A surgical Case of Synchronous Multiple Primary Lung Cancers with Small Cell Carcinoma and Squamous Cell Carcinoma

Hajime WATANABE[*1,3], Sakura TOMITA[*2], Yoichiro IKOMA[*3], Mitsutomo KOHNO[*3], Ryota MASUDA[*3] and Masayuki IWAZAKI[*3]

[*1]*Division of Thoracic Surgery, Tokai University Oiso Hospital*
[*2]*Division of Pathology, Tokai University School of Medicine*
[*3]*Division of Thoracic Surgery, Department of Surgery, Tokai University School of Medicine*

(Received November 9, 2020; Accepted December 22, 2020)

The incidence of synchronous multiple primary lung cancers has increased in recent years, however, there are few reports of cases involving small cell carcinoma. A 72-year-old man was referred to our department because of an abnormal shadow on chest radiography. He was receiving treatment for pulmonary fibrosis, emphysema, rheumatoid arthritis, and prostate cancer. Computed tomography revealed two lung nodules in the left lower lobe. A definitive diagnosis was unable to be made based on transbronchial lung biopsy. Positron emission tomography demonstrated abnormal fluorodeoxyglucose uptake in the two lung nodules and lung cancer (cT3N0M0) was suspected. Thoracoscopic partial resection of the left lower lobe was performed. As primary lung cancer was diagnosed using the frozen specimen, we performed left lower lobectomy with lymph node dissection. Pathological examination of the S9 and S6 tumors revealed combined small cell carcinoma and squamous cell carcinoma, respectively. Both tumors were separated and diagnosed as synchronous multiple primary lung cancers. No lymph node metastasis was found. We report a rare case of synchronous multiple primary lung cancers, including small cell carcinoma.

Key words: Lung cancer, Synchronous primary lung cancer, Small cell lung cancer, Surgery

INTRODUCTION

The incidence of synchronous multiple primary lung cancers has recently increased because of advances in diagnostic imaging. However, there are few reports of these cases involving small cell carcinoma. We report a case of synchronous multiple primary lung cancers demonstrating small cell carcinoma and squamous cell carcinoma in the same lung lobe.

CASE REPORT

A 72-year-old man was referred to our department because of an abnormal shadow on chest radiography (Fig. 1A). He was receiving treatment for pulmonary fibrosis, emphysema, rheumatoid arthritis, and prostate cancer with bone metastases. He smoked 20 cigarettes/day for the past 50 years and the smoking index was 1000. His regular medications included a bronchodilator, immunosuppressive agent, steroid, and hormonal agent. Physical examination revealed no abnormalities. Laboratory findings were within normal limits, except for a CEA level of 11.9 ng/mL and KL-6 level of 664 U/mL. Computed tomography (CT) revealed two solid lung nodules in the left lower lobe. One 6-mm lesion was located in segment 6 (S6) and another 11-mm lesion was located in segment 9 (S9) of the left lung (Fig. 1B, C). The lesion in S9 increased in size compared with its size 1 year ago. CT also revealed honeycomb lung in the subpleural portion of the bilateral lung base. Positron emission tomography (PET) demonstrated abnormal fluorodeoxyglucose (FDG) uptake in the two left lung nodules, multiple bones, suspected to be metastases of prostate cancer, and no abnormalities in other body parts. A definitive diagnosis was unable to be made based on transbronchial lung biopsy. Lung cancer with intralobar pulmonary metastasis (cT3N0M0) was suspected and surgery was planned. However, the possibility of metastatic lung tumors of prostate cancer and synchronous multiple primary lung cancers was also considered. The patient underwent thoracoscopic lung surgery. The lesion in S9 was diagnosed as primary lung cancer using the frozen specimen and left lower lobectomy with lymph node dissection was performed. Pathological examination of the S9 tumor revealed combined small cell carcinoma with adenocarcinoma (Fig. 2A, B). On immunohistochemical staining, synaptophysin, cluster of differentiation-56 (Fig. 2C), and chromogranin A expression were positive. Histologically, the tumor in S6 was squamous cell carcinoma (Fig. 3A, B). Both tumors were separated and diagnosed as synchronous multiple primary lung cancers. No lymph node metastasis was found. There were no postoperative complications and the patient was discharged on the eighth day after surgery.

