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Case report

Small cell lung cancer transformation during immunotherapy with nivolumab: A case report

Takuma Imakita [a, b], Kohei Fujita, M.D, Ph.D. [a, *], Osamu Kanai [a], Tsuyoshi Terashima [c], Tadashi Mio [a]

[a] Division of Respiratory Medicine, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
[b] Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Hyogo, Japan
[c] Division of Clinical Pathology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

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ABSTRACT

We report a rare case of transformation of non-small cell lung cancer (NSCLC) to small cell lung cancer (SCLC), without epidermal growth factor receptor (EGFR) gene mutation, during immunotherapy treatment with nivolumab. A 75-year-old man was referred to our hospital following the observation of a 64 mm mass in a chest computed tomography (CT) scan. A transbronchial biopsy of the mass identified the pathological presence of poorly differentiated NSCLC, with no histological signs of SCLC. No mutations were identified in the EGFR gene. A clinical diagnosis of NSCLC (cT3N3M1a, stage IV) was made following a positron emission tomography (PET)–CT scan and enhanced brain magnetic resonance imaging. Docetaxel and bevacizumab were selected as the first-line chemotherapy regimen; however, after two cycles, the patient developed a gastrointestinal perforation, and discontinuation of cytotoxic chemotherapy was recommended. Owing to gradual disease progression, immunotherapy with nivolumab was selected as the second-line regimen. During the immunotherapy, the tumor continued to progress and some subcutaneous tumors emerged. Biopsy of a subcutaneous tumor revealed SCLC, with positive immunostaining for cluster of differentiation 56, synaptophysin, and thyroid transcription factor-1. Serum tumor markers of SCLC were also elevated. Based on these results, we concluded that in this case NSCLC had transformed to SCLC during immunotherapy with nivolumab.

1. Introduction

The immune checkpoint inhibitor nivolumab, an anti-programmed death-1 (PD-1) antibody, causes inhibition of the PD-1/programmed death ligand-1 (PD-L1) pathway. In phase III trials, treatment with nivolumab for both advanced squamous cell lung cancer and non-squamous non-small cell lung cancer (NSCLC), improved the overall survival of patients compared to treatment with docetaxel [1,2]. In December 2015, nivolumab was approved for use in the treatment for patients with advanced or recurrent NSCLC in Japan. Nivolumab is now widely used for NSCLC, but its potential effects are not fully known.

During the treatment of lung cancer, the development of resistance to chemotherapy is inevitable.

Adenocarcinomas with an epidermal growth factor receptor (EGFR) mutation are often treated with EGFR-tyrosine kinase inhibitors (TKIs), as these drugs are most effective for this type of NSCLC. Resistance to EGFR-TKIs frequently occurs within 1–2 years of treatment [3,4], due to the development of a secondary mutation in the EGFR gene (e.g. T790M mutation) in approximately 50–60% of cases [5,6]. Tumor transformation to small cell lung cancer (SCLC) is another treatment resistance mechanism, and occurs in 3–14% of cases [5–7]. As EGFR-TKIs are most commonly used for the treatment of EGFR-mutant adenocarcinoma, most of the reported transformation cases are of adenocarcinoma with EGFR mutation. There are a few cases of transformation from adenocarcinoma with wild-type EGFR, but these cases are seldom reported [8]. To the best of our best knowledge, SCLC transformation during immunotherapy treatment of NSCLC with nivolumab has not previously

* Corresponding author. Division of Respiratory Medicine, National Hospital Organization Kyoto Medical Center, 1-1, Fukakusa-Mukaihata-Cho, Fushimi-Ku, Kyoto, Japan.
E-mail address: kfujita-oka@umin.ac.jp (K. Fujita).

