A case of second primary lung cancer diagnosed by surgical resection at salvage setting

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Abstract

We report a case of metachronous second primary lung cancer; it was initially clinically favored as progression of primary disease and finally diagnosed as a second primary lung cancer by surgical resection at salvage setting. A 73-year-old man was diagnosed with stage IV lung adenocarcinoma at initial presentation. He underwent two lines of chemotherapy, and the tumors regressed dramatically. However, the residual lung mass shadow expanded after 22 months. We performed resection at salvage setting. The gene status and histological subtype were not identical with that of the primary tumor, suggesting this to be a second primary lung cancer.

Keywords Second primary lung cancer · Salvage surgery · Gene status

Introduction

Recently, surgical treatment for the progressive and/or residual disease after radical chemotherapy and/or radiation has been termed as “salvage surgery”. The patient selection and practical contributions for outcomes remain unclear.

In clinical practice, distinguishing between a second primary lung cancer and progressive disease is sometimes hard. It is necessary to take into account all clinical, pathological, and biomarker information to make an accurate diagnosis of multiple lesions [1]; meanwhile, the indications of the salvage surgery are sometimes determined mainly on the basis of clinical findings without rebiopsy.

Case report

A 73-year-old man complained of a stiff neck and was referred to the previous doctor. Chest computed tomography (CT) demonstrated a solid mass shadow in the right

lower lobe of his lung measuring 6.4 cm (Fig. 1a). Bilateral hilar and mediastinal lymphadenopathy were identified, which had extended to the left side of his neck. The pathological specimen of the neck biopsy was revealed to be adenocarcinoma consistent with the metastasis from lung cancer (Fig. 2a). He was referred to our hospital for further examinations and treatment.

18-Fluoro-deoxyglucose positron-emission tomography-computed tomography (18FDG-PET/CT) scanning revealed FDG uptake in the mass of the right lung, hilum/mediastinum, and the left side of the neck (Fig. 1d). We diagnosed his disease as stage IV (cT2bN3M1b, IV, UICC TNM 7th) lung adenocarcinoma. The tumor specimen was examined genetically, being negative for alterations in *EGFR*, *KRAS*, and *ALK* genes.

He underwent 4 cycles of carboplatin (AUC6) and pemetrexed (500 mg/m²) treatment as the first-line chemotherapy. However, the tumor progressed gradually after 4 cycles of chemotherapy. Subsequently, he underwent 4 cycles of docetaxel (60 mg/m²) as the second-line treatment, and the tumors regressed dramatically. The therapeutic effect was PR, with almost complete remission (Fig. 1b). Twenty-two months after the completion of the second-line chemotherapy, the chest CT scan revealed an expansion of the residual shadow measuring 4.9 cm (Fig. 1c). Whole-body examinations, including CT and FDG-PET, and brain MRI were performed. Finally, we diagnosed his disease as

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Fig. 1 Chest computed tomography scan shows a time-dependent change of the tumor shadow during the treatment. **a** Solid mass measuring 6.4 cm in the right lower lobe of the lung at initial presentation. Bulky lymph nodes were observed in the lower pretracheal (#4R) and para-aortic station (#6), **b** dramatic regression of the mass shadow was observed after the second-line chemotherapy, and **c** regrowth of

mass shadow measuring 4.9 cm was observed 22 months after the completion of chemotherapy. **d** Fluoro-deoxyglucose (FDG) positron-emission tomography shows FDG uptake in the mass of the right lung, mediastinum, and the left side of the neck at initial presentation and **e** localized-FDG uptake in the right lung shadow at the mass regrowth

Fig. 2 Pathological findings of the primary and secondary tumor. **a** Pathological specimen of the neck biopsy shows atypical cells with huge irregular nuclei and papillary pattern formation of the tumor. **b** Pathological specimen of the resected tumor shows tumor cells with solid proliferation. **c** Thyroid transcription factor-1 immunohistochemistry shows positive staining in the neck biopsy specimen and **d** faintly positive staining in the resected specimens

local progression of the primary site, ycT3N0M0, stage IIB (Fig. 1e).

We performed a right S6 segmentectomy and combined chest wall resection including the 5th ribs as a salvage treatment. Pathological diagnosis of the resected specimens was solid predominant adenocarcinoma (Fig. 2b). The tumor cells were weakly positive for thyroid transcription factor-1 (TTF-1) staining (Fig. 2d), which was apparently a different phenotype from the primary tumor (Fig. 2c). Furthermore, genetic exploration revealed a *KRAS* G12D mutation and a *p53* I272M mutation that were not identical with the status of the primary tumor, wherein both *KRAS* and *p53* were wild type. Alterations in *EGFR*, *ALK*, *HER2*, *MET*, *ROS1*, and *BRAF* genes were not detected in either specimen. Accordingly, we diagnosed his disease as a metachronous second primary lung cancer and not progression of the primary tumor.

