Synchronous Primary Lung Cancer and Epidermal Growth Factor Receptor Mutation

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We describe a 75-year-old Chinese man who presented with three separate tumors in three different lobes of the lung, without evidence of mediastinal or systemic involvement. All three tumors were surgically resected by minimal invasive approach. Based on a differing epidermal growth factor receptor (EGFR) mutation status, the tumors were characterized as synchronous triple primary rather than intrapulmonary metastases. This report highlights the clinical usefulness of molecular cancer biomarkers to determine prognosis and to guide management decision in multiple lung tumors.

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An increasing number of patients are encountered who present with multiple lung tumor; this is most likely due to the availability of high-resolution thoracic imaging techniques and a rising incidence of adenocarcinoma histology among non-small cell lung cancers (NSCLCs) [1]. A central issue regarding multiple lung tumors is to distinguish between synchronous primary lesions or metastases. This information is clinically important for staging, management plan, and prognosis. The new lung cancer staging system of the International Association for the Study of Lung Cancer [2] defines separate tumor nodules in the same lobe as $T3_{Satell}$, separate tumor nodules in a different ipsilateral lobe as $T4_{Ipsi\ Nod}$, and separate tumor nodules in a contralateral lobe as $M1a_{Contr\ Nod}$. The application of molecular cancer biomarkers in the characterization of multiple lung tumors is not mentioned. Mounting, recent evidence has confirmed that gene mutations of EGFR and downstream molecules in the signaling pathway define subsets of NSCLC and provide important predictive information on therapeutic response [3]. We report a Chinese man who presented with synchronous triple primary NSCLC as defined by EGFR gene mutation status.

A 75-year-old Chinese man who was an ex-smoker had a left upper lobe lung shadow incidentally detected on routine chest roentgenogram examination. He was a retired chef with no history of asbestos exposure. The patient enjoyed good exercise tolerance and his physical examination was unremarkable. Positron emission tomography combined with computed tomography of the thorax showed multiple lung lesions (Fig 1A) of variable metabolic activity. The first lesion at the apical posterior segment of the left upper lobe (LUL) showed a central core of nodular reticular pattern surrounded by a bigger zone of ground glass appearance and mild focal increased positron emission tomographic activity (standardized uptake value max = 1.7). The second lesion at the apical anterior segment of the right upper lobe (RUL) was smaller but showed similar character and also mild focal increased activity (standardized uptake value maximum = 1.0). The third lesion at the apical segment of the left lower lobe (LLL) showed no significant uptake. There was no radiologic evidence of mediastinal lymphadenpathy or distant spread. A brain scan by magnetic resonance imaging was negative.

Bilateral video-assisted thoracic surgery was performed for tissue diagnosis and resection. An intraoperative bronchoscopy showed no endobronchial lesions. The left video-assisted thoracic surgery showed no pleural deposit or effusion. The LUL and LLL masses were wedged out, and the mediastinal lymph nodes were sampled. The right video-assisted thoracic surgery also showed no pleural deposit or effusion. The RUL mass, despite showing adhesions to the chest wall, was also wedged out. The patient made an uneventful recovery and was discharged on postoperative day 5.

The LUL and LLL tumors measured 4 cm and 1.5 cm in greatest dimension, respectively, and shared similar morphological features (Figs 1B and C). The pattern of the tumor growth was lepidic and focal stromal invasion was observed. The malignant cells were cuboidal to columnar in shape showing mild nuclear pleomorphism and hyperchromasia. No pleural invasion or lymphovascular permeation was seen. The resection margins were all clear. The histopathologic diagnosis was well-differentiated adenocarcinoma. The RUL tumor measured 1.5 cm in greatest dimension. It was composed of columnar and nonmucinous cells that lined up along the alveolar septa (Fig 1D), showing more obvious nuclear pleomorphism and slightly more complex architecture than the tumors on the left lung. There was no desmoplastic stromal reaction, no pleural invasion, and no lymphovascular permeation. The resection margin was clear. The histopathologic diagnosis was bronchioloalveolar carcinoma.

Detection of EGFR gene mutation was performed by polymerase chain reaction Sanger sequencing as previously published [4]. The LUL and LLL tumors were found to harbor different EGFR gene mutations. The LUL tumor was positive for p.Leu858Arg mutation at exon 21 (Fig 1B, inset), whereas the LLL tumor was positive for a 15-nucleatide in-frame deletion p.Glu746_Ala750del removing glutamic acid-leucine-arginine-glutamic acid-alanine (ELREA) at exon 19 (Fig 1C, inset). The RUL tumor was negative for the EGFR gene mutation. Subsequent testing of the RUL tumor showed that it was also negative for Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation, B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) mutation, and echinodermal microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) gene fusion.

