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CASE REPORT

Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report

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Abstract

BACKGROUND

The treatment of small-cell lung cancer (SCLC) has progressed little in recent years because of its unique biological activities and complex genomic alterations. Chemotherapy combined with radiotherapy has been widely accepted as the first-line treatment for SCLC.

CASE SUMMARY

Here, we present a 68-year-old male smoker who was diagnosed with SCLC of the right lung. After several cycles of concurrent chemoradiotherapy, the tumor progressed with broad metastasis to liver and bone. Histopathological examination showed an obvious transformation to adenocarcinoma, probably a partial recurrence mediated by the chemotherapy-based regimen. A mixed tumor as the primary lesion and transformation from SCLC or/and tumor stem cells may have accounted for the pathology conversion. We adjusted the treatment schedule in accord with the change in phenotype.

CONCLUSION

Although diffuse skeletal and hepatic metastases were seen on a recent computed tomography scan, the patient is alive, with intervals of progression and shrinkage of his cancer.

Key Words: Small-cell lung cancer; Adenocarcinoma; Transformation; Chemotherapy; Case report

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Core Tip: In this report, we present a male patient with a diagnosis of small-cell lung cancer (SCLC) who developed metastatic adenocarcinoma, a subtype of non-SCLC, after standard chemotherapy regimens. He has survived for 90 mo since the first diagnosis, which is longer than expected.

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INTRODUCTION

Small-cell lung cancer (SCLC) is a subtype of lung cancer because of its histology and morphology, and it accounts for 15%-20% of newly diagnosed cases worldwide every year[1]. Owing to its rapid growth and progression, it is often diagnosed at an advanced stage by histopathological examination, indicating a life expectancy of less than 1 year. As for treatment, there is a consensus that normative chemotherapy and appropriate-dose radiotherapy lead to high response rate in a clinical pathology selection-dependent manner that is recommended by American Society of Clinical Oncology[2,3]. It should be noted that targeted therapy and immunotherapy, which are likely to be effective in the treatment of non-SCLC (NSCLC)[4], are not recommended for SCLC because of the absence of mutation-driven evolution and its characteristic histological and molecular features[5]. However, histological transformation is likely to change the treatment strategy, facilitating appropriate and rational decisions in SCLC management. Here we present a male patient with an initial diagnosis of SCLC who developed metastatic adenocarcinoma, a subtype of NSCLC, after standard chemotherapy regimens. He has survived for 76 mo since the first diagnosis, which longer than expected.

CASE PRESENTATION

Chief complaints

A 68-year-old man with a smoking history of 40 pack-years came to seek medical advice in light of cough, expectoration, and shortness of breath.

History of present illness

A contrast-enhanced computed tomography (CT) scan of the chest (which cannot be found at present) indicated a malignant tumor of the lung. Ultrasound-guided percutaneous biopsy confirmed the lesion characteristics and histopathology. At high magnification, cells in two biopsy samples of same lesion were uniform in size and arrangement, fusiform in shape with hyperchromatic nuclei (Figure 1D), and having an aggressive growth pattern. Coupled with immunohistochemistry (IHC), these results indicated a SCLC diagnosis (Figure 2). Molecular pathology was tested by amplification-refractory mutation system (ARMS)-PCR, which indicated an absence of sensitive mutation (Supplementary Figure 1A). According to the American Society of Clinical Oncology Endorsement of the American College of Chest physicians guidelines, the patient was treated with concurrent chemoradiotherapy consisting of six cycles of etoposide and carboplatin with thoracic radiotherapy Dt45Gy/30F twice per day. After treat, his clinical symptoms improved and the lesion in the right lower lobe shrank dramatically on CT scanning (Figure 1A).

History of past illness

The patient suffered from chronic obstructive pulmonary disease, hypertension, and diabetes for at least 10 years. As they were not thought to be associated with the progression of lung cancer, we did not include a detailed description in this article.

