



Case report

Synchronous multiple primary lung cancers with shared EGFR mutation but differential imaging findings and pathological subtypes: A case report

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ABSTRACT

Lung cancer is a leading cause of cancer mortality worldwide. As the incidence of lung cancer increases in recent years, the number of patients diagnosed with synchronous multiple primary lung cancers (SMPLC) is also rising. SMPLC diagnosis is often made based on the clinical course, imaging findings, and histologic and molecular features. Standard lobectomy is the main therapeutic modality for SMPLC. Because maximum retention of lung function is essential, sublobectomy is also a commonly used surgical strategy when appropriate. The question is how to optimize the sequence of lobectomy and sublobectomy for patients with SMPLC. Thoracoscope lobectomy for the primary lesion plus sublobectomy for the secondary lesions is the most commonly used approach. Here we present a case of SMPLC with sublobectomy followed by lobectomy.

1. Introduction

SMPLC is defined as 2 or more primary tumors identified in the same patient at the same time and the second malignant lesion must not represent a metastasis from the first lesion. Commonly used surgical principles for SMPLC are as follows: (1) the most aggressive lesions should be removed first, followed by peripheral lesions; (2) larger lesions should be removed first, followed by smaller lesions. However, the pulmonary function of the proposed second-stage operation should be considered during the planning the first-stage operational strategy.

2. Case presentation

A 51-year-old female patient was admitted to our hospital due to bilateral lung nodules first noted two months ago. She denied fever, productive cough, or shortness of breath. Physical examination was unremarkable. Chest CT scan (Fig. 1) showed bilateral lower lobe pulmonary nodules, including a pure ground-glass opacity (pGGO) lesion (size 16 × 15 mm) in the right lower lobe (RS6) and a noncalcified lobulated solid nodule (size 12 × 9mm) in the left lower lobe (LLL). No

mediastinal lymphadenopathy was found. No abnormal uptake of fluorine-18-fluorodeoxyglucose was observed in the right lower lobe lesion during positron emission tomography-CT (PET-CT), whereas the uptake was SUVmax = 2.17 in the left lesion. Thus, a minimally invasive adenocarcinoma (MIA) was suspected in RS6 and an invasive adenocarcinoma in the LLL.

The patient underwent segmentectomy to remove the pGGO lesion in the right lower lobe (S6), followed by LLL lobectomy one month later. Preoperative lung function index and pathological and molecular diagnosis, including EGFR mutation, are shown in Table 1.

3. Discussion

3.1. Definition and differential diagnosis

Clinicopathological criteria for the diagnosis of MPLC were initially introduced by Martini and Melamed in 1975[1]. In 2007, the American College of Chest Physicians released new diagnostic criteria for MPLC [2]. Recent studies have reported that 2.6%–7.9% of patients who underwent resection of non-small cell lung cancer (NSCLC) have SMPLC,

Abbreviations: ARMS, amplification refractory mutation system; CT, Computed tomography; EGFR, Epidermal growth factor receptor; FEV1, Forced expiratory volume in the first second; FVC, Forced vital capacity; LLL, Left lower lobe; LUL, left upper lobe; MIA, minimally invasive adenocarcinoma; MPLC, Multiple primary lung cancer; MVV, Maximum voluntary ventilation; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PET-CT, Positron emission tomography-CT; pGGO, pure ground glass opacity; SMPLC, Synchronous multiple primary lung cancer; SUV, Standardized uptake value; TLC, Total lung capacity; VC, Vital capacity.

