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Original article

Bilateral synchronous multiple lung nodules: Surgical experience from two cases

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ABSTRACT

Synchronous multiple lung cancer (SMPLC) has been increasingly detected as a result of improved imaging techniques, though the incidence of SMPLC is rare. Surgery is currently the only treatment offering potential cure and long-term survival in patients with SMPLC, and complete resection is widely accepted as the first choice of procedure for this type. However, due to the rarity of this clinical scenario, many surgeons lack experience in surgical treatment of SMPLC. Here, we present two cases whose SMPLC was successfully managed with aggressive surgical therapy through video-assisted thoracoscopic surgery.

1. Introduction

Synchronous multiple primary lung cancer (SMPLC), defined as multiple primary lung cancer discovered around the same period of time (Detterbeck et al., 2003; Kozower et al., 2013), is rare with an incidence around 0.5% (Ferguson, 1993). However, in case of two or more nodules having identical histology, it is intractable to differentiate pulmonary metastases from SMPLC because genetic and molecular analyses are not routinely performed in clinical practice. A simple analysis of EGFR and KRAS mutations in the tumors seems a cost-effective way to identify true SMPLC from the cases that were hard to diagnosis by merely clinical characteristics (Liu et al., 2016). When confronted with respectable bilateral multiple pulmonary nodules, the thoracic surgeons often find himself in a dilemma. Surgical treatment is still the first choice for these patients when possible, and the 5-year disease-free survival and overall survival rates can be close to 60% and 80%, respectively (Zhang et al., 2016). Although surgery was believed to prolong the survival of SMPLC patients, pneumonectomy was reported to be an indicator of poor prognosis (Liu et al., 2016; Trousse et al., 2007). Therefore, the surgical treatment of SMPLC is critical. Here, we report two cases of SMPLC which was managed by video-assisted thoracoscopic surgery.

2. Case report

2.1. Patient 1

A 71-year-old man without history of smoking had an abnormal chest computed tomography (CT) in his regular health examination. Two nodules in his right upper lobe and a material mass in his left upper lobe without mediastinal or hilar lymphadenopathy were disclosed (Fig. 1). He was asymptomatic and had nothing remarkable in his medical and family history. A physical examination also failed to reveal any significant abnormalities. A pulmonary function test showed a restrictive pattern on spirometry with a forced expiratory volume-one second (FEV1) of 1.55 L (65.6% of predicted), a forced vital capacity (FVC) of 2.22 L (79.9% of predicted), and an FEV1/FVC ratio of 69.83%.

The patient was administered with double-lumen endotracheal intubation after general anesthesia. He was firstly placed in a left

Abbreviations: CT, computed tomography; FEV1, forced expiratory volume-one second; FVC, forced vital capacity; GGO, ground glass opacity; NSCLC, non-small cell lung cancer; SMPLC, synchronous multiple lung cancer.

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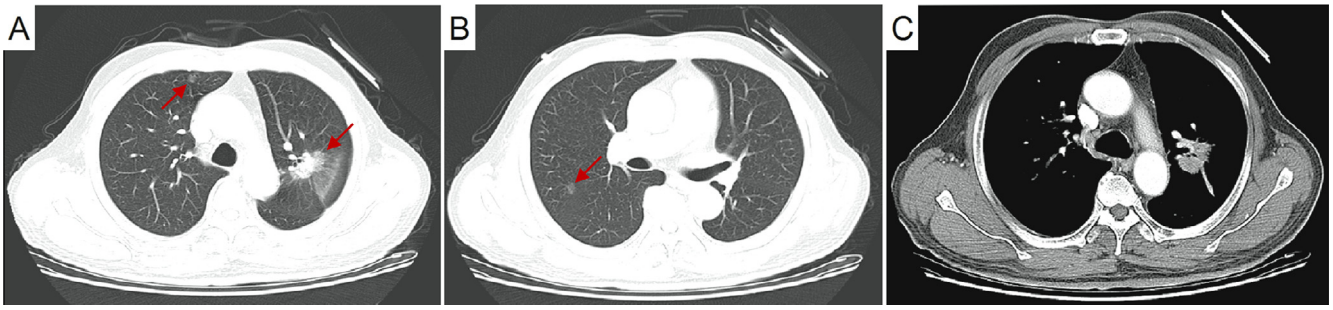

