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CASE REPORT

# Transformation of Lung Squamous Cell Carcinoma to Small Cell Lung Cancer After Immunotherapy Resistance: A Case Report

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**Abstract:** The transformation of lung adenocarcinoma to small cell lung cancer (SCLC) following treatment with epidermal growth factor (EGFR) receptor tyrosine kinase inhibitors (TKIs) is a relatively common phenomenon. However, transformation of non-small cell lung cancer (NSCLC) to SCLC following treatment with immunotherapy is very rare. Here, we report a case of a 56-year-old patient diagnosed with driver gene mutation-negative lung squamous cell carcinoma (SCC). He received four cycles of immunotherapy with sugemalimab and chemotherapy with albumin paclitaxel in combination with carboplatin, and a partial response was achieved. Subsequently, the patient received 5 cycles of immunotherapy with sugemalimab. However, he developed rapid progression of mediastinal lymph nodes, and biopsy results showed transformation to SCLC. His tumor did not respond to the next line of carboplatin combined with etoposide, and he died six months after the discovery of SCLC transformation. In conclusion, SCLC transformation is also an important resistance mechanism for lung SCC patients treated with immunotherapy and predicts a very poor outcome. Repeat biopsy is needed for advanced lung SCC that has progressed with immunotherapy.

**Keywords:** lung squamous cell carcinoma, immunotherapy, small cell transformation

## Introduction

Currently, immunotherapy has changed the treatment strategy for non-small cell lung cancer (NSCLC) patients.[1] In particular, antibodies specific for the programmed death (PD-1) receptor and programmed death ligand 1 (PD-L1) are preferred as first- or second-line treatment for advanced NSCLC.[2,3] In addition, several studies have found that neoadjuvant immunotherapy for locally advanced lung squamous cell carcinoma (SCC) leads to superior pathological response rates.[4,5] In the real world, a proportion of patients with advanced lung SCC treated with immunotherapy show durable clinical benefits.[6] Nevertheless, some patients also present with relatively rapid disease progression.[7] However, the resistance mechanisms for immune checkpoint inhibitors (ICIs) are still unclear.[8] Several studies have shown that small cell transformation is commonly recognized as one of the resistance mechanisms to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR-mutant NSCLC, which accounts for 3–14% of resistant cases.[9–11] In addition, small cell transformation in advanced NSCLC patients treated with EGFR-TKIs is associated with poor survival outcomes.[12] Recently, small cell transformation is extremely rare for advanced NSCLC patients who have failed immunotherapy.[13] It was recently reported that when first-line treatment with EGFR-TKIs fails for patients with advanced NSCLC, repeat biopsy for detecting EGFR T790M is preferred.[14] However, repeat biopsy is not regularly recommended for advanced NSCLC patients treated with ICIs after disease progression.[15] Here, we report a case of small cell transformation in locally advanced lung SCC treated with immunotherapy.