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and incidence rate was rising[3–7]. If multiple lung cancers are of different histologic types, differential diagnosis is relatively straightforward. However, if the histologic type is the same, the differentiating SMPLC from intrapulmonary metastasis remains challenging. In our opinion, the real issue in the management of synchronous carcinoma is a definitive preoperative diagnosis, which can be achieved by chest CT scan. The coexistence of a large tumor with multiple smaller nodules within the lung strongly suggests metastasis, whereas multiple nodules with similar size but different morphology suggest the possibility of SMPLC. The case presented here provides an example of the latter scenario, with a pure GGO lesion in the RS6 and a noncalcified lobulated solid nodule in the LLL, and a final diagnosis of double primary lung cancers. This diagnosis has facilitated the decision-making on the appropriate surgical treatment for this case.

3.2. Surgical strategy

The Union for International Cancer Control TNM Classification of Malignant Tumors (8th Edition, 2017) [8] was used for the pathological staging of each lesion. Surgical resection has become the mainstay of treatment for patient with SMPLC. The operation sequence varies depending on whether the tumor lesions are ipsilateral or contralateral and major or minor tumor size.

Careful consideration should be given to the timing of the surgery for patients with bilateral SMPLC, which includes synchronous or staged surgery, surgical approach, lobectomy or sublobectomy, and the sequence of surgical side. Synchronous surgery for bilateral tumors is considered an effective strategy for preventing disease progression[9]. However, two-stage surgical treatment is safe, reasonable and effective for patients with bilateral SMPLC, especially for those who need

Table 1

Clinical presentations of the patient with SMPLC.

	first-stage operation	second-stage operation
Imaging features		
Location (lobe)	RLL (S6)	LLL
Size (mm)	16 × 15	12 × 9
Types of nodules	p-GGO	solid
PET-CT	Negative	Positive
Lung function index		
TLC(L)	4.2	3.64
VC (L)	2.76	2.37
FVC(L)	2.76	2.43
FEV1(L)	2.29	1.99
MVV(L/min)	99	102.37
Extent of operation	Segmentectomy	Lobectomy
Pathologic		
Histologic subtype	Acinar predominant	Papillary predominant
Perineural invasion	Negative	Positive.
Nodal status	N0 (0/6)	N0 (0/18)
TNM	T1bN0M0	T1bN0M0
Ki-67 expression (%)	10	20
EGFR mutations	L858R	L858R
Hospitalization days	5	7

lobectomy[5–7].

According to the preoperative imaging characteristics of this patient, left lower lobectomy should be performed as the first stage surgery to remove the major lesion, and then lesion on the right. As the lobes assume different lung function, the LLL bears the most important lung function second only to the left upper lobe (LUL). If this surgical sequence were carried out, the lung function during the second stage of the right lung lesion resection might have been compromised. We thus