Fig. 1. Chest CT on admission revealed two lung nodules in the right lobe and a tumour mass in the left upper lobe of patient 1. (A) A 7-mm ground-glass nodule was detected in anterior segment of right upper lobe. A 25-mm solid nodule was located in left upper lobe. (B) A 9-mm partially solid nodule was located in posterior segment of right upper lobe. (C) No enlarged lymph nodes were found in the mediastinum.

lateral decubitus position. Under left single lung ventilation, a 1.5-cm incision was made for endoscopic observation in the seventh intercostals space at the posterior axillary line, and a 3.5-cm incision was served as operation in the fourth intercostals space at the anterior axillary line. Each of the two lesions was identified through CT-guided hook wire before the surgery. Wedge resection was performed using curved endostaplers with margins $\geq$2 cm. The frozen section revealed an adenocarcinoma *in situ* in the S3 segment and a microinvasive adenocarcinoma in the S2 segment. The values of the pulmonary function test suggested that bilateral upper lobectomy would have caused a considerable decline of pulmonary function, which was not acceptable for the patient. Accordingly, only systematic lymph node dissection was performed in the next step. A thoracic drainage tube was placed at the bottom incision. After the right-side operation, the patient was rotated to the opposite side for left upper lobectomy. The left upper pulmonary veins were exposed, followed by exposure of either bronchi or arterial branches, which were then dissected using staplers. Finally, systematic lymph node dissection was performed. One chest tube was placed at the bottom incision. Conventional pathology revealed that the nodule in the right upper lobe S3 and S2 segment were adenocarcinoma *in situ* (Tis) (Fig. 2A) and minimally invasive adenocarcinoma (T1a) (Fig. 2B), respectively. The nodule in the left upper lobe was invasive adenocarcinoma (T2a) (Fig. 2C).

2.2. Patient 2

a 72-year-old woman was referred to our pulmonary clinic for evaluation of multiple lung nodules on chest imaging. In October 2012, the patient underwent excision of a lesiofibroadenoma in her right breast. Chest CT scan revealed bilateral multiple pulmonary nodules during the latest hospitalization. After discharge, she was followed up using chest CT regularly (Fig. 3). On admission the physical examination was unremarkable. Laboratory tests were all in the normal ranges. The FVC was 2.67 L or 104.7% of predicted value, with a FEV1 of 2.29 L or 106.7% of predicted value in this patient.

Double-lumen endotracheal intubation after general anesthesia was also performed in this patient. She was firstly placed in a right lateral decubitus position to undergo a thoracoscopic partial resection of the left lower lobe. Frozen-section examination confirmed an inflammatory nodule. After the left-side operation, the patient was rotated to the opposite side for the further surgery. Wedge resections were performed for the two nodules in the right lower lobe and the right middle lobe. The frozen section showed an atypical adenomatous hyperplasia in the right lower lobe and a minimally invasive adenocarcinoma in the right middle lobe. The nodule in the right upper lobe is solid and irregular. A wedge resection is sufficient for an atypical adenomatous hyperplasia but not