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## Case Presentation

A 56-year-old male was admitted to the Oncology Department of the Anhui Chest Hospital in March 2022 due to cough and expectoration for 1 month. Chest computed tomography (CT) revealed an irregular mass (3.5×3.6 cm) in the lower lobe of his right lung with intramediastinal lymph node metastasis (Figure 1A and B). The patient had a 30-year history of smoking. Serum tumor marker levels at diagnosis were carcinoembryonic antigen (CEA) 1.7 ng/mL and neuron-specific enolase (NSE) 10.5 ng/mL. On 8 April 2022, bronchoscopy was performed, and the pathological findings were compatible with lung SCC (Figure 2A). Immunohistochemical (IHC) staining was positive for P40 (Figure 2B) but negative for CD56 and synaptophysin (Figure 2C and D). The patient was diagnosed with driver gene mutation-negative lung SCC. The tumor was classified as clinical T2N2M0, which is stage IIIA according to the TNM classification of the UICC, 8th edition. Based on multidisciplinary team discussions, we performed neoadjuvant therapy to reduce staging and reassess the disease. From 10 April 2022 to 10 July 2022, the patient received four cycles of immunochemotherapy: sugemalimab 1200 mg ig d1, albumin paclitaxel 400 mg ig d1, and carboplatin area under the curve (AUC) 5 ig d1/q3w. After the patient received 4 cycles of treatment on July 10, 2022, chest CT showed significant remission compared with baseline CT (27 March 2022) and achieved a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors 1.1 (Figure 1C). In addition, chest CT showed that the lymph nodes achieved complete response (CR) compared with baseline CT (Figure 1D). After a multidisciplinary team discussion, we suggested that surgical removal was possible. However, the patient refused surgical treatment and radiotherapy. From July 2022 to October 2022, the patient received 5 cycles of sugemalimab treatment. However, chest CT (3 November 2022) showed that the mass was slightly larger than the previous CT scan (12th, October 2022), and the lymph nodes were very significantly increased (Figures 1E, F and 3A, B), which was evaluated as progressive disease (PD). In addition, a CT scan revealed thoracic spine bone destruction, which suggested a neoplastic lesion in the thoracic spine. Notably, serum tumor marker levels at progression were CEA 2.9 ng/mL and NSE 60.5 ng/mL, significantly higher than the baseline levels. We were surprised by the rapid progression of this patient after seven months of immunotherapy. Therefore, we performed endobronchial ultrasound-guided transbronchial needle aspiration in the

