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CASE REPORT

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Ureteral metastasis of small cell lung cancer transformed from lung adenocarcinoma: A case report

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Abstract

Targeted therapy offers a new option for patients with advanced lung adenocarcinoma patients. However, long-term targeted therapy may transform lung adenocarcinoma into small cell lung cancer (SCLC). Herein, we report a 48-year-old female patient with pulmonary adenocarcinoma and ureteral metastasis which transformed from adenocarcinoma to SCLC after surgical and targeted therapies. She was diagnosed with invasive adenocarcinoma undergoing the surgery. Two years later recurrence and metastasis occurred and she was given targeted therapy with gefitinib and osimertinib. Two years after targeted therapy, a right ureteral mass (4.9 × 3.7 × 3.8 cm) pathologically diagnosed with SCLC was found, which indicated that the pathological subtype has changed from adenocarcinoma to SCLC. Ultimately, multiple metastases occurred after two cycles of chemotherapy consisting of cis-platinum plus etoposide.

KEYWORDS
pulmonary adenocarcinoma, small cell lung cancer, targeted therapy, ureteral metastasis

INTRODUCTION

Targeted therapy has thoroughly changed the treatment pattern of locally advanced and unresectable lung cancer in recent years.[1] Epidermal growth factor receptor (EGFR) is the most commonly mutated gene in lung cancer, and a number of patients with *EGFR* mutations benefit from EGFR tyrosine kinase inhibitors (EGFR-TKIs).[1] However, most patients receiving targeted therapy will develop drug resistance within 1 year and the common causes of acquired drug resistance in non-small cell lung cancer (NSCLC) include the occurrence of a second mutation of the *EGFR* gene and pathological subtype transformation.[2,3] EGFR-TKI therapy could also partially result in the transformation of pathological subtypes in lung adenocarcinomas.[3] Furthermore, the transformation of adenocarcinoma to small cell lung cancer (SCLC) usually interferes the clinical diagnosis and treatment approaches. Once this transformation occurs in lung adenocarcinoma patients, the disease progresses rapidly with worse survival rates.[4] Meanwhile, ureteral metastasis is rare in NSCLC patients, and it is even rarer if accompanied by SCLC transformation. Here, we report the case of a lung adenocarcinoma patient who experienced ureteral metastasis and pathological subtype transformation (adenocarcinoma to SCLC) after 2 years of targeted therapy.

CASE REPORT

A 48-year-old female patient was admitted to our hospital in April 2016 because a solid pulmonary mass was found on chest computed tomography (CT) during a routine physical examination (Figure FIGURE 1a,b). The patient did not have any symptoms. All physical examinations were negative. Enhanced CT imaging examination suggested a mass of

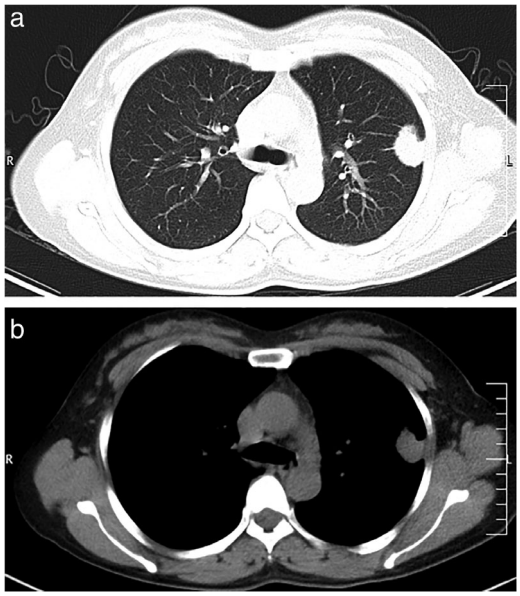

FIGURE 1 Chest CT images when the tumor was first discovered. (a) Pulmonary window. (b) Mediastinal window

approximately 2.8 × 2.5 × 2.2 cm in the peripheral left upper lobe, with burrs, lobulation, vacuoles, and pleural traction. In addition, no distant metastasis was found.

Subsequently, the patient underwent thoracoscopic left superior lobectomy and systemic lymph node dissection. Postoperative pathology indicated poorly differentiated adenocarcinoma (Figure FIGURE 2) and pleural invasion with the pathological stage of T2aN0M0(IB).