Hajime WATANABE, Division of Thoracic Surgery, Tokai University Oiso Hospital, 21-1 Gakkyo, Oiso, Kanagawa 259-0198, Japan
Tel: +81-463-72-3211 Fax: +81-463-72-2256 E-mail: wh110193@tsc.u-tokai.ac.jp

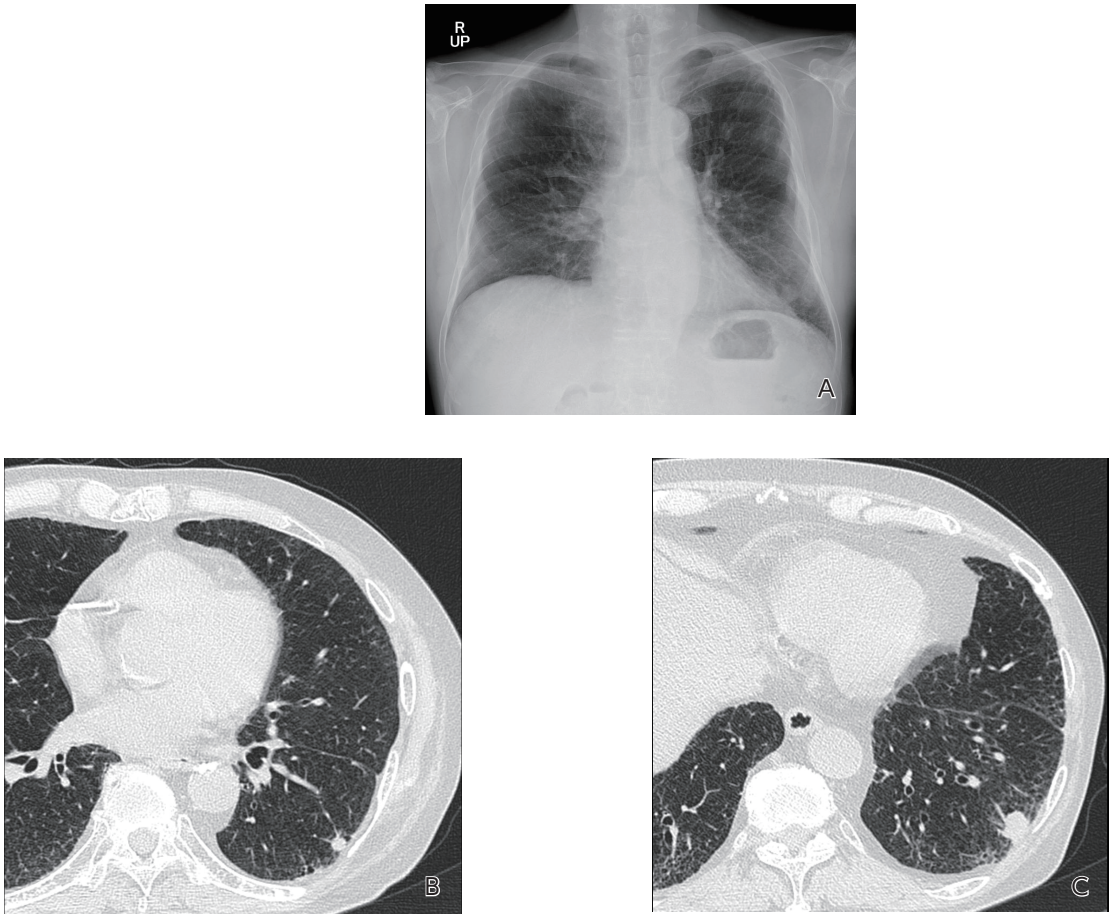

Fig. 1 Chest X-ray showing a nodule in the left lung field (A).
Computed tomography showing a solid nodule in the left segment 6 (B).
Computed tomography showing a solid nodule in the left segment 9 (C).

