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CASE REPORT

Different EGFR gene mutations in two patients with synchronous multiple lung cancers: A case report

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Abstract

Routine clinical and pathological evaluations to determine the relationship between different lesions are often not completely conclusive. Interestingly, detailed genetic analysis of tumor samples may provide important additional information and identify second primary lung cancers. In the present study, we report cases of two synchronous lung adenocarcinomas composed of two distinct pathological subtypes with different *EGFR* gene mutations: a homozygous deletion in exon 19 of the papillary adenocarcinoma subtype and a point mutation of L858R in exon 21 of the tubular adenocarcinoma. The present report highlights the clinical importance of molecular cancer biomarkers to guide management decisions in cases involving multiple lung tumors.

Introduction

An increasing number of patients with multiple lung tumors are encountered, likely a result of the availability of high-resolution thoracic imaging techniques and the rising incidence of adenocarcinoma histology among non-small cell lung cancers.[1] It is important to determine the relationship between various lesions of multiple malignant lung tumors to define the best treatment strategy. A better understanding of the molecular alterations present in different lesions may help to define this relationship. In the present study, we report the cases of two synchronous lung adenocarcinomas, composed of two distinct pathological subtypes harboring different *EGFR* gene mutations.

Case report

Case 1

A 69-year-old man without a smoking history was referred to our hospital for a detailed examination of an abnormality detected on a routine chest X-ray examination. The patient enjoyed good exercise tolerance and his physical examination was unremarkable. Chest computed tomography (CT) revealed right middle lobe (RML) and left upper lobe (LUL) masses without enlarged bilateral mediastinal lymph nodes (Fig 1). A positron emission tomography-CT (PET-CT) scan revealed maximum standardized uptake values (SUVmax) of 0.8 and 2.0 in the RUL and LUL lesions, respectively. Levels of specific tumor markers, such

as squamous cell carcinoma (1.3 ng/mL), CYFRA (1.1 ng/mL), and carcinoembryonic antigen (CEA) (2.0 ng/mL) were not elevated. Subsequently, a transbronchial lung biopsy of the RML mass was performed for pathological diagnosis, which revealed an adenocarcinoma. Brain contrast-enhanced magnetic resonance imaging and PET-CT did not detect any metastatic lesions, including mediastinal lymph node metastasis; therefore we considered the LUL mass a synchronous multi-primary lung cancer. Further, the patient underwent a lobectomy of the RML with mediastinal lymph nodal dissection and a wide superior segmental resection of the left upper lobe with mediastinal lymph nodal dissection, using video-assisted thoracic surgery on each side. The RML and LUL tumors exhibited similar morphological features of adenocarcinomas (Fig 1). The predominant pattern of the growth in both tumors was papillary adenocarcinoma. No pleural invasion or lymphovascular permeation was evident and resection margins were clean. The *EGFR* gene mutation was detected using PCR, which revealed that the RML and LUL tumors harbored a G719A mutation in exon 18 and a L858R mutation in exon 21, respectively. The final pathological diagnosis and staging of the RML and LUL tumors were invasive adenocarcinoma, papillary adenocarcinoma, pT2a (35 mm) N0M0 stage IB; and invasive adenocarcinoma, papillary adenocarcinoma, pT1c (25 mm) N0M0 stage IA3, respectively. The patient was alive and had not experienced any relapse eight years and four months after the first surgery.