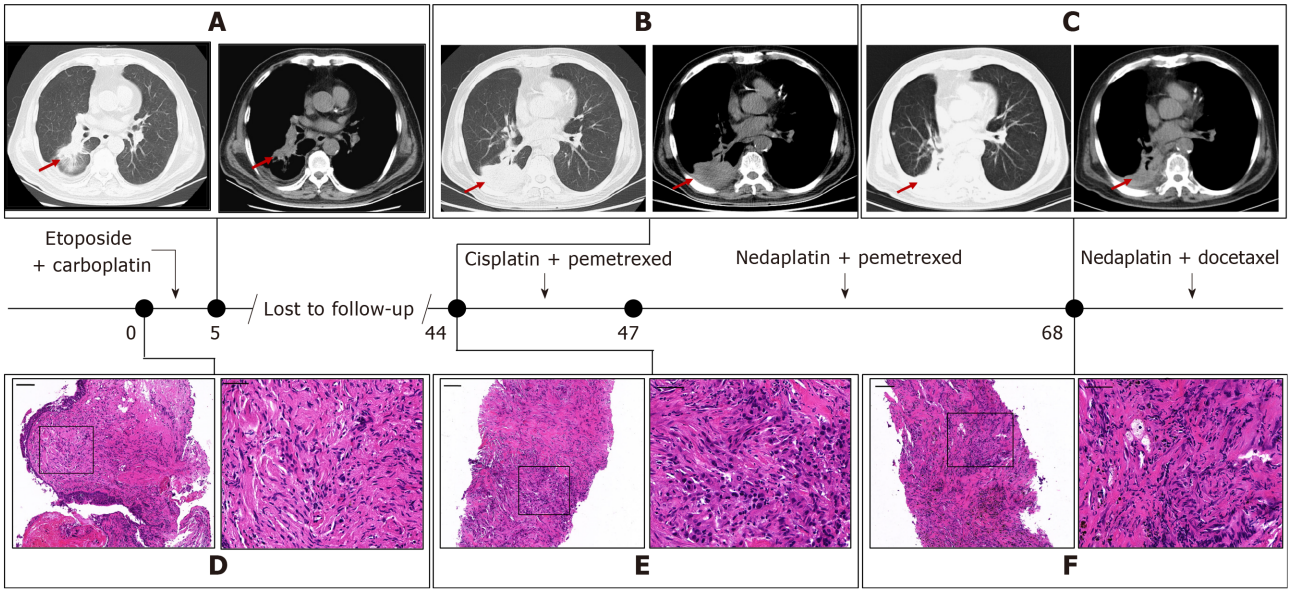

Figure 1 Clinical history of the histological transformation from small-cell lung cancer to adenocarcinoma in this patient. A-C: Computed tomography changes of the right lesion in different months with the indicted chemotherapy. D-F: Hematoxylin-eosin staining of bronchoscopy needle aspiration biopsy shows different characteristics and histopathology in corresponding weeks. Magnifications are × 10 (left) and × 40 (right) with 100 μm and 50 μm scale bars.

Laboratory examinations

The presence of bilateral pulmonary interstitial hyperplasia and inhomogeneous emphysema were consistent with tumor progression and deterioration of the patient's condition. Ultrasound-guided percutaneous biopsies were performed to determine the reason why the standard SCLC treatment did not have a curative effect. The tumor cells were ovoid with hyperchromatic nuclei and arranged in strips or nests (Figure 1E). Immunohistochemistry (IHC) indicated poorly differentiated adenocarcinoma owing to the presence of some specific pathological markers (Figure 2). What needed more attention was that several SCLC markers, such as thyroid transcription factor (TTF)-1, cytokeratin (CK)5/6, and P40, were expressed only in individual cells, and Ki-67-positive cells accounted for more than 25%, indicating rapid growth and proliferation of tumor cells. Genetic analysis found that the patient had no epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement (D5F3 Ventana IHC). However, repeated molecular pathology showed that after standard chemotherapy, the patient bore a *KRAS* mutation (Supplementary Figure 1B), which corresponded with the histology findings. Four cycles of cisplatin and pemetrexed achieved a decrease in the size of the lesion in the right lower lung, which further supported the diagnosis of adenocarcinoma.

Imaging examinations

With the remission of clinical symptoms, the patient failed to continue regular follow-up and periodic imaging. It was beyond our expectation that the patient suffered thoracalgia in the lower right chest 3 years after the last CT examination. A CT examination of his chest indicated growth and consolidation of the lesion in the lower right lung, with scattered nodules, and right inferior lobe insufficiency compared with a CT obtained 3 years previously. (Figure 1B).

FINAL DIAGNOSIS

Advanced lung cancer.

TREATMENT

After the patient stopped treatment, he experienced persistent dull pain in the right hypochondriac region and back with no noticeable improvement after odynolysis. Follow-up imaging revealed that the parietal pleura were eroded by invasive