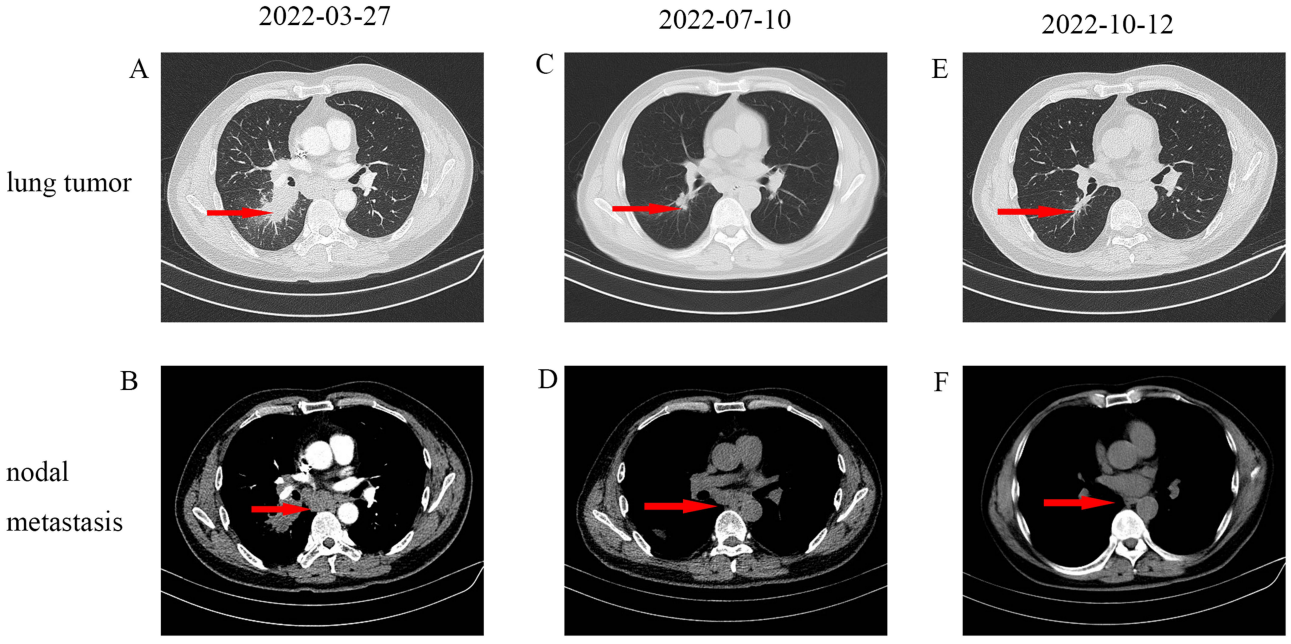


**Figure 1** (**A** and **B**) Baseline CT images. The red arrow in figure A indicates tumors and the red arrow in figure B indicates lymph nodes. (**C** and **D**) Lung mass and nodal metastasis achieved PR after four cycles of AP (albumin paclitaxel 400 mg and carboplatin AUC 5) and sugemalimab 1200 mg. The red arrow in figure C indicates tumors and the red arrow in figure D indicates lymph nodes. (**E** and **F**) Lung mass achieved SD, and nodal metastasis achieved CR after five cycles of 1200 mg of sugemalimab. The red arrow in figure E indicates tumors and the red arrow in figure F indicates lymph nodes.
**Abbreviations**: PR, partial response; SD, stable disease; CR, complete response; CT, computed tomography; AUC, area under the curve.