Case 2

A 77-year-old woman with a former three pack-year smoking history was referred to our hospital by her primary care physician because of chest pain and an abnormality detected on chest X-ray. Physical and laboratory examinations revealed no abnormalities. Chest CT detected two contralateral pulmonary lesions, a solid lesion in the right upper lobe (RUL) and a pure ground-glass appearance in the LUL. The lesion in the LUL appeared to be radiologically compatible with a second primary tumor. A PET-CT scan revealed a hot spot of uptake in the RUL lesion only (SUV max = 3.2), no uptake in the LUL lesion, and no metastatic lesions. There was no radiological evidence of mediastinal lymphadenopathy or distant spread. Levels of the specific tumor markers, such as squamous cell carcinoma, CYFRA, and neuron-specific enolase, were not elevated, except for slight elevations in CEA (4.5 ng/mL) and Pro-gastrin-releasing peptide (81.4 pg/mL) levels. The clinical presentation of this patient suggested two independent lung lesions. It was difficult to obtain a pathological diagnosis from the RUL primary lesion as it was located in the mediastinal side of the RUL; therefore, a lobectomy of the RUL with mediastinal lymph nodal dissection and a wide wedge resection of the LUL were performed using video-assisted thoracic surgery on each side. Definitive pathological diagnosis revealed that the RUL tumor was invasive adenocarcinoma, papillary adenocarcinoma with no pleural invasion or lymphovascular permeation, and the LUL tumor was a minimally invasive adenocarcinoma (Fig 2). In addition, *EGFR* gene mutation analysis revealed a G719A mutation in exon 18 in the RUL tumor and a L858R mutation in exon 21 in the LUL tumor. Consequently, final staging showed that the RUL tumor was pT1b (15 mm) N2M0 stage IIIA, and the LUL tumor was pT1a (5 mm) N0M0 stage IA1 with synchronous double primary lung adenocarcinoma. The patient was alive and had not experienced any relapse five and half years after the first surgery.

Discussion

Among all subtypes of lung cancers, adenocarcinoma currently accounts for approximately 70% of all newly diagnosed primary lung malignancies, and the prevalence of this disease in Japan has increased over the past decade.[2] Although most patients are diagnosed with a single primary lung adenocarcinoma, identifying two or more adenocarcinomas at presentation is not uncommon, with an estimated incidence ranging from 1% to 8%, particularly in Asia.[3,4] The lungs represent a major site of metastasis from common solid tumors. Consequently, these tumors are variably included in patients with multiple distant metastases, synchronous second primary lung cancer, and additional nodules. In patients with multiple lung tumors, understanding the clonal relationship between the various tumors is important to decide appropriate treatment.

In 2003, the American College of Chest Physician guidelines proposed new criteria, which were a slightly modified version of the Martini and Melamed criteria, and involved tumor classification according to different histology, N2 and N3 status, systemic metastases, and four-year interval. However, the main limitations of these approaches are the challenges in patient management and the use of clinical rather than pathological features to define the patients. Pathological data are generally not available until after surgical treatment and because the majority of cases with synchronous second primary lung cancer involve the same histology, mostly adenocarcinoma, as in our present two cases. Therefore, it is suggested that patients with multiple lesions that are at least partially ground glass and are suspected to be malignant are classified as multi-primary lung cancer and can thus undergo surgery without a preoperative pathological diagnosis (Figs 1–2).

In 2015, the World Health Organization Classification of Tumors of the Lung, Pleura, Thymus and Heart proposed a new classification that distinguishes adenocarcinoma on the basis of the proportion of different histological patterns

Figure 1 Summary of case 1 according to radiological and pathological examinations and relationship between *EGFR* mutations in the (**a**) right middle and (**b**) left upper lobe tumors.