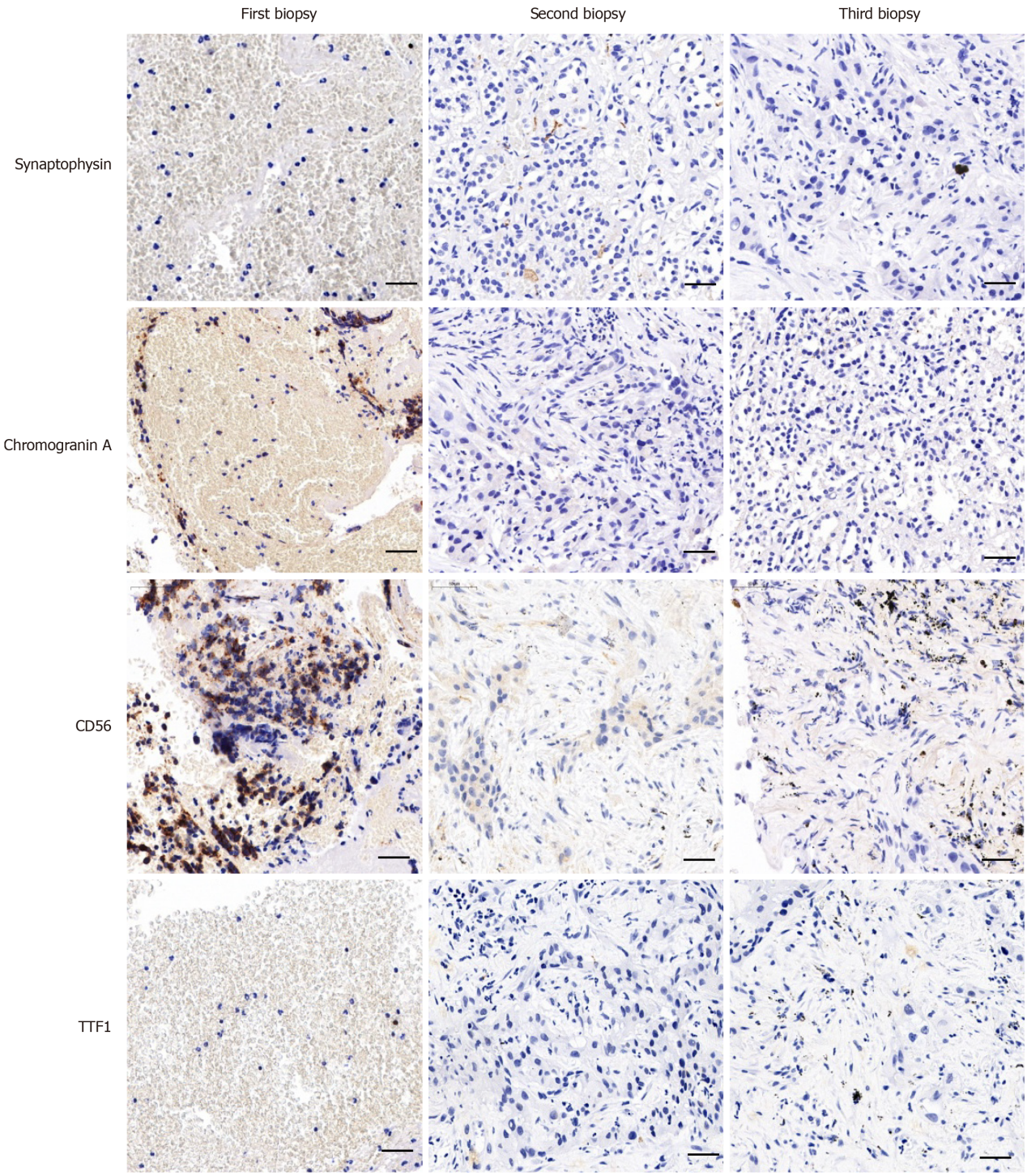

Figure 2 Immunohistochemical staining of three biopsies. Several typical biomarkers of small-cell lung cancer were examined repeatedly at different stages. Synaptophysin, chromogranin A, CD56 and TTF1 indicate histological transformation. Magnifications are × 40; The scale bar is 50 μm.

malignant cells, and that there was a strong possibility that tumor cells had invaded bone, brain, liver, and local and distant lymph nodes. According to the patient's condition and his tolerance of chemotherapeutic drugs, nedaplatin plus pemetrexed, together with intermittent local radiation, were seen as the best treatment choice. After several cycles, the clinical manifestations were improved. However, after a 4 mo interval, CT revealed that the solid pulmonary nodules in the right lung had enlarged, pleural effusion had emerged in the right thoracic cavity, and a nodule embedded in upper lobe of the left lung had progressed, all of which indicated tumor progression (Figure 1C). A third ultrasound-guided biopsy of the same nodules in the right lung found large cells with hyperchromatic nuclei arranged as in an adenoma, and with aggressive characteristics (Figure 1F). IHC staining and molecular examination supported the previous diagnosis of adenocarcinoma of the lung (Figure 2 and

Supplementary Figure 1C). Combination treatment with nedaplatin and pemetrexed were continued for two cycles, until the patient reported the appearance of blood in the phlegm.

OUTCOME AND FOLLOW-UP

Subsequently, pemetrexed was substituted for docetaxel in previous therapeutic schedule in several cycles to now. At this time, the patient is alive 76 mo after the definitive diagnosis.