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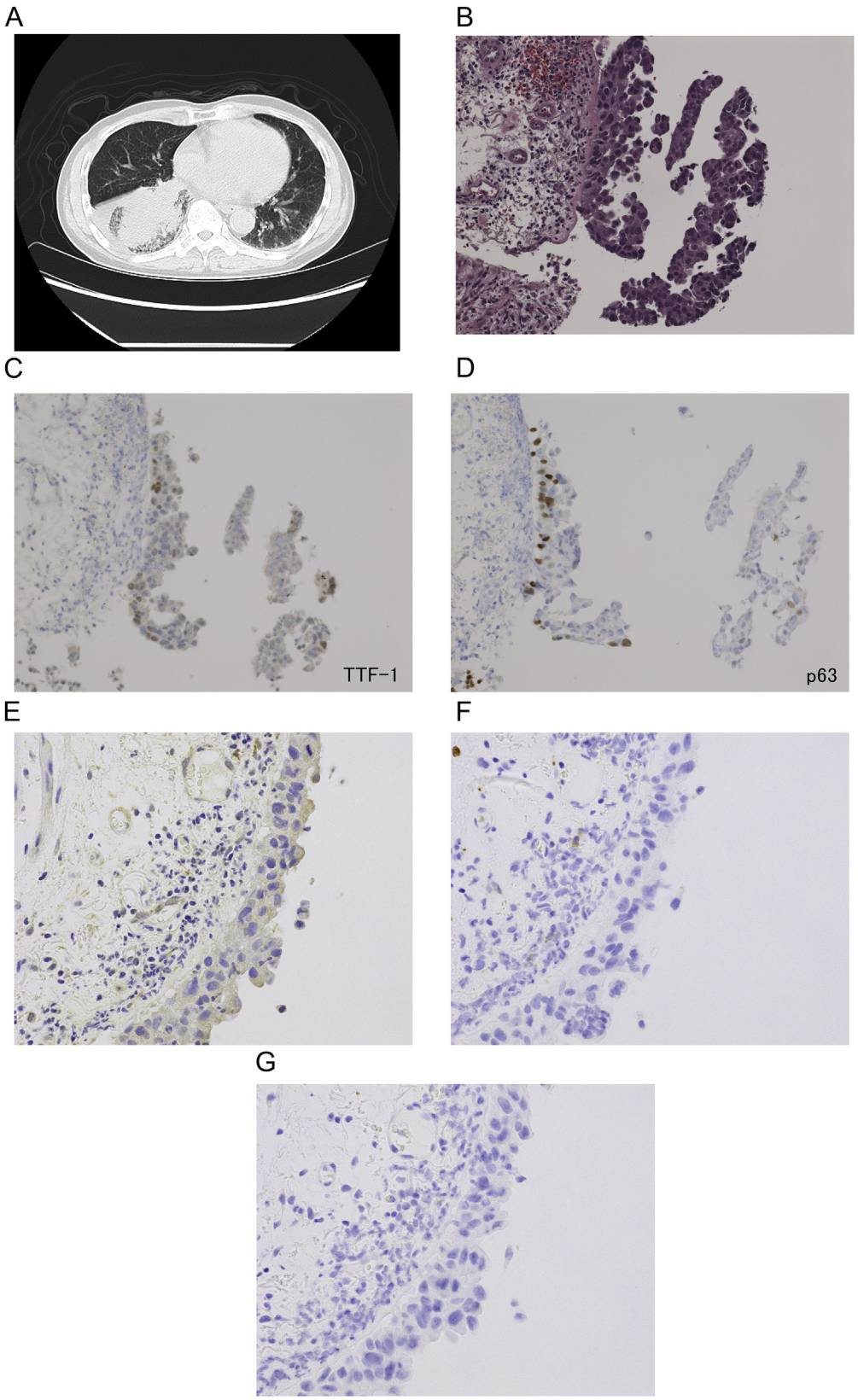

Fig. 1. A: Computed tomography scan shows a mass in the lower lobe of the right lung, accompanied by small subpleural nodules and right pleural effusion. Fig. 1B–D: Initial biopsy specimens showing malignant cells with anisokaryosis and hyper chromatic nuclei (B, hematoxylin and eosin [H&E] staining × 200). Immunohistopathological analysis demonstrated weakly positive staining for thyroid transcription factor 1 (TTF-1) (C, × 200) and p63 (D, × 200), which suggested non-small cell lung cancer with unclear differentiation. Fig. 1E–G: Immunohistopathological analysis demonstrated negative staining for neuron specific enolase (NSE) (E, × 400), CD56 (F, × 400) and synaptophysin (G, × 400).

been reported. Here, we describe a rare case of SCLC transformation from NSCLC without EGFR mutation during immunotherapy with nivolumab.