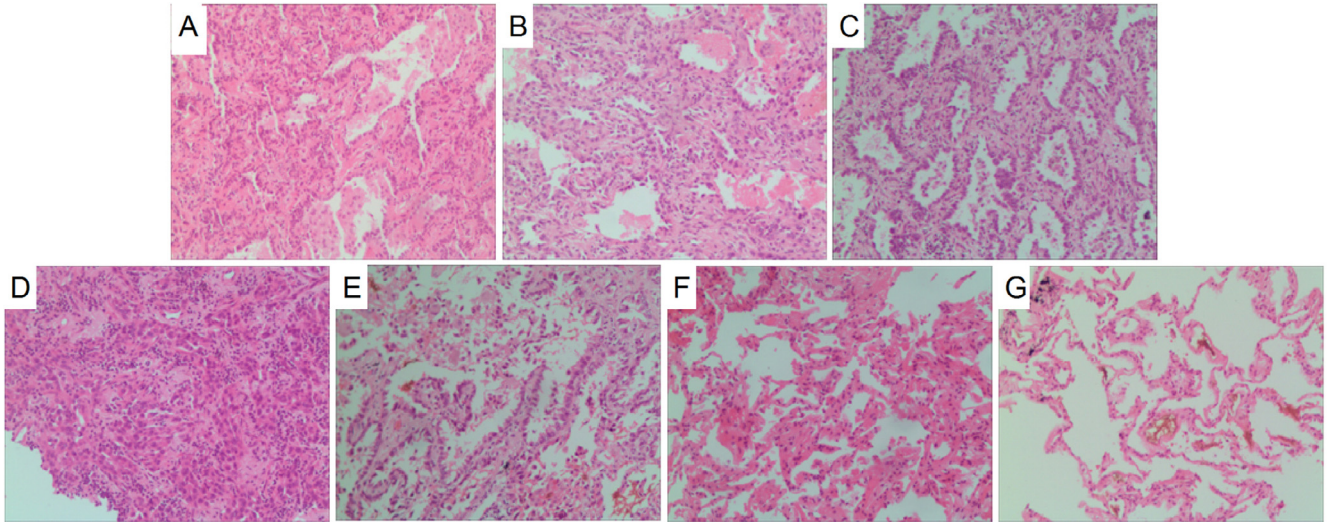

Fig. 2. Photomicrographs of the tissue sections from the surgical specimens on hematoxylin and eosin staining. (A) An adenocarcinoma *in situ* in the right S3 segment of patient 1. (B) A minimally invasive adenocarcinoma in the right S2 segment of patient 1. (C) A well-differentiated adenocarcinoma in the left upper lobe of patient 1. (D) A well-differentiated adenocarcinoma in the right upper lobe of patient 2. (E) A minimally invasive adenocarcinoma in the right middle lobe of patient 2. (F) An atypical adenomatous hyperplasia in the right lower lobe of patient 2. (G) An inflammatory nodule in the left lower lobe of patient 2.