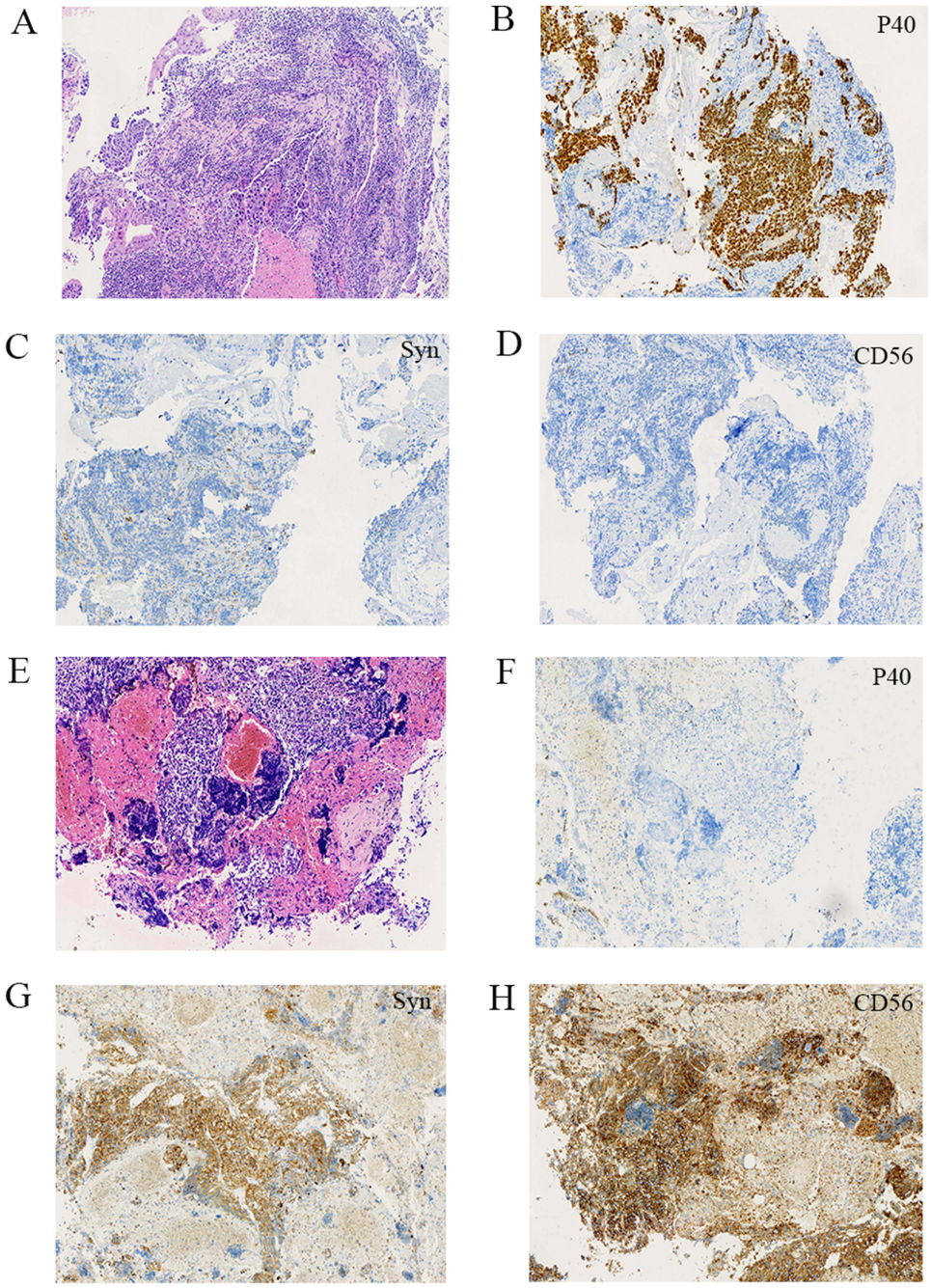


**Figure 2** (**A**) Microscopic appearances of the pulmonary tumor showed lung SCC (HE staining x100). (**B**–**D**) Immunohistochemical staining for P40(+), Syn (-) and CD56(-), which are the optimal immunohistochemical markers for SCC (HE staining x100). (**E**) Microscopic appearances showed transformed SCLC (HE staining x100). (**F**–**H**) Immunohistochemical staining for P40(-), Syn (+) and CD56(+), which are the optimal immunohistochemical markers for transformed SCLC (HE staining x100).
**Abbreviations**: SCC, squamous cell carcinoma; Syn, synaptophysin; SCLC, small cell lung cancer; HE, hematoxylin and eosin.

diagnosis of mediastinal lymph nodes on November 05, 2022. The pathological diagnosis was small cell carcinoma (Figure 2E). Immunohistochemical (IHC) staining was positive for CD56 and synaptophysin but negative for P40 (Figure 2F–H). Subsequently, this patient was treated with 2 cycles of etoposide combined with cisplatin, and the CT scan showed sustained disease progression (Figure 3C and D). He died 6 months after the detection of small cell transformation.

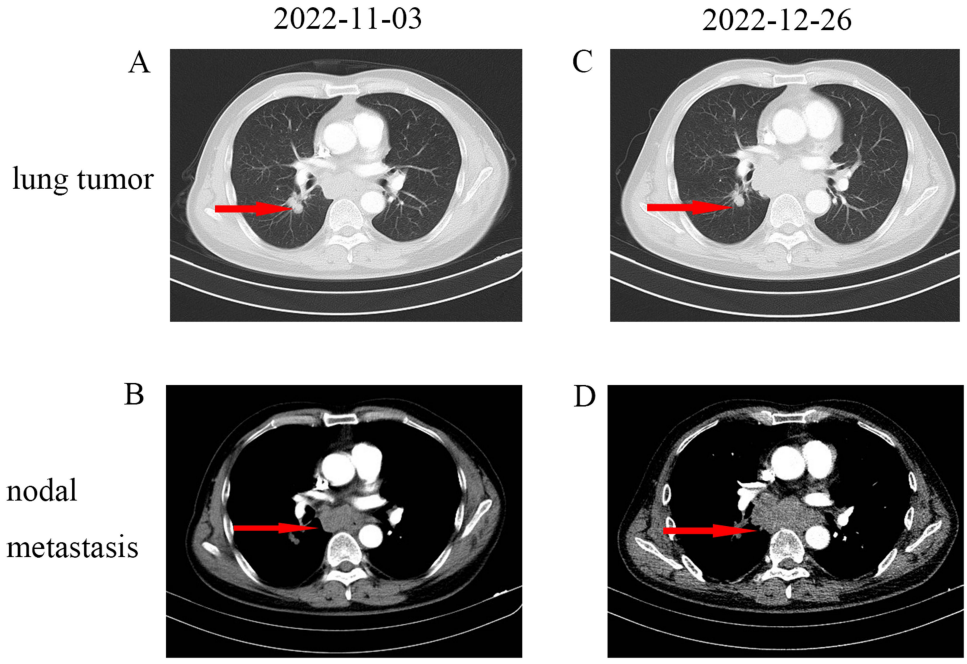


**Figure 3** (**A** and **B**) Lung mass and nodal metastasis were evaluated as PD compared with CT (12 October 2022). The red arrow in figure A indicates tumors and the red arrow in figure B indicates lymph nodes. (**C** and **D**) The lung mass achieved SD, and nodal metastasis achieved PD after two cycles of etoposide combined with cisplatin. The red arrow in figure C indicates tumors and the red arrow in figure D indicates lymph nodes.
**Abbreviations**: PD, progressive disease; SD, stable disease; CT, computed tomography.