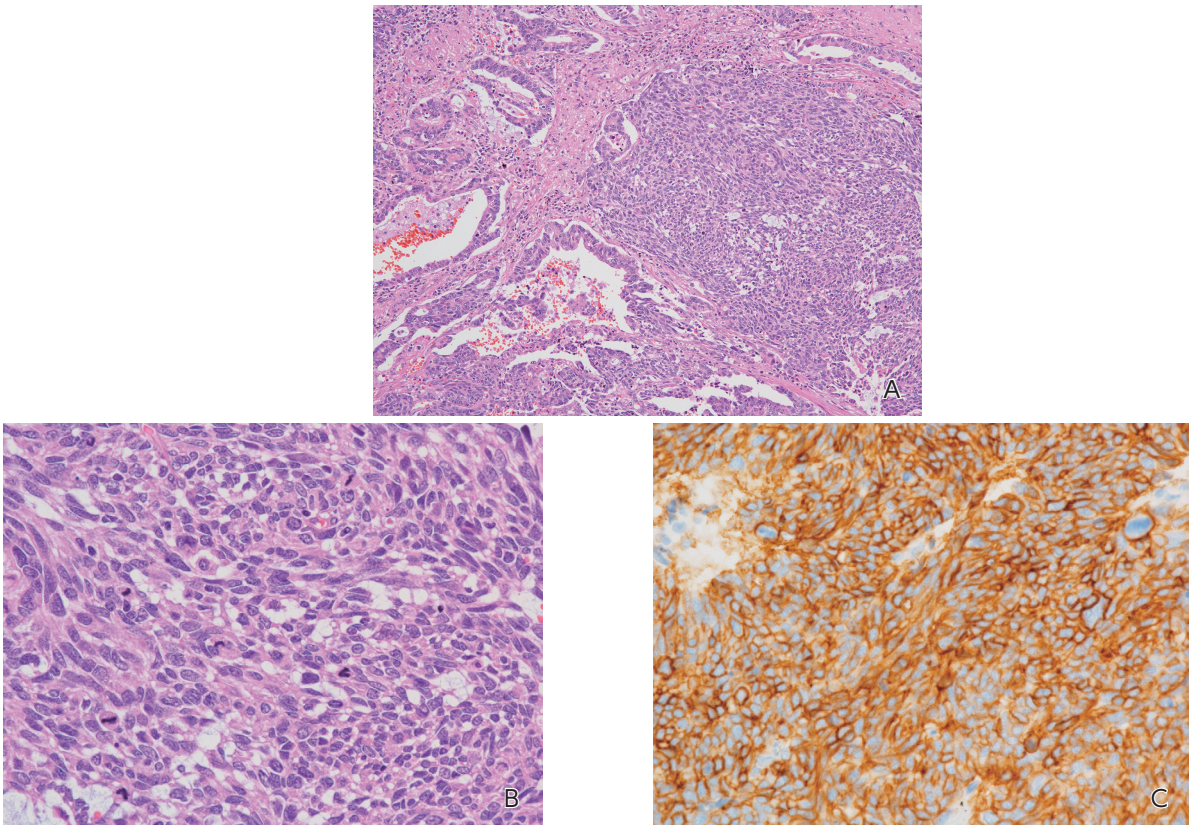

Fig. 2 Microscopic findings of the segment 9 tumor revealing combined small cell carcinoma
A low-power view of hematoxylin and eosin staining (A)
A high-power view of hematoxylin and eosin staining (B)
Immunostaining demonstrated that the tumor cells were positive for cluster of differentiation-56 (C).

