Pap invasion and no solid feature. Because of critical histopathological difference, the present tumor was considered to be a third primary lung cancer.

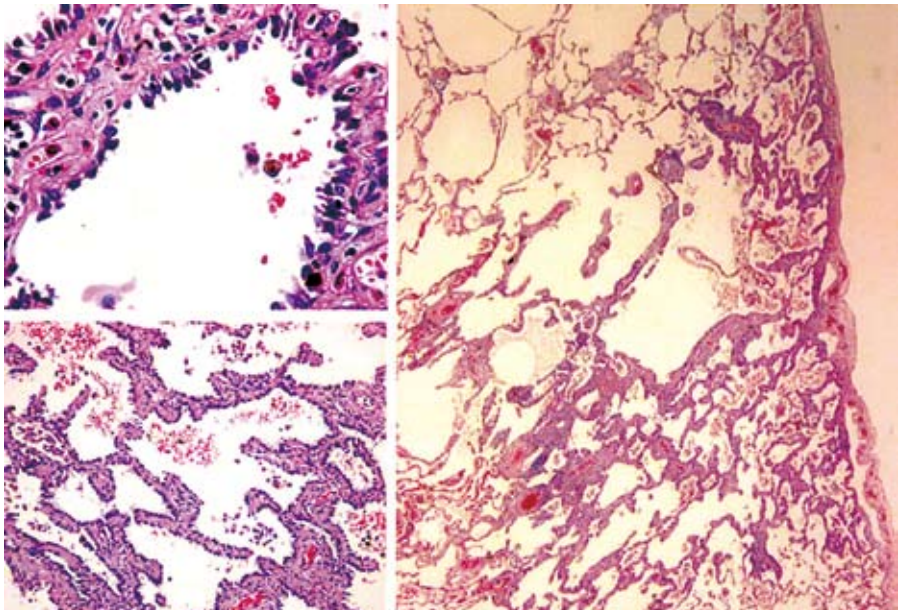
Although no gross tumor could be identified in the upper lobe that was partially resected along with the middle lobe, histological examination revealed peg-shaped or cuboidal tumor cells proliferating densely along alveolar septa in an area of 5 × 3 mm immediately beneath the pleura (pT1N0M0, bronchiloalveolar carcinoma [BAC]), which was considered to be a fourth primary lung cancer (Fig. 3D). There was fibrous thickening of part of the pleura, which had probably been adherent to the middle lobe, with no neoplastic changes.

Because a tumor developed along the stapled resection line in the middle lobe, resection of the remaining middle lobe and lymph node dissection were performed in March 2009. Pathologically, the tumor was a poorly differentiated adenocarcinoma closely resembling Sol in the middle lobe that was resected in July 2008, suggesting recurrence in the surgical margin. Lymph node metastases were confined to a bronchial lymph node (n1). The patient is currently following a favorable course and is being closely monitored for the development of new lesions on an outpatient basis.









A

B

C

D

Fig. 3.

A: Chest CT scan demonstrating a well-circumscribed, irregularly bordered nodule in the right S4 segment.

B: Histologically, the tumor consisted of solid invasive nests. Alveolar elastic fibers were completely destroyed in Elastica–van Gieson stain.

C: Alcian blue-periodic acid-schiff staining identified scattered cytoplasmic mucin droplets (arrow).

D: In part of the coresected upper lobe, peg-shaped or cuboidal tumor cells grew densely along the alveolar wall.

Discussion

Deschamps et al. reported that 117 (1.2%) of 9,611 patients were diagnosed with multiple synchronous or metachronous primary lung cancers.[3] Recently the incidence of multiple primary lung cancer is increasing because of longer survival after surgery and improvements in early detection methods, and it is generally thought to vary from 1% to 10% for synchronous and metachronous cancers together.[4–6] The risk of developing a new primary lung cancer after undergoing definitive surgical therapy for a nonsmall cell lung cancer is estimated to be 1% to 2% per patient per year.[7,8] Double or triple lung cancer is not uncommon now, but resected cases of quadruple lung cancer are extremely rare.[1] In this patient, all cancers were stage IA and surgically resected. For the first lung cancer, thoracoscopic partial resection of the lung was performed, followed by left lower lobectomy based on an intraoperative frozen-section diagnosis of microinvasive adenocarcinoma. For the second lung cancer, which was considered a metachronous primary lung cancer, only thoracoscopic partial resection of the lung was performed in consideration of its small size and the lung function. The third lung cancer (of the middle lobe) was poorly differentiated and, as a rule, required lymph node dissection. However, considering the future risk of developing a metachronous lung cancer, we selected thoracoscopic partial resection of the lung. The fourth lung cancer (of the upper lobe) was incidentally resected. Initially, surgical techniques were selected with emphasis on the permanent cure of cancer, but after the development of a second lung cancer, it was necessary to consider the possible development of a new lung cancer in the selection of surgical resections. Several authors reported that operations for multiple cancers facilitated survival that approximated with the expected survival for lung cancer.[9–11] Surgical intervention should be considered as a safe and effective treatment for resectable multiple lung cancers in patients with an adequate physiological pulmonary reserve.

The multicentric nature of many bronchioloalveolar carcinomas could reflect either a multifocal origin or a metastasis. Molecular studies of multifocal bronchioloalveolar carcinomas have led to controversies, and there is currently no consensus as to whether they represent independent lesions or metastases derived from a single source.[12,13] A pathological examination of all four tumors in this patient revealed different histological features and cell morphologies, leading to a diagnosis of quadruple primary lung cancers. The four lung cancers developed in the chronological order of AMS → AMS → Sol, BAC, and the earliest-stage cancer (BAC) developed last at 6 years after the appearance of the first lung cancer. This sequence of events also excludes the possibility of metastases. It is generally difficult to differentiate primary from metastatic multiple lung cancers by preoperative imaging and biochemical findings; therefore the determination of surgical indications requires comprehensive evaluation, including the clinical course.

The last BAC was incidentally resected and was difficult to identify grossly, justifying its designation as a latent cancer. Because of the view that atypical adenomatous hyperplasia (AAH) is a premalignant phenotype, multiple AAH lesions might have represented the earliest morphological change in the stepwise development of peripheral adenocarcinoma. However, in this patient no AAH was pathologically observed in the background lung. There seems to be no clear reason for lung cancer other than heavy smoking, but the patient appeared to be predisposed to it and developed lung cancers metachronously and synchronously. It is very likely that lung cancers remain latent in the residual lung, suggesting that the patient needs to be closely monitored for the development of new lesions.

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