Because of several risk factors for recurrence including poor differentiation and pleural invasion, she then received six cycles of chemotherapy consisting of paclitaxel (D1, 180 mg) plus nedaplatin (D2, 150 mg). No signs of recurrence or metastasis were found on re-examination after 6 months. Two years after the operation, the patient's chest CT scan showed multiple small nodules in both lungs (Figure FIGURE 3a). Combined with the medical history and radiographic features, recurrence and metastasis were considered. Genetic tests of the surgical specimens revealed an EGFR p. Glu746_Ala750del (exon 19) mutation; therefore, gefitinib (250 mg, QD) was given as the targeted therapy. Two months later, the number and volume of multiple

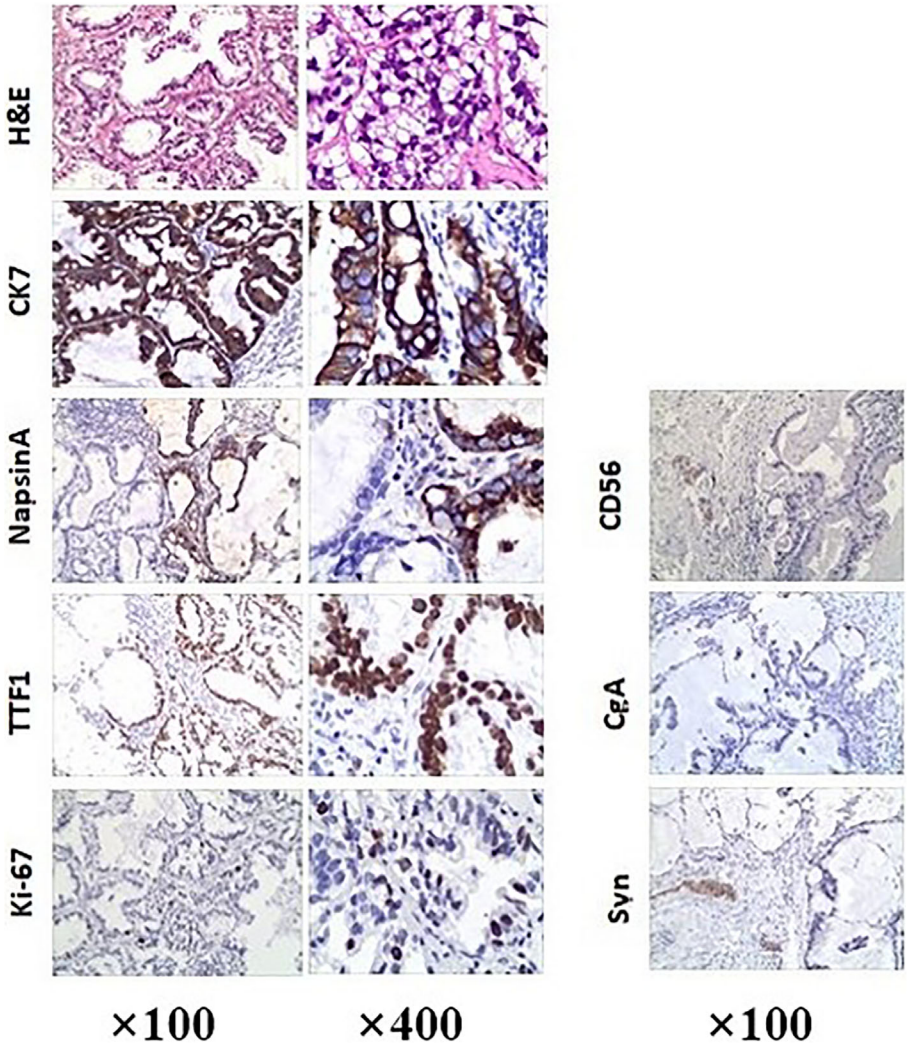

FIGURE 2 The pathological features demonstrated by H&E staining and immunohistochemical staining in primary lung adenocarcinoma. Immunohistochemical staining was positive for TTF-1, Napsin A and CK7 but negative for Syn, CD56, CgA, CK20 and CDX-2. The Ki-67 labeling index was approximately 40%