Moreover, 3 months after pulmonary resection, he experienced metastases in his right fibula and ipsilateral hilum, which were diagnosed as recurrence of the second cancer on the basis of the pathological and genetic findings of the hilum biopsy specimen. The chemotherapy has since been restarted.

Discussion

In clinical practice, it is sometimes challenging to distinguish between a primary lung cancer that has metastasized and an additional primary tumor. The diagnoses can strongly affect the treatment strategy as well as the prognosis of the patient.

In the present case, considering that the second tumor developed from the residual site of the primary one, we made the diagnosis of a re-progression of the primary cancer. We initially performed pulmonary resection as a salvage treatment. Eventually, the surgical specimen was diagnosed as a second primary tumor, not re-progression, on the basis of the distinct histologic subtype and biomarker pattern. If we could have diagnosed the second primary lung adenocarcinoma before surgical treatment, we may have considered an option other than a segmentectomy.

In 1975, Martini and Melamed suggested the definition of the criteria for diagnosing multiple primary lung cancer, and they have been widely used in our clinical practice [2]. These criteria were mainly based on clinical and histologic factors. At present, while we have utilized biomarker analyses, there are no other confirmed standards in diagnosing multiple primary lung cancers. The IASLC Lung Cancer Staging Project proposed a criterion to distinguish second primary lung cancers from a primary cancer. According to them, we should base our decision on the experienced multidisciplinary team taking into account various factors (e.g., clinical, imaging, histologic,

and genetic factors); therefore, a comprehensive judgment is required to make the diagnosis.

Although clinical findings and adenocarcinoma histology were consistent with re-progression of the primary tumor in the present case, discrepancies in *KRAS* and *p53* status revealed a different genotype from the primary tumor. Those findings eventually led us to a diagnosis of a second primary lung cancer that had developed from the residual site of the primary tumor.

Indeed, several authors reported as low as 13.6–31% of discordance in *KRAS* status between the primary lesion and metastatic lesions [3, 4]. Kalikaki et al. have documented that 2 of the 10 NSCLC cases with wild-type *KRAS* status showed new *KRAS* mutation following chemotherapy, while wild-type status remained in 8 cases following chemotherapy [5]. Contrastively, *p53* gene is almost clonal in non-small cell lung cancer [6] and discordance in *p53* status between the primary lesion and metastatic lesions is rare [7]. On the basis of these reports, although simultaneous mutation of *KRAS* and *p53* can be occur, we consider that this phenomenon is rare for progressive disease following chemotherapy.

Accordingly, gene status in addition to clinical and pathological findings suggested a second primary lung cancer; finally, our multidisciplinary tumor board diagnosed the second tumor as a separate primary lung cancer.

Herein, we report a case of metachronous second primary lung adenocarcinoma, which clinically behaved like a re-progressive tumor. Therefore, physicians should acknowledge that we consider all clinical, pathological, and biomarker findings in challenging cases, particularly when the diagnosis affects the treatment strategy, including indication of salvage surgery.

References

1. Detterbeck FC, Nicholson AG, Franklin WA et al (2016) The IASLC lung cancer staging project: summary of proposals for revisions of the classification of lung cancers with multiple pulmonary sites of involvement in the forthcoming eighth edition of the TNM classification. *J Thorac Oncol* 11(5):639–650
2. Martini N, Melamed MR (1975) Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 70(4):606–612
3. Quere G, Descourt R, Robinet G et al (2016) Mutational status of synchronous and metachronous tumor samples in patients with metastatic non-small-cell lung cancer. *BMC Cancer* 16:210
4. Schmid K, Oehl N, Wrba F et al (2009) EGFR/KRAS/BRAF mutations in primary lung adenocarcinomas and corresponding locoregional lymph node metastases. *Clin Cancer Res* 15(14):4554–4560
5. Kalikaki A, Koutsopoulos A, Trypaki M et al (2008) Comparison of EGFR and K-RAS gene status between primary tumours and corresponding metastases in NSCLC. *Br J Cancer* 99(6):923–929
6. Jamal-Hanjani M, Wilson GA, McGranahan N et al (2017) Tracking the evolution of non-small-cell lung cancer. *N Engl J Med* 376(22):2109–2121
7. Vignot S, Frampton GM, Soria JC et al (2013) Next-generation sequencing reveals high concordance of recurrent somatic alterations between primary tumor and metastases from patients with non-small-cell lung cancer. *J Clin Oncol* 31(17):2167–2172