2. Case presentation

A 75-year-old man with a 50 pack-year history of smoking and a 4-year history of chronic cough was referred to our hospital following an abnormal shadow on a chest computed tomography (CT) scan in February 2016. The CT scan showed a mass 64 mm in diameter, located in the lower lobe of the right lung, accompanied by small sub-pleural nodules and right pleural effusion (Fig. 1A). A bronchoscopy was performed, and pathology from a transbrachial lung biopsy revealed a poorly differentiated NSCLC (Fig. 1B–D). No immunohistopathological findings of SCLC were detected in the initial dissected specimens (Fig. 1E–G). Serum tumor marker levels were carcinoembryonic antigen (CEA) 17.5 ng/mL; Sialyl-Lewis X (SLX) 68.2 U/mL; pro-gastrin-releasing peptide (pro-GRP) 299.4 pg/mL; and neuron-specific enolase (NSE) 14.2 ng/mL. No mutations were identified in EGFR, and anaplastic lymphoma kinase (ALK) translocation was found to be negative using fluorescent immunohistochemical assay. Positron emission tomography (PET)-CT scan and enhanced brain magnetic resonance imaging (MRI) revealed pleural dissemination, enlarged mediastinal lymph nodes, but no other metastatic lesions. NSCLC (cT3N3M1a, stage IV) was clinically diagnosed based on these findings. Participation in a clinical trial investigating the combination of docetaxel and bevacizumab was offered to the patient, to which he consented. This combination was assigned as the first-line chemotherapy regimen, which was administered in April 2016. Following two cycles of chemotherapy, a CT scan revealed partial response and tumor markers gradually decreased (CEA 3.0 ng/mL; SLX 32.9 U/mL); however, the following month he presented to our emergency department complaining of abdominal pain. He was diagnosed with sigmoid colon perforation and underwent an emergency sigmoid colon resection. As gastrointestinal perforations are a rare, but well-known adverse event associated with bevacizumab treatment, we thought that this event occurred because of bevacizumab. After this serious adverse event, we judged that continuation of cytotoxic chemotherapy was no longer recommended. During a careful follow-up period, the disease gradually progressed and tumor markers remained on the same level (CEA 3.7ng/mL; SLX28.3 U/mL), and immunotherapy using nivolumab was selected as the second-line regimen in August 2016. The tumor continued to progress despite three cycles of nivolumab, and additionally the right pleural effusion increased, and some subcutaneous tumors emerged. Cytopathologic examination of the pleural fluid revealed SCLC. Moreover, SCLC was also identified in a biopsy from a subcutaneous tumor of the right chest, with positive immunohistochemical staining for CD56, synaptophysin and TTF-1, and negative staining for PD-L1 (Fig. 2A–D). Serum tumor markers of SCLC were elevated (NSE 117.6 ng/mL and pro-GRP 5157.5 pg/mL). From these results, we diagnosed that the patient's tumor had transformed from NSCLC to SCLC. Amurubicin was administered as the third line regimen, predominately for alleviation of symptoms, but his respiratory condition deteriorated and he died in October 2016.