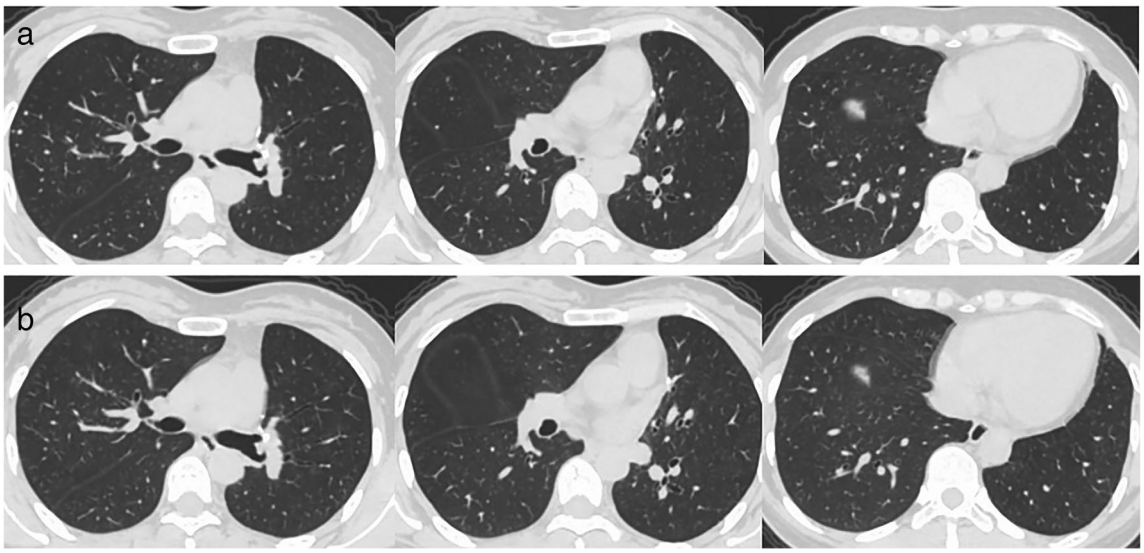

FIGURE 3 Chest CT images before and after targeted therapy with gefitinib. (a) Chest CT scan showed multiple small nodules in both lungs. (b) Chest CT scan showed that the number and volume of multiple solid nodules in both lungs decreased 2 months after targeted therapy with gefitinib