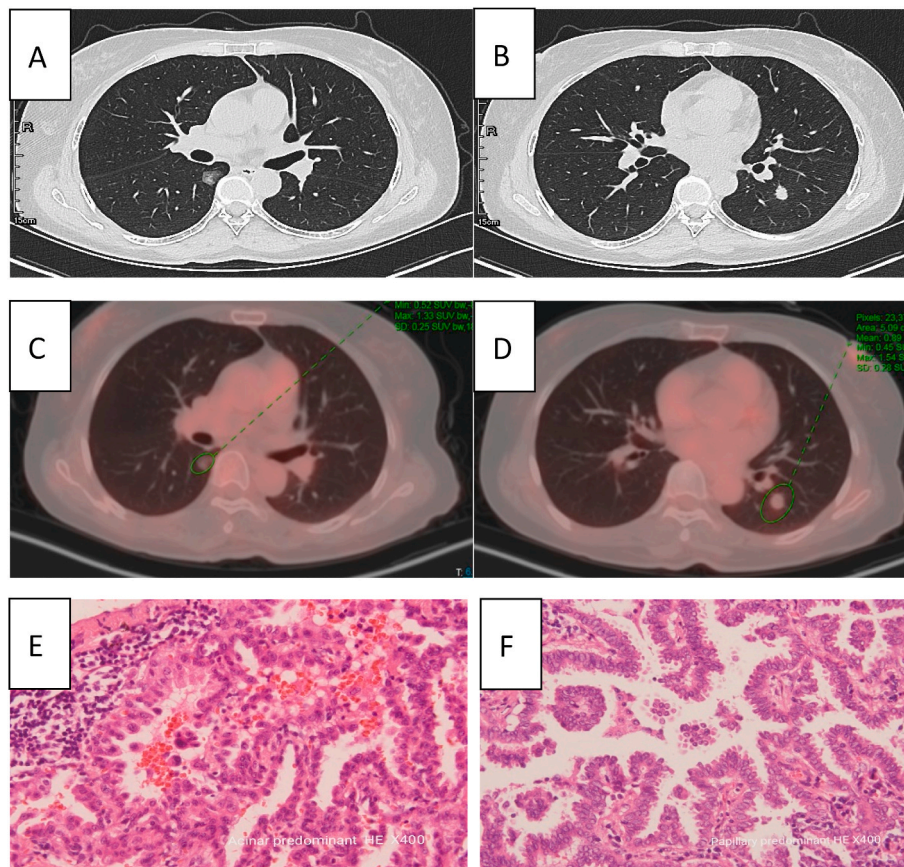


Fig. 1. CT scan of the chest showing a pGGO lesion in the right lower lobe(A) and a noncalcified lobulated solid nodule in the left lower lobe (B). No abnormal uptake of PET-CT scan was observed in the right lower lobe lesion (C), whereas the uptake was SUVmax = 2.17 in the left lesion (D). Invasive acinar predominant adenocarcinoma in RS6(E), papillary predominant adenocarcinoma in LLL (F).

chose to perform the RS6 thoroscopic segmentectomy first, and the patient was discharged 5 days after operation. The post-surgery lung function index remained similar to that before the surgery, which enabled a successful second-stage of LLL lobectomy. The patient was discharged 7 days later.

3.3. Pathologic and molecular findings

The pathological diagnoses were determined on the basis of the postoperative findings, including tissue morphology and cellular atypia. World Health Organization (WHO) has adopted the classification for histological subtyping of invasive adenocarcinoma recently developed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society[10]. For invasive adenocarcinoma, the new classification has introduced histological subtyping according to the predominant pattern of the growth of neoplastic cells.

The pathological diagnoses in this case were invasive acinar predominant adenocarcinoma in RS6 and the papillary predominant adenocarcinoma in LLL, without lymphovascular invasion, pleural invasion or lymph node metastasis. But perineural invasion was positive in the latter (Fig. 1). Ki-67 expression was 10% and 20% for the RS6 and LLL lesions, respectively. This accurate histologic differentiation was helpful in managing our SMPLC case.

The most important genes linked with the development of lung cancer include EGFR, KRAS, BRAF, PIK3CA, ALK, MET, ROS1 and RET [2–5]. The analysis of the lung cancer genome has profoundly changed our understanding of SMPLC at a molecular level[2,4,11,12]. Identifying the differences in the mutation profiles of multiple tumors from one patient will help determine their clonal origin and enable the differentiation between primary and metastatic tumors[4,11]. EGFR mutations are often present in exons 18, 19, 20, and 21 in the primary lung cancer but not in its metastases[4,11]. Upon amplification refractory mutation system (ARMS), the patient was determined to harbor an EGFR mutation (exon 19 deletion) in both tumors of RS1 and LLL. Most recent studies using next-generation sequencing (NGS) demonstrated a high concordance rate (94%) for driver somatic alterations between primary lung tumors and matched metastases[12].

4. Conclusion

The SMPLC gradually increased, and the number, site, side and

pathological stage of the lesions varied. These factors and the patient's tolerance to surgery, especially the lung function, need to be taken into account when planning surgery. Analyzing of the main driving genes of the multiple lesions can serve as clonal markers affording a more accurate understanding of the pathology of SMPLC, and providing a might target for gene therapy.

Conflicts of interest

No conflict with any one.

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