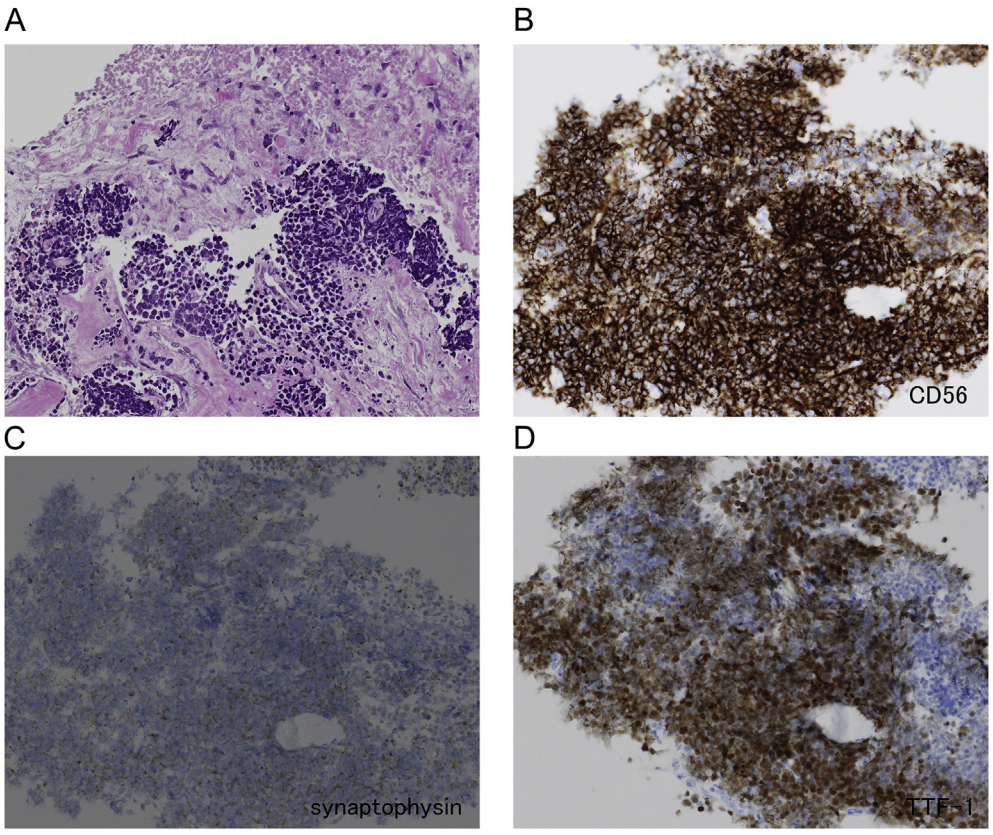

Fig. 2. Second biopsy specimens showing malignant cells with diffuse proliferation of small-sized broken cells with scant cytoplasm and hyper chromatic nuclei (A, H&E staining × 200). Immunohistopathological analysis demonstrated positive staining for CD56 (B, × 200), synaptophysin (C, × 200), and TTF-1 (D, × 200), which suggested small cell lung cancer.

3. Discussion

This case suggests that initiation of nivolumab caused the transformation from NSCLC to SCLC. As far as we know, this is the first case reporting the possibility of SCLC transformation due to the immunotherapy with nivolumab.

The precise mechanism of tumor transformation in this case is not clear, and two kinds of transformation mechanisms are proposed. One hypothesis is that the initial tumors consisted of both NSCLC and SCLC. As the number of NSCLC cells decreased owing to the chemotherapy with docetaxel and bevacizumab, the SCLC component of initial tumor became dominant. This mechanism is also suggested in case of transformations of EGFR-mutant adenocarcinoma. It has been reported that approximately 2% of SCLC tumors contain histological NSCLC components [9]. In our case, the serum tumor marker pro-GRP was slightly elevated at 299.4 pg/mL upon referral to our hospital. Considering the elevation of pro-GRP, as well as CEA and SLX, it is likely that the tumor consisted of both NSCLC and SCLC components initially, but the SCLC component might have been too insufficient to detect pathologically in the initial sample from the transbronchial lung biopsy. Negative immunohistochemial staining of NSE, CD56 and synaptophysin on the initial biopsy specimens (Fig. 1E–G) also supported this result.

The alternate hypothesis is that NSCLC cells underwent histological transformation to SCLC cells owing to nivolumab. The mechanism for this is unclear, but some previous reports support this hypothesis. In previous reports of SCLC transformation in EGFR-mutant adenocarcinoma, each transformed SCLC tissue exhibited the same EGFR-mutation as detected in adenocarcinoma [3,8,10]. Oser et al. suggested the existence of common tumor stem cells that have potential to differentiate into either SCLC or NSCLC [5]. Although the potential mechanism for this tumor transformation due to treatment with nivolumab is unknown, the possibility cannot be excluded.

Additionally, the effect of the first-line regimen on tumor transformation must be considered. We think that the transformation was less influenced by docetaxel and bevacizumab than nivolumab for three reasons. First, the cancer responded to these drugs, and was not likely to acquire resistance to them. The tumor size was smaller in CT scans after the first-line chemotherapy. Serum tumor markers also decreased according to chemotherapy. Second, there was a sufficient period from the last time administration of the first-line drugs to the second-line treatment; it was long enough to insulate their influence. Third, although docetaxel has been used for approximately 20 years, there have been no reports of docetaxel causing SCLC transformation. For these reasons, it is likely that tumor transformation was triggered by nivolumab rather than docetaxel or bevacizumab.

In conclusion, we report a case of NSCLC that transformed to SCLC during the immunotherapy with nivolumab. The possibility of tumor transformation should be considered when treating NSCLC with nivolumab, as well as when treating EGFR-mutant adenocarcinoma with EGFR-TKI.

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Conflict of interest

We have no conflicts of interest to declare.

Ethical approval

Our institution does not require institutional ethical approval for case reports. This submission was approved by the patient relatives. We obtained written consent from the patient and his relatives.

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