Comment

Because surgical resection of all tumor nodules were undertaken and also sent separately for an EGFR gene mutation study, we had the opportunity to determine the clonal relationship between the tumors and correlate them with histologic findings. The LUL and LLL nodules, although

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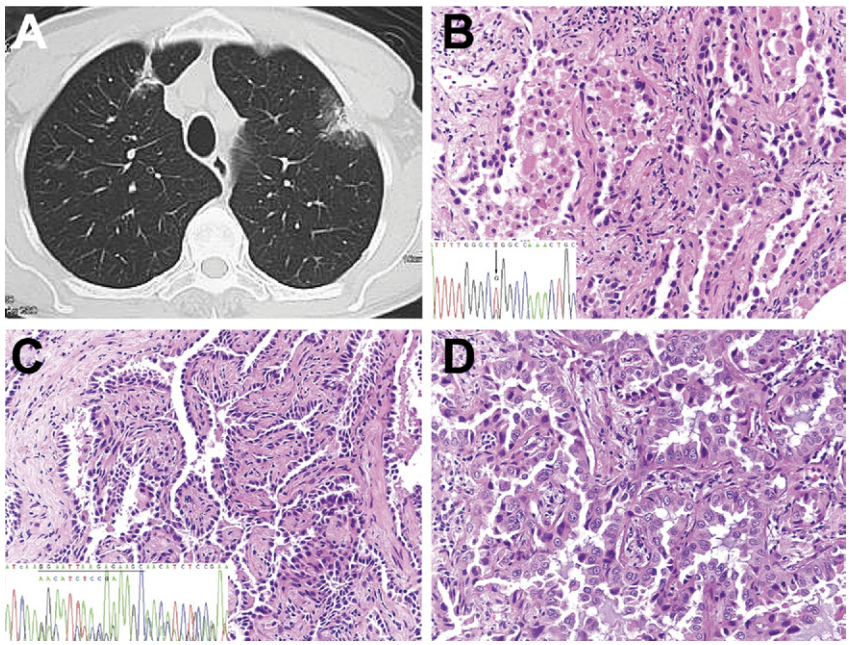

Fig 1. (A) Computed tomographic scan (axial section) showing separate lesions at the right upper lobe (RUL) and left upper lobe (LUL), respectively. (B) Histology of the LUL tumor. (Hematoxylin and eosin; ×200.) (Inset, epidermal growth factor receptor [EGFR] L858R mutation). (C) Histology of the left lower lobe tumor. (Hematoxylin and eosin; ×200.) (Inset, EGFR exon 19 deletion). (D) Histology of the RUL tumor. (Hematoxylin and eosin; ×200.)

sharing similar histology, were shown to harbor two different EGFR mutations, both belonging to mutational hotspots of the gene in NSCLC [3]. The RUL nodule showed subtle histologic difference and was negative for a panel of molecular markers. A caveat of the present case study was that small mutant clones in the tumor tissue might escape detection, owing to the limited analytical sensitivity of direct nucleotide sequencing in mutation detection. Notwithstanding the aforementioned limitation and lack of a positive molecular marker to identify the RUL nodule, we considered synchronous triple primary NSCLC as the most probable scenario for our patient. Taken individually, the T stage of the LUL nodule was T2a, whereas both the RUL and LLL nodules belonged to T1a. Since lymph node and distant metastasis were absent, the overall stage would be stage 1a–1b. The $M1a_{Contr\ Nod}$ category, indicative of stage IV disease, of the new International Association for the Study of Lung Cancer staging system was not applicable for our patient, as the tumors were genetically dissimilar. This implied an entirely different prognostic outlook, as well as a different strategy for adjuvant chemotherapy and recurrence monitoring for our patient.

When combined EGFR and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation testing is used to define clonal relationships among multiple lung adenocarcinomas, discrepancies with existing clinical criteria were identified, thus further highlighting the inherent difficulty of distinguishing synchronous primary from metastasis based solely on clinical criteria [5]. The recent American College of Chest Physician guideline recognizes the usefulness of genetic marker analysis in distinguishing between multiple primary lung cancer and a metastasis [6], especially in nodules of the same histologic type. Having nodules in different lobes with different EGFR mutation status and absence of mediastinal and systemic involvement, our patient clearly satisfies the American College of Chest Physician definition of synchronous primary, thus testifying to the usefulness of a combined clinical and molecular genetic approach to multiple lung tumors.

References

1. Wahbah M, Boroumand N, Castro C, El-Zeky F, Eltorky M. Changing trends in the distribution of the histologic types of lung cancer: a review of 4,439 cases. Ann Diagn Pathol 2007;11:89–96.
2. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260–71.
3. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169–81.
4. Ma ES, Wong CL, Siu D, Chan WK. Amplification, mutation and loss of heterozygosity of the EGFR gene in metastatic lung cancer. Int J Cancer 2007;20:1828–31.
5. Girard N, Deshpande C, Azzoli CG, et al. Use of epidermal growth factor receptor/Kirsten rat sarcoma 2 viral oncogene homolog mutation testing to define clonal relationships among multiple lung adenocarcinomas: comparison with clinical guidelines. Chest 2010;137:46–52.
6. Shen KR, Meyers BF, Larner JM, Jones DR; American College of Chest Physicians. Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines, 2nd ed. Chest 2007;132(3 Suppl):290S–305S.