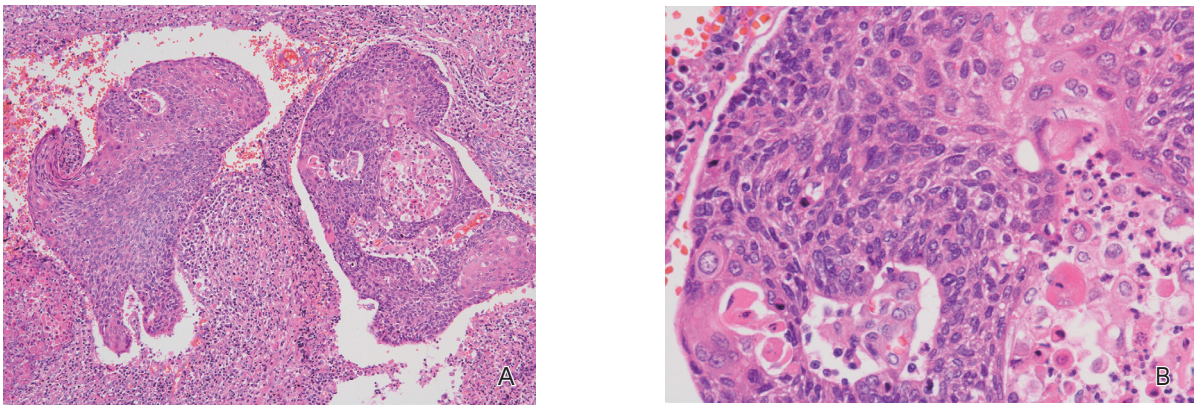

Fig. 3 Microscopic findings of the segment 6 tumor showing squamous cell carcinoma
A low-power view of hematoxylin and eosin staining (A)
A high-power view of hematoxylin and eosin staining (B)

DISCUSSION

The diagnostic criteria for synchronous multiple primary lung cancers reported by Martini in 1975 remain widely used [1]. Tumors of different histological types are defined as synchronous multiple primary lung cancers if they are separated. For tumors of the same histological type, the following cases are defined as synchronous multiple primary lung cancers: (a) origin from carcinoma in situ, (b) no carcinoma in the lymphatic system common to both, and (c) no extrapulmonary metastases [1]. The incidence of synchronous multiple primary lung cancers was reported to be 0.97% in 1975 [1], but it ranged from 4.5% to 5.6% in 2007 [2–3]. This increase may be because of the recent improvement in the accuracy of CT image-based diagnosis. According to several studies, most tumors are of the same histological type [2–4]. Hiraki *et al.* reported in 1999 that the most common combinations were squamous cell carcinoma and squamous cell carcinoma [5]. However, based on the analysis of 125 patients with synchronous multiple primary lung cancers reported by Trousse *et al.* in 2007, the combination with adenocarcinoma accounted for 52% and that with squamous cell carcinoma accounted for 28.8%; the proportion of adenocarcinoma has increased in recent years [2]. Synchronous multiple primary lung cancers, including small cell carcinoma, are markedly rare [6]. The reported incidences are 0.03% and 0.04% for small cell carcinoma and adenocarcinoma, and small cell carcinoma and squamous cell carcinoma, respectively [5]. In recent series of synchronous multiple primary lung cancers, squamous cell carcinoma and small cell carcinoma represented only 8.3% of these cases [7]. Most small cell lung cancer is found with advanced stage and not peripheral small nodule. Additionally, the reported cases of synchronous multiple primary lung cancers including small cell carcinoma were also advanced stage so that there were contraindications of surgery [8–9]. However, in our case, the two lesions were located as small peripheral nodules. This is an extremely rare case.

The treatment strategy for multiple lung tumors that may be malignant is important because they differ in terms of prognosis and whether they are synchronous multiple primary lung cancers or pulmonary metastasis. There are many clinical cases in which a definitive diagnosis was not made before surgery. In the case of primary lung cancer, intralobar pulmonary metastasis is indicated for surgery, but extralobar pulmonary metastasis is not. If the patients have a history of other malignant tumors, metastatic lung tumors should be considered as a differential diagnosis. In these cases, surgical indications depend on the situation. In our case, if the lung tumors were primary lung cancers, surgery would have been indicated. However, if the lung tumors were pulmonary metastases of prostate cancer that included bone metastases, surgery would not have been indicated. Although a definitive diagnosis was unable to be made before surgery, we considered the possibility of pulmonary metastases being low because the value of prostate-specific antigen was normal. We performed lung surgery and the postoperative course was uneventful. The final diagnosis was synchronous multiple primary lung cancers, but we did not suspect the combination of small cell carcinoma and squamous cell carcinoma before surgery. Distinguishing solid lung nodules from small cell carcinoma and non-small cell carcinoma based on CT or FDG-PET is difficult [10]. Small cell carcinoma generally progresses more rapidly than non-small cell carcinoma [11], but it cannot be judged by this feature alone.