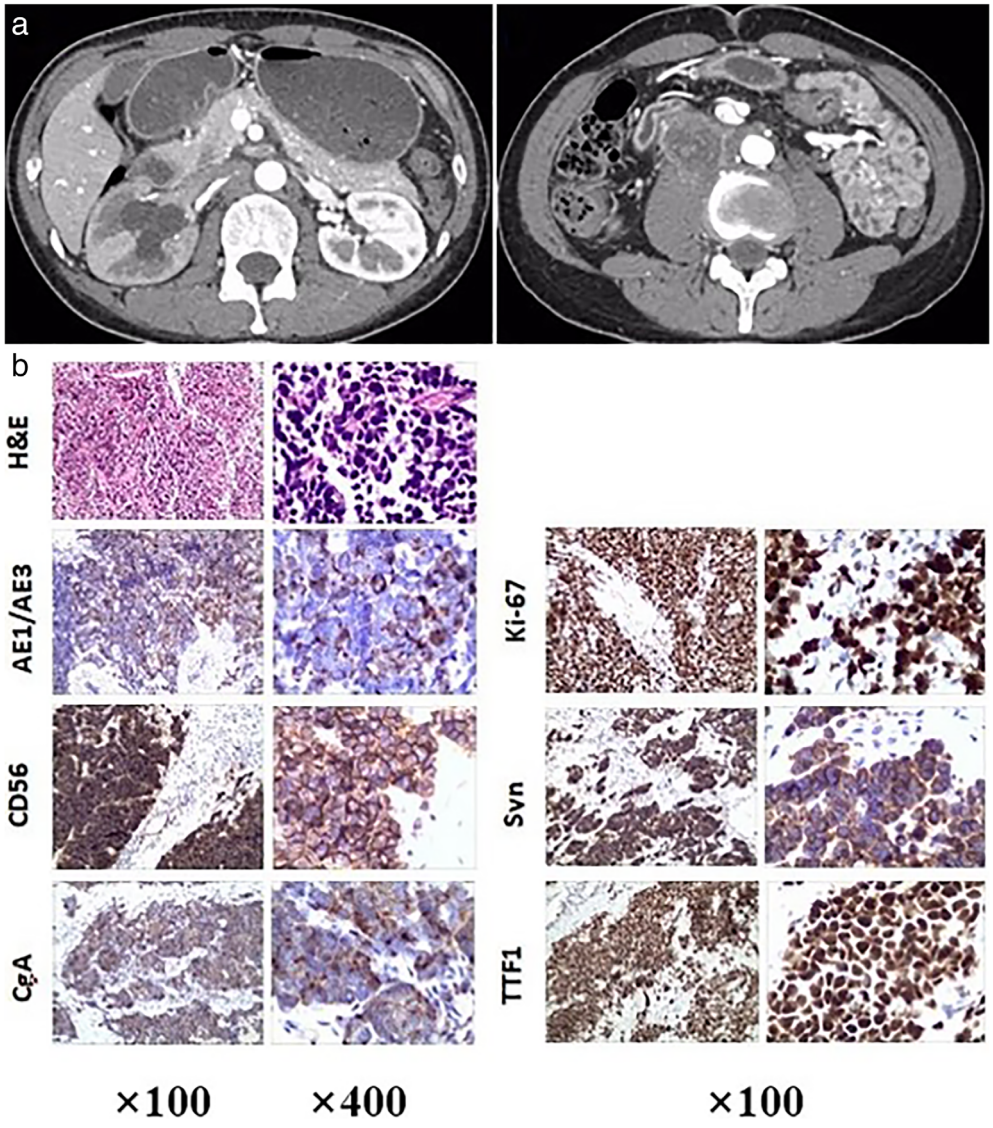

FIGURE 4 (a) Total abdominal enhanced CT. A mass in the right ureter (4.9 × 3.8 × 3.7 cm) with hydronephrosis of the right kidney. (b) The pathological features demonstrated by H&E staining and immunohistochemical staining of ureteral metastatic small cell lung cancer. The immunohistochemical staining indexes AE1/AE3, TTF-1, Syn, and CD56 were positive, and CgA was negative. The Ki-67 marker index was approximately 90%

solid nodules in both lungs decreased (Figure FIGURE 3b), indicating the effectiveness of the targeted therapy. Therefore, this patient continued taking targeted drugs. However, 18 months after receiving targeted therapy, the patient returned to our hospital because of weight loss, decreased mental state and cough. The chest CT scan showed that the pulmonary nodules had increased in number and were enlarged; however, bone scan, brain-enhanced magnetic resonance imaging (MRI), and enhanced upper abdominal CT did not reveal any metastatic lesions. Plasma-based next-generation sequencing (NGS) detection suggested *EGFR* T790M mutation. Subsequently, the third-generation TKI osimertinib (80 mg, QD) was administered and the targeted drug therapy showed effectiveness again after 3 months.

Unfortunately, after 6 months of osimertinib, the patient experienced right lower back pain without an apparent cause, accompanied by persistent pain and frequent, urgent and increased nocturnal urination. Total abdominal enhanced CT and color Doppler ultrasound of the urinary system showed a mass in the right ureter (4.9 × 3.8 × 3.7 cm), with hydronephrosis of the right kidney (Figure 4a). No other obvious metastatic lesions were detected. Intraoperative exploratory laparotomy revealed extensive tumor invasion and a biopsy was conducted. The pathological examination indicated small cell carcinoma (Figure 4b) and the pathologists ultimately made a diagnosis of ureteral metastasis of SCLC. Meanwhile, genetic testing of biopsied specimens and liquid biopsy of peripheral blood showed the presence of the EGFR p.Glu746_Ala750del (exon 19) PIK3CA p.Glu545Lys (exon 10) and PIK3CA p.Glu726Lys(exon 14) mutations. The oncologists at our hospital then recommended chemotherapy consisting of cis-platinum (75 mg/m^2, d1) plus etoposide (100 mg/m^2, d1–d3). Unfortunately, after two cycles of chemotherapy, multiple metastases involving the lung, liver, thoracic vertebrae, lumbar vertebrae, humeri and ribs were obversed on the CT. The patient subsequently refused any further treatment.

DISCUSSION

In 1979, Babaian et al. reported two cases of ureteral metastasis among 1 281 lung cancer patients, and the proportion was 0.156%.[5] Thus, ureteral metastasis is extremely rare, with few reported cases to date. On the other hand, a few studies have revealed the transformation from adenocarcinoma to SCLC to be a rare mechanism of resistance to EGFR-TKI therapy which is also related to the PIK3CA mutation.[6] However, cases with combined ureteral metastasis and transformation of the pathological subtype from adenocarcinoma to SCLC have not been reported until now.

So far, there is no better treatment strategy for this kind of patients. After careful team discussion, we recommended the chemotherapy consisting of cis-platinum plus etoposide which is suitable for SCLC patients. Unfortunately, after two cycles of chemotherapy, multiple metastases appeared throughout the body. Thus, more attention should be paid to identify appropriate treatment strategies for these patients.

In conclusion, we report an extremely unusual case of lung adenocarcinoma in a patient who experienced ureteral metastasis and pathological subtype transformation (adenocarcinoma to SCLC) after 2 years of targeted therapy. In addition, this case also highlights that attention should be paid to the possibility of pathological subtype transformation after long-term EGFR-TKI therapy.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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