## Discussion

Immunotherapy constitutes irreplaceable treatment for locally advanced lung SCC.[16] Sugemalimab is a fully human, full-length, anti-PD-L1 monoclonal antibody developed by CStone Pharmaceuticals.[17] It is an immunoglobulin G4 monoclonal antibody engineered to block interaction between PD-L1 and PD-1 on T cells and CD80 on immune cells and exhibits antitumor activity by eliminating the immunosuppressive effect of PD-L1 on cytotoxic T cells.[18] The GEMSTONE-301 study[19] showed that sugemalimab can significantly prolong progression-free survival in patients with stage III NSCLC whose disease has not progressed after sequential or concurrent chemoradiotherapy. In addition, the GEMSTONE-302 study[20] showed a clinically significant meaningful outcome for patients with advanced lung SCC treated with first-line therapy with sugemalimab plus chemotherapy. The present case is a locally advanced lung SCC treated with sugemalimab combined with chemotherapy. When the patient's disease progressed rapidly, repeat biopsy pathology was performed to assess transformed small cell carcinoma.

Notably, the transformation of NSCLC to small cell lung cancer (SCLC) after immunotherapy is rare, and the mechanism is unclear.[21] Bar et al[22] and Sehgal et al[23] reported the detection of the same genomic features in initial non-small cell lung cancer and secondary small cell carcinoma. They suggested that NSCLC cells may be histologically transformed into small cell carcinoma cells. Imakita et al[13] described two lung SCC patients with tumors that transformed to small cell carcinoma after immunotherapy. However, the treatment options and prognosis after conversion to small cell carcinoma were not reported.[13] Dong et al[24] presented a case of stage IIIA lung SCC by bronchoscopic biopsy. Subsequently, this patient was treated with neoadjuvant immunotherapy and surgical pathology of SCC, carcinosarcoma, and SCLC. Unfortunately, this case was not labeled as small cell carcinoma in the initial pathological diagnosis. In our case, the patient was initially diagnosed with lung SCC and was excluded by immunohistochemistry for small cell, neuroendocrine, and adenocarcinoma components. In addition, we also understand that bronchoscopy biopsy does not reveal the histology of the whole tumor. The presence of mixed histology of small and non-small cells at diagnosis is possible. However, there are no guidelines on how to distinguish transformed small cell carcinoma from primary SCLC.

Currently, etoposide in combination with platinum is still the preferred treatment option for transformed SCLC patients who have failed EGFR-TKIs.[25] However, the treatment options for NSCLC patients who have failed

immunotherapy and then undergo transformation to small cell carcinoma are unclear. Sehgal et al[23] reported a case of advanced lung SCC transformed to SCLC after receiving nivolumab in the second line, then received etoposide in combination with carboplatin, yet progressed again after 10 months. This is similar to the previously reported overall survival of 10.9 months (95% CI, 8.0 months–13.7 months) for transformation to SCLC after EGFR-TKIs in patients with EGFR-mutated lung adenocarcinoma.[25] In this case, etoposide in combination with cisplatin was chosen after transformation to small cell carcinoma, but the disease continued to progress after 2 cycles.

In conclusion, it is rare for advanced lung SCC with immunotherapy to transform into SCLC in the real world, and this may be related to the lack of knowledge about repeat tissue biopsy after disease progression. Therefore, it is very important to conduct another biopsy after the progression of lung SCC patients treated with immunotherapy in the future. In addition, the treatment of lung SCC transformed into SCLC with immunotherapy needs to be further investigated.

## Ethical Approval

This study was approved by the Human Research Ethics Committee of Anhui Chest Hospital.

## Disclosure

Diming Wang and Wei Ye are co-first authors for this study. The authors have no conflicts of interest to declare for this work.

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