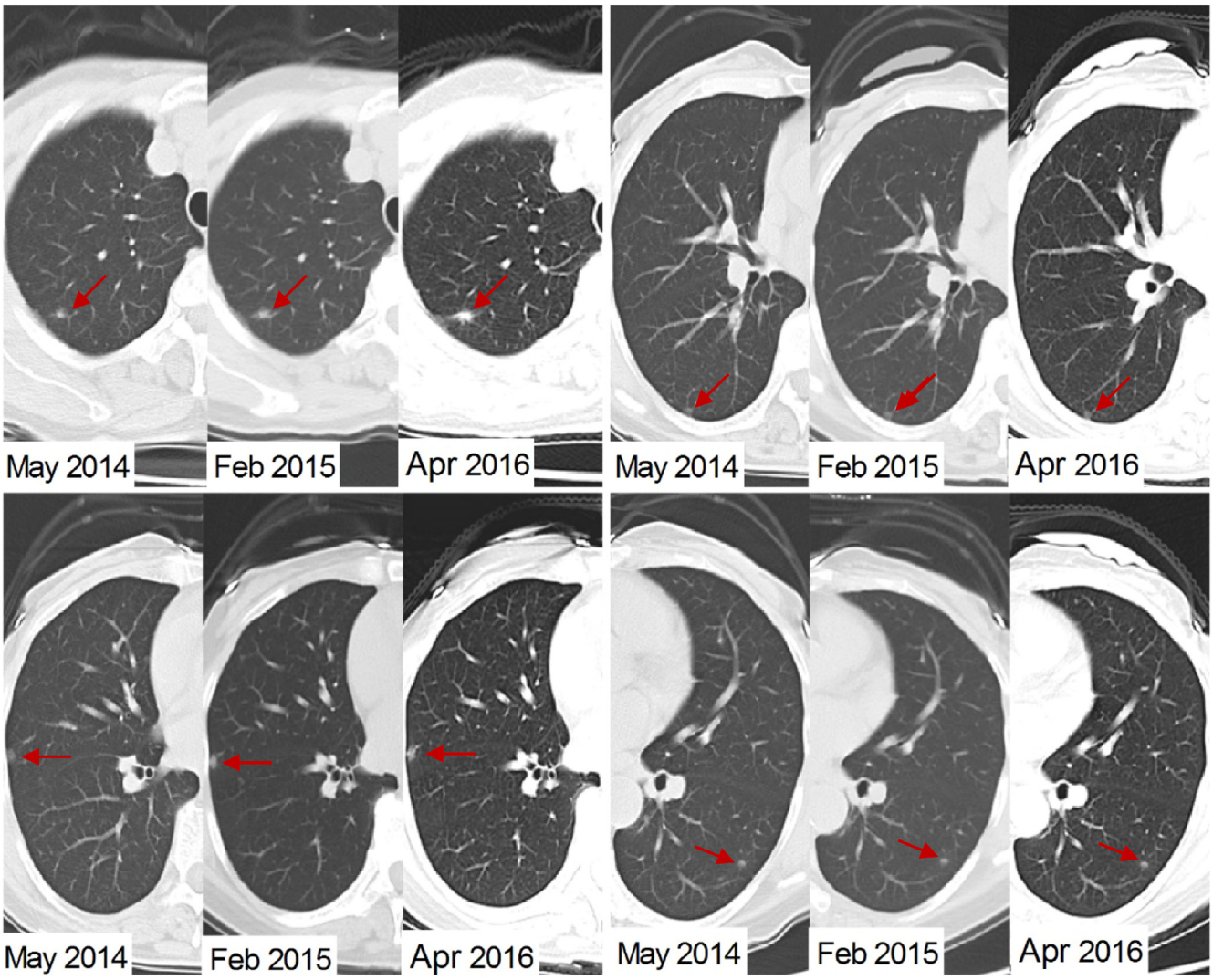

Fig. 3. Sequential chest CT images of the lesions showed four pulmonary nodules in four different lobes of patient 2. (A) A 10-mm solid nodule with an irregular margin was located in the right upper lobe. (B) A 6-mm pure ground-glass nodule was located in dorsal segment of the right lower lobe. (C) A 7-mm partially solid nodule was located in lateral segment of the right middle lobe. (D) A 5-mm solid nodule was located in basal segment of the left lower lobe.

for a minimally invasive adenocarcinoma. Consequently, right middle lobectomy and right upper lobectomy with lymph node dissection were performed. Chest tube strategy was the same as did for the previous patient. The final pathology demonstrated that the nodule in the right upper lobe was invasive adenocarcinoma (T1a) (Fig. 2D), the nodule in the right middle lobe was microinvasive adenocarcinoma (T1a) (Fig. 2E), the nodule in the right lower lobe was atypical adenomatous hyperplasia (Tis) (Fig. 2F), and the nodule in the left lower lobe was an inflammatory nodule (Fig. 2G).

