Two Lung Adenocarcinomas in the Same Lobe: Multiple Primaries or Intrapulmonary Metastasis?

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Abnormal nodules were found in the left lung of a 52-year-old woman in segments 6 and 10 on a chest CT. These nodules showed no changes for 18 months, and we discontinued follow-up. Almost 5 years later, an abnormal shadow was found in her left lower lung field on a medical check-up chest X-ray. Chest CT revealed that the left segments 6 and 10 nodules had grown. We diagnosed these lesions as synchronous double primary lung cancers in the same lobe based on the disease history and performed a left lower lobectomy and lymph node dissection. Pathological examination of both tumors revealed adenocarcinoma of a mixed subtype with papillary and bronchioloalveolar carcinoma. Epidermal growth factor receptor gene mutations were examined, and the 2 lesions shared an L858R mutation. Although we expected EGFR gene mutation analysis would help us distinguish the 2 lesions from each other, it was of little help. Disease history can be more important in evaluating multiple pulmonary cancers.

Keywords: synchronous multiple primary lung cancers, gene mutation, epidermal growth factor receptor

Introduction

Multiple lung cancer cases are not rare. Unless multiple cancers are clearly of different histologic types, we are distressed whether these are multiple primary lung cancers or a primary cancer and its pulmonary metastases. Exact differential diagnosis is desired, because the diagnosis affects disease stage and treatment options. Gene mutation analysis is expected to help differential diagnoses.

Case Report

In September 2001, computed tomography (CT) detected abnormal nodules in the left lung of a 52-year-old woman in segment (S) 6 and S10, 8 mm and 5 mm in size, respectively. Follow-up CTs showed no changes for 18 months, and we diagnosed these lesions as benign tumors and discontinued follow-up.

In January 2008, an abnormal shadow was found in her left lower lung field on a medical check-up chest X-ray. Chest CT revealed that the left S6 and S10 nodules had grown, 26 mm and 8 mm in size (Fig. 1). Bronchoscopy biopsy confirmed adenocarcinoma in the S6 tumor. We diagnosed these lesions as synchronous double primary lung cancers in the same lobe and performed left lower lobectomy and lymph node dissection in March 2008.

Pathological examination of the S6 tumor revealed...
adenocarcinoma of a mixed subtype with papillary (70%), bronchioloalveolar carcinoma (BAC; 20%), and solid (10%) components, and in the S10 nodule, adenocarcinoma of a mixed subtype with BAC and papillary adenocarcinoma (Fig. 2). Epidermal growth factor receptor (EGFR) gene mutations were examined by polymerase chain reaction assay, which showed that the 2 lesions shared an L858R mutation. These histologic and genetic findings suggested that the 2 nodules might be a primary adenocarcinoma and its intrapulmonary metastasis. However, the disease history strongly suggested they were synchronous double primary lung cancers, T1N1M0, stage IIA (S6) and T1N0M0, stage IA (S10), according to the 6th edition TNM classification.

Discussion

If the patient had visited us without her past CT history in 2001–2003, we would have probably diagnosed the S10 nodule as intrapulmonary metastasis in the same lobe from the S6 tumor, because these 2 tumors both had papillary adenocarcinoma and BAC component and L858R EGFR mutations. However, both nodules were already there 6.5 years previously. If the S10 nodule had been intrapulmonary metastasis from the S6 tumor, other metastatic lesions would have developed within those 6.5 years.

In case of synchronous multiple lung cancers or intrapulmonary metastasis, it is very important that these lesions are staged correctly. According to the 7th edition TNM staging system, our case corresponds to intrapulmonary metastasis in the same lobe, pathological T3N1M0, stage IIIA or synchronous double primary lung adenocarcinomas, T1bN1M0, stage IIA (S6) and T1aN0M0, stage IA (S10). Although adjuvant chemotherapy is indicated for both stages IIIA and IIA patients, prognostic prospect is completely different between these stages.

Little has been added or modified since Martini et al. described their criteria for accepting multiple separate carcinomas as primary lesions in the lung in 1975, despite a better understanding of tumor biology in recent
decades. According to their criteria, this case would be diagnosed as a primary adenocarcinoma and its intrapulmonary metastasis, and the EGFR mutations shared by the tumors support the diagnosis. However, the disease history strongly suggests these tumors were synchronous double primary lung cancers, and Martini’s criteria appear to be of little use in the differential diagnosis of this case.

Several researchers have reported the usefulness of gene mutation analysis in evaluating multiple pulmonary cancers. Gallegos et al. concluded that EGR and k-ras mutation analysis enabled clonal relationship identification among various lung lesions. Nakao et al. reported a case of synchronous lung cancers that had different EGFR mutations. Takuwa et al. reported a similar case of double primary cancers with identical histologic findings. Girard et al. concluded comprehensive histologic assessment methodology is a powerful tool in determining whether multiple adenocarcinomas or squamous cell carcinomas are metastatic or multiple primaries. In their series, however, the diagnoses based on the methodology were inconsistent with molecular characterization results in 2 (9%) of the 22 comparison pairs. Based on their methodology, our case is diagnosed as double primaries, but both tumors had the same EGFR mutation.

We expected EGFR gene mutation analysis would help us distinguish the 2 lesions from each other. However, only when mutation patterns are different in a primary tumor and separate tumor nodule(s) can we conclude these lesions are of separate origins. As L858R is one of the two most frequent EGFR mutations and is reported to cause oncogene addiction, it is possible that the 2 tumors in our case acquired the same mutation individually by chance or by field carcinogenesis. Gene mutation analysis is not always helpful, and disease history can be more important in evaluating multiple pulmonary cancers. We need to be very careful in interpreting gene mutation analysis results, not to miss a surgical opportunity in cases of multiple tumors in the same lobe.

Fig. 2 Pathological findings of the S6 (a, b) and S10 (c, d) lesions. The S6 tumor was mixed adenocarcinoma, with predominant papillary components. The S10 tumor was mixed adenocarcinoma, predominantly bronchioloalveolar carcinoma.
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References