DISCUSSION

It is well known that SCLC accounts for a small proportion of newly diagnosed lung cancer worldwide every year. The incidence is the highest in male and female smokers, and SCLC has a high mortality less than 1 year after diagnosis[1]. On the basis of the location of the lesion and distant metastasis, SCLCs are generally staged as limited and extensive disease, which have different prognoses and treatment schedules. Its characteristic rapid progression and late diagnosis as metastatic disease determine its poor prognosis, with a median survival of 3 mo in untreated patients. A high response rate and sensitivity to chemotherapy and radiotherapy make it possible to alleviate SCLC to some extent, but lead to relapse within the first year after chemoradiotherapy[6].

Even though genome-based diagnosis has increased the options for targeted therapy for NSCLC patients, SCLC treatment options remain limited to regimens based on chemotherapy and radiotherapy. In addition, therapeutic effectiveness varies with the patient's condition, drug dose and frequency, and the quantity of radiation. It is noteworthy that, compared with NSCLC, biomolecular aberrations such as mutations of *EGFR*, *KRAS* and *BRAF* genes or *ALK* gene rearrangements are rare in SCLC, which leads to a lack of indications for the use of tyrosine kinase inhibitors[7]. Instead, mutations of genes involved in p53 and RB and deletions or increased copy number in specific chromosomes contribute to carcinogenesis, and few effective, targeted drugs are available[8]. Surprisingly, a recent study reported that atezolizumab, a programmed cell death ligand 1 (PD-L1) inhibitor of immunotherapeutic drugs, combined with etoposide and carboplatin extended overall survival of SCLC patients and has been approved as first-line treatment of advanced-stage SCLC, indicating the feasibility of immunotherapy to extend the life expectancy of SCLC patients[9].

In this case, the biopsy had SCLC characteristics, and the patient received several cycles of combination treatment with chemotherapy plus radiotherapy. A second biopsy of the same lesion was found to be adenocarcinoma of lung cancer. Other than improper procedures and ineluctable errors in drawing samples, there are several explanations for this phenomenon. (1) The first involves mixed types of lung cancer at the initial diagnosis. After combined treatment with chemotherapy and radiotherapy, the dominant SCLC component was suppressed or eliminated, leading to development of the adenocarcinoma component. Although both are sensitive to platinum-based drugs, SCLC is more vulnerable to chemotherapy compared with other types of lung cancer. However, the first histological examination revealed no significant expression of adenocarcinoma-related biomarkers in either of two samples from the same lesion. Furthermore, comparison of the two biopsies found that there were indeed different types of lung cancer in the same lesion, which excludes mixed tumors in this case; (2) The second explanation is histopathological transformation from SCLC to NSCLC. It has been widely reported that transformation from EGFR-mutated NSCLC to SCLC while using tyrosine kinase inhibitors (TKIs) is a potential mechanism to mediate resistance to targeted drugs[8]. Histological transformation in SCLC is rarely reported, however. Three biopsies were obtained from this patient, and IHC staining and molecular pathology revealed changes in particular biomarkers that indicated histological transformation of the lung cancer. Moreover, switching the treatment regimen based on the histopathological results alleviated the clinical manifestations, which further supported our previous diagnosis; and (3) The third is tumor stem-cell oriented adenocarcinoma. Tumor stem cells are liable to be stimulated in particular circumstances, leading to differentiation, proliferation, and the formation of lesions[10,11]. However, given that the number of stem cells is limited and the methods of detection are not well advanced, tumor stem-cell oriented adenocarcinoma

should also be taken into account. In this patient, repeated biopsies indicated a possibility that he experienced an SCLC-NSCLC transformation, mainly because of pathology-oriented diagnosis and variable characteristics on CT scans. Although a rational diagnosis of histological transformation is not possible without surgical samples, it is seemly proper to take transformation into account after excluding other underlying possibilities. Further verification is needed.

CONCLUSION

Our experience with this case highlights several key points that are critical for clinical diagnosis and treatment. The first is the necessity for several ultrasound- or CT-guided biopsies. Repeated biopsies dynamically monitor phenotypic alterations of tumor cells, which facilitates the use of appropriate treatment regimens. Secondly, sampling multiple sites in primary and metastatic organs contributes to increased accuracy of diagnosis, avoiding the limitation of single site. In this patient, samples at different lesions in first biopsy helped to determine the presence of a mixed tumor or only one type of tumor cell. Thirdly, genetic analysis or DNA sequencing help physicians to diagnose pathology, select the best treatment schedule, and assess patient prognosis. Somatic mutations in several oncogenes, including *EGFR*, *ALK*, *ROS1*, and others, drive abnormal proliferation of mutant cells that can be targeted by TKIs, even though the mutations are rare in SCLC. Detecting mutations is conducive to discovering histological transformation and expanding therapeutic alternatives. Finally, the implementation of standard diagnostic and therapeutic programs is important to inhibit the development of malignant lesions and further improve healing.

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