3. Discussion

The bilateral type comprises 60–70% of SMPLC, while the unilateral type is fewer (Matsuge et al., 2000). Lobectomy, removal of one of the five lobes of the lung (excision of all lung parenchyma and associated lymph nodes within a single pleural membrane) is the current standard of treatment for early-stage non-small cell lung cancer (NSCLC) in the general population (Scott et al., 2007). Limited resection such as segmentectomy or wedge resection has been demonstrated as an alternative method of treating early lung cancer (Iwasaki et al., 2004). Recent evidence has demonstrated that in stage I NSCLC, wedge resection could be equivalent to lobectomy with regard to long-term survival (Griffin et al., 2006).

Lung carcinomas are divided into three categories according to the status of ground glass opacity (GGO): pure GGO, part solid, and pure solid. Based on the previous experience, when lesions contain 50% or more GGOs, we tend to keep them under observation instead of performing surgical resection immediately. The timing of surgical resection for bilateral SMPLC is under debate. In general, patients can either undergo surgery following an observed increase on follow-up CT images, or due to their own concerns even though there are no changes in the size of the tumor during follow-up. From our perspective, if a slice of GGOs are scattered in multiple lobes or peripherally in one lobe, multiple limited resection or lobectomy was selected based on performance status and pulmonary function of the patient as well as the size and high-resolution CT findings of the lesions. The estimation of the amount of lung tissue that can be safely removed is very important. Most studies that have reported on FEV1 have used absolute values. Generally, early recommendations of FEV1 values for safe resections were more than 2 L for pneumonectomy and more than 1.5 L for lobectomy (British Thoracic Society, 2001). Later guidelines

added that FEV1 should not be lower than 80% of the predicted value, in case of both lobectomy and pneumonectomy (Colice et al., 2007). At six months after upper lobectomy, lung function were significantly worse than their preoperative values: upper lobectomy patients had lost 20% of FEV1 (Win et al., 2007). Compared with patient 1, patient 2 had adequate pulmonary function reserve. Meanwhile, wedge resection is normally sufficient for adenocarcinoma *in situ* but not for microinvasive adenocarcinoma. It is very difficult to undergo right upper lobectomy for patient 1 in that time due to the significant loss of pulmonary function. It was also reported that long-term survival after surgical resection is better for patients with synchronous primary lung tumors than in patients with tumors in an advanced stage (Girard et al., 2009). Consequently, wedge resection rather than lobectomy was performed for patient 1. Conversely, several recent studies have evaluated the role of sublobar resection in treating small peripheral adenocarcinomas that usually no larger than 2 cm in size. It has been demonstrated that wedge resection and segmentectomy may be viable alternatives to lobectomy in early-stage peripheral adenocarcinomas (Altorki et al., 2014; El-Sherif et al., 2006; Okada et al., 2006). Nonrandomized series comparing patients underwent sublobar resection because of compromised lung function and those underwent formal lobectomy showed similar long-term survival and cancer-free survival, especially in stage IA tumors which less than 2 cm (Bilfinger and Baram, 2008). Long-term survival of patients with stage I NSCLC who underwent a wedge resection can be affected by gender and histology. Male patients underwent wedge resection for adenocarcinomas had outcomes inferior to those of patients with squamous carcinomas (Mediratta et al., 2014).

In summary, it needs to be very careful for thoracic surgeons in designing the surgical treatment scheme about the appropriate extent of resection for bilateral multiple pulmonary nodules. Surgeons should balance factors such as operative morbidity/mortality, local recurrence, postoperative quality of life, and accessibility of a surgical opportunity in cases of multiple pulmonary nodules in the same lobe or different lobes.

Conflict of interests

None.

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References

Altorki, N.K., Yip, R., Hanaoka, T., Bauer, T., Aye, R., Kohman, L., Sheppard, B., Thurer, R., Andaz, S., Smith, M., Mayfield, W., Grannis, F., Korst, R., Pass, H., Straznicka, M., Flores, R., Henschke, C., Investigators, I.-E.L.C.A.P., 2014. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J. Thorac. Cardiovasc. Surg. 147, 754–762.

Bilfinger, T.V., Baram, D., 2008. Sublobar resection in nonsmall cell lung carcinoma. Curr. Opin. Pulm. Med. 14, 292–296.