The analysis of 175 patients with synchronous multiple primary lung cancers reported by Finley *et al.* revealed the postoperative 3-year survival rates to be 74% and 65% in patients with stage ⅠA and ⅠB cancer, respectively [12]. These survival rates are similar to those of patients with the same stages of single lung cancer [12]. Trousse *et al.* also reported that the 5-year survival rate in 125 resected cases of synchronous multiple primary lung cancers that involved no lymph node metastases was 51.4% [2]. These reports were all regarding non-small cell carcinoma because synchronous multiple primary lung cancers, including small cell carcinoma, are markedly rare. The prognosis of synchronous multiple primary lung cancers including small cell carcinoma is unknown. According to the analysis of effectiveness of postoperative adjuvant chemotherapy in patients with resected small cell lung cancer, the 5-year survival rate was 73% in patients with stage IA cancer [13]. This suggested that surgery is a treatment choice for early-stage small cell lung cancer. Surgery may be effective for synchronous mul-

tiple primary lung cancers if the stage is indicated for surgery.

CONCLUSION

We reported a rare case of synchronous multiple primary lung cancers, including small cell carcinoma. Careful consideration of the treatment strategy is important for multiple lung tumors that may be malignant because there is a possibility of pulmonary metastases in synchronous multiple primary lung cancers. Individual treatment is required in each case.

CONFLICT OF INTEREST

There were no conflicts of interest.

REFERENCES

1) Martini N, Melamed MR. Multiple primary lung cancers. *J Thorac Cardiovasc Surg.* 1975; 70: 606–612.
2) Trousse D, Barlesi F, Loundou A, Tasei AM, Doddoli C, Giudicelli R, *et al.* Synchronous multiple primary lung cancer: An increasing clinical occurrence requiring multidisciplinary management. *J Thorac Cardiovasc Surg.* 2007; 133: 1193–1200.
3) Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. *J Thorac Cardiovasc Surg.* 2007; 134: 630–637.
4) Ferguson MK, DeMeester TR, DesLauriers J, Little AG, Piraux M, Golomb H. Diagnosis and management of synchronous lung cancers. *J Thorac Cardiovasc Surg.* 1985; 89: 378–385.
5) Hiraki A, Ueoka H, Yoshino T, Chikamori K, Onishi K, Kiura K, *et al.* Synchronous primary lung cancer presenting with small cell carcinoma and non-small cell carcinoma: diagnosis and treatment. *Oncol Rep.* 1999; 6: 75–80.
6) Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Operative approach for multiple primary lung carcinomas. *J Thorac Cardiovasc Surg.* 1998; 115: 836–840.
7) Ghattas C, Hundal M, Agustin M, Unterborn J. A rare type of synchronous multiple primary lung cancer: staging and treatment dilemma. *Am J Resp Crit Care.* 2016; 193: A6125.
8) Jiang L, Zheng X, Wu S, Zhang J, Ru G, Li Y. A Rare Case Of Synchronous Multiple Primary Lung Cancer: Squamous Cell Cancer And Small Cell Lung Cancer. *OncoTargets and Therapy* 2019: 12 8801–8806.
9) Wu X, Huang W, Geng T, Wei Y. Next-Generation Sequencing of Synchronous Multiple Primary Lung Cancers in a Patient with Squamous Cell Carcinoma and Small Cell Lung Cancer. *OncoTargets and Therapy* 2020: 13 11621–11626.
10) Park KY, Koh JS, Choe DW, Kim CH, Lee JC. Synchronous small and non-small cell lung cancer in a patient with previous tuberculosis. *Intern Med.* 2007; 46: 1677–1678.
11) Kalemkerian GP, Akerley W, Bogner P, Borghaei H, Chow LQ, Downey RJ, *et al.* Small cell lung cancer. *J Natl Compr Canc Netw.* 2013; 11: 78–98.
12) Finley DJ, Yoshizawa A, Travis W, Zhou Q, Seshan VE, Bains MS, *et al.* Predictors of outcomes after surgical treatment of synchronous primary lung cancers. *J Thorac Oncol.* 2010; 5: 197–205.
13) Tsuchiya R, Suzuki K, Ichinose Y, Watanabe Y, Yasumitsu T, Ishizuka N, *et al.* Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: the Japan Clinical.