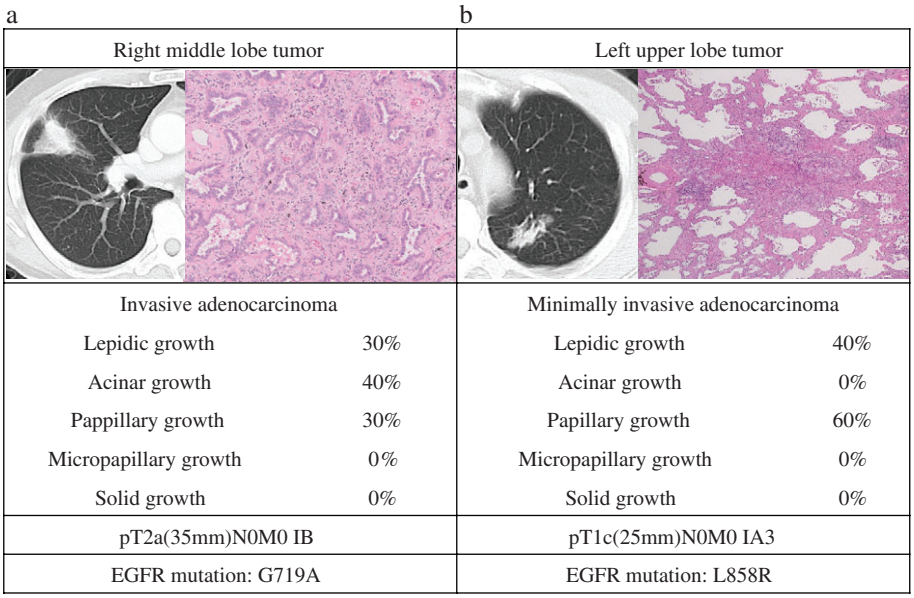
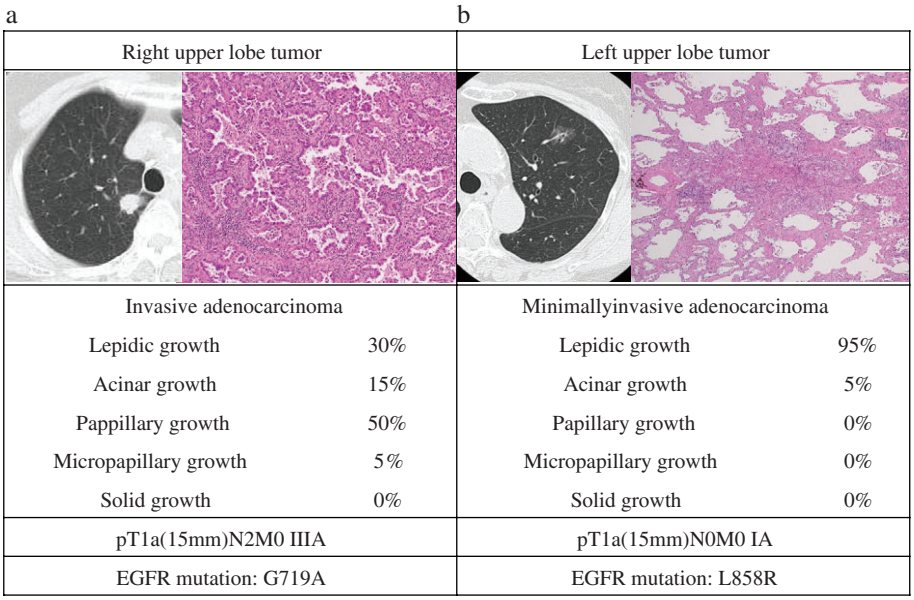


Figure 2 Summary of case 2 according to radiological and pathological examinations and relationship between *EGFR* mutations in the (**a**) right upper and (**b**) left upper lobe tumors.



(lepidic, acinar, papillary, micropapillary, and solid). This diagnostic approach allows a more accurate histological comparison between multiple adenocarcinomas, which appears reasonable and should be included in a judgment regarding the classification of a particular pair of tumors, consist with our present two cases (Figs 1–2).

Histopathological examinations of multiple lesions are often not conclusive in terms of the differential diagnosis of second primary lung cancer or pulmonary metastasis, and a more extensive examination of the genomic changes (e.g. the detection of gene mutations, deletion amplifications, or fusions such as *EGFR* and *ALK* genes) that occur may help with diagnosis. Several reports have used specific molecular markers or mutations and showed promising results. *EGFR* gene mutations were detected by PCR sequencing, a routine procedure at our institute.

Most recently, next-generation sequencing assays for the detection of genomic alterations with therapeutic, diagnostic, and prognostic significance in lung cancer have been routinely utilized in major medical centers. Saab *et al.* reviewed 18 patients with a total of 52 lung adenocarcinomas to evaluate the efficacy of comprehensive histopathological evaluation supplemented with molecular analysis using next-generation sequencing.[5] The combined morphological and genomic data approach proved to be of significant value and achieved a conclusive diagnosis in 94% of the patients tested.

This method may improve staging accuracy and can also identify genetic alterations for therapeutic implications. These results implied an entirely different prognostic outlook and a different strategy for adjuvant chemotherapy and monitoring of recurrence for our patients.

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Disclosure

No authors report any conflict of interest.

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