British Thoracic Society; Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party, 2001. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax 56, 89–108.

Colice, G.L., Shafazand, S., Griffin, J.P., Keenan, R., Bolliger, C.T., American College of Chest Physicians, 2007. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 132,161S–177S.

Detterbeck, F.C., Jones, D.R., Kernstine, K.H., Naunheim, K.S., American College of Physicians, 2003. Lung cancer. Special treatment issues. Chest 123, 244S–258S.

El-Sherif, A., Gooding, W.E., Santos, R., Pettiford, B., Ferson, P.F., Fermando, H.C., Urda, S.J., Luketich, J.D., Landreneau, R.J., 2006. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. Ann. Thorac. Surg. 82, 408–415.

Ferguson, M.K., 1993. Synchronous primary lung cancers. Chest 103, 398S–400S.

Girard, N., Ostrovnaya, I., Lau, C., Park, B., Ladanyi, M., Finley, D., Deshpande, C., Rusch, V., Orlow, I., Travis, W.D., Pao, W., Begg, C.B., 2009. Genomic and mutational profiling to assess clonal relationships between multiple non-small cell lung cancers. Clin. Cancer Res. 15, 5184–5190.

Griffin, J.P., Eastridge, C.E., Tolley, E.A., Pate, J.W., 2006. Wedge resection for non-small cell lung cancer in patients with pulmonary insufficiency: prospective ten-year survival. J. Thorac. Oncol. 1, 960–964.

Iwasaki, A., Shirakusa, T., Shiraishi, T., Yamamoto, S., 2004. Results of video-assisted thoracic surgery for stage I/II non-small cell lung cancer. Eur. J. Cardiothorac. Surg. 26, 158–164.

Kozower, B.D., Larner, J.M., Detterbeck, F.C., Jones, D.R., 2013. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143, e369S–399S.

Liu, M., He, W., Yang, J., Jiang, G., 2016. Surgical treatment of synchronous multiple primary lung cancers: a retrospective analysis of 122 patients. J. Thorac. Dis. 8, 1197–1204.

Matsuge, S., Hosokawa, Y., Satoh, K., Murakami, Y., Yamakawa, T., Hatakeyama, H., Ishigooka, M., Yamazaki, S., 2000. Surgical treatment for bilateral multiple lung cancers. Kyobu Geka 53, 89–94.

Mediratta, N., Shackcloth, M., Page, R., Woolley, S., Asante-Siaw, J., Poullis, M., 2014. Should males ever undergo wedge resection for stage 1 non-small-cell lung cancer? A propensity analysis. Eur. J. Cardiothoracic. Surg. 46, 267–273.

Okada, M., Koike, T., Higashiyama, M., Yamato, Y., Kodama, K., Tsubota, N., 2006. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J. Thorac. Cardiovasc. Surg. 132, 769–775.

Scott, W.J., Howington, J., Feigenberg, S., Movsas, B., Pisters, K., American College of Chest Physicians, 2007. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132, 234S–242S.

Trousse, D., Barlesi, F., Loundou, A., Tasei, A.M., Doddoli, C., Giudicelli, R., Astoul, P., Fuentes, P., Thomas, P., 2007. Synchronous multiple primary lung cancer: and increasing clinical occurrence requiring multidisciplinary management. J. Thorac. Cardiovasc. Surg. 133, 1193–1200.

Win, T., Groves, A.M., Ritchie, A.J., Wells, F.C., Cafferty, F., Laroche, C.M., 2007. The effect of lung resection on pulmonary function and exercise capacity in lung cancer patients. Respir. Care 52, 720–726.

Zhang, Z., Gao, S., Mao, Y., Mu, J., Xue, Q., Feng, X., He, J., 2016. Surgical outcomes of synchronous multiple primary non-small cell lung cancers. Sci. Rep. 6, 23252.