Early Multiple Primary Lung Cancer without Fluorodeoxyglucose Uptake on Positron Emission Tomography-Computed Tomography and Displaying Different *EGFR* Molecular Profiles

Chang Liu, Yun-Xia An, Li-Jun Ma, Xiao-Ju Zhang

Department of Respiratory Medicine, People's Hospital of Zhengzhou University, Zhengzhou, Henan 450003, China

To the Editor: Multiple primary lung cancer (MPLC) refers to the synchronous or metachronous appearance of more than one primary lung cancer in a single patient. The diagnosis of MPLC is complicated and it is often difficult to differentiate MPLC from metastatic lung cancers based on radiologic and histopathologic criteria alone. Moreover, the therapeutic regimens and prognosis for early MPLC and metastatic lung cancers are quite different.

In November 2016, a 63-year-old female was admitted to People's Hospital of Zhengzhou University with intermittent right chest pain for >5 years. She had a 10-year history of diabetes and was prescribed oral metformin (0.5 g twice daily). Blood glucose levels were under control and she denied other medical disorders. At the time of admission, the physical examination and laboratory test results were normal, with the exception of a slightly elevated blood tumor marker (CYFRA21-1: 5.2 ng/ml, normal range: 0–3.3 ng/ml). A chest computed tomography (CT) scan revealed a ground glass opacity (GGO) in the middle lobe of the right middle lung (RML) measuring 16.0 mm × 9.8 mm, and a round, sheet-like image in the upper lobe of the left upper lung (LUL), encroaching on the pleura and measuring 24.6 mm × 19.6 mm [Figure 1]. A positron emission tomography-CT (PET-CT) scan obtained at Henan Provincial People's Hospital revealed that the maximum standardized uptake values of the right and left lesions were 1.01 and 1.85, respectively. There was no mediastinal lymphadenopathy and no distant metastases. After obtaining informed consent, CT-guided percutaneous transthoracic biopsy of the left lesion was performed and the histopathologic examination was consistent with an adenocarcinoma. The diagnosis and treatment of the GGO in the right lung remained to be determined. After a multidisciplinary discussion including radiologists, pathologists, and pulmonologists, the medical team chose to apply the Mayo risk prediction model analysis of the GGO, which indicated that the patient was at high risk (21.7%). After a discussion with the patient and her family members, the patient underwent percutaneous lung biopsy of the right lesion; the histopathologic examination indicated adenocarcinoma *in situ*. The possibility of MPLC or a primary lung cancer with multiple intrapulmonary

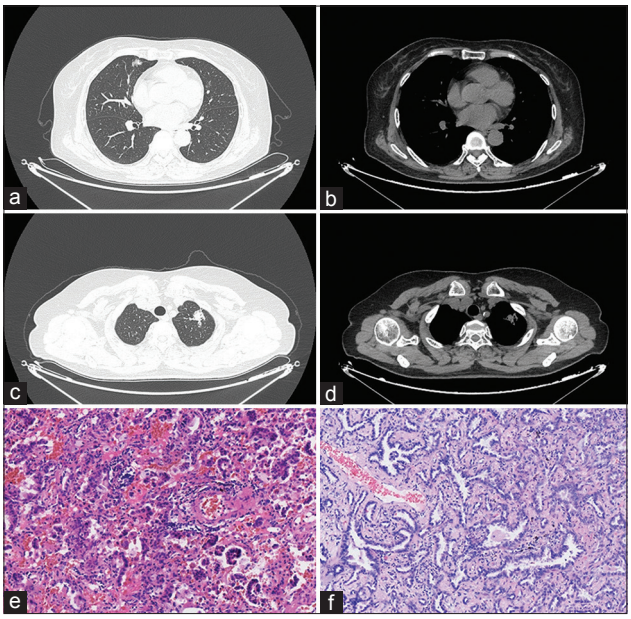

Figure 1: (a–d) Computed tomographic scan obtained in November 2016 showing a ground glass opacity in the middle lobe of the right lung measuring 16.0 mm × 9.8 mm, and a mass in the superior lobe of the left lung measuring 24.6 mm × 19.6 mm. (e) Histopathologic examination of the left upper lobe lesion showed adenocarcinoma (H & E staining; ×100). (f) Histopathologic examination of the right middle lobe lesion showed adenocarcinoma *in situ* (H & E staining; ×100).

Address for correspondence: Dr. Xiao-Ju Zhang, Department of Respiratory Medicine, People's Hospital of Zhengzhou University, No. 7, Weiwu Road, Jinshui District, Zhengzhou, Henan 450003, China
E-Mail: zhangxiaoju1012@163.com

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metastases was considered. Subsequently, mutation analysis was performed and showed that the tumor cells in the RML lesion, but not the LUL lesion, harbored a mutation (19-del) within exon 19 of the *EGFR* gene. According to the Martini–Melamed diagnostic criteria[1] and the different *EGFR* molecular profiles of the bilateral lesions, the final diagnosis was MPLC. Given that the tumor, node, and metastasis stages of the LUL and the RML lesions were T2N0M0 and T1N0M0, respectively, and the patient's physical conditions, staging surgical resection was performed for the bilateral lesions. All of the resected lymph nodes were negative. The patient made an uneventful recovery and has had progression-free survival.

According to the literature, the incidence of MPLC is between 0.2% and 20.0%.[2] The American College of Chest Physicians[3] recommended new diagnostic criteria for MPLC in 2013; however, the diagnosis of MPLC is still complex, and it is often difficult to differentiate MPLC from lung cancer metastases, especially when the same histologic cell type is identified. Due to the significant differences in treatment plan and prognosis between MPLC and lung cancer metastases, the differential diagnosis is critical.

In this case, the fluorodeoxyglucose uptake of bilateral lesions did not enhance, thus benign lesions and early lung cancer were the initial working diagnosis. In this situation, we implemented a new diagnostic strategy, applying the Mayo risk prediction model analysis on the right GGO that eventually led to the final diagnosis.

The mathematical risk prediction model is an auxiliary diagnostic method to evaluate the likelihood of benign lesions or malignancies based on single nucleotide polymorphisms (SNPs). This model includes the patient's age, family history of cancer, tumor size, tumor angiogenesis, and other high-risk factors, which generates the likelihood of benign lesions or malignancies of SNPs. Due to the high sensitivity and specificity, the model is recognized by the industry.[4,5] Thus, for early lung cancer, especially a negative PET-CT, the model can be an effective auxiliary diagnosis method.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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