A Malignant Tumor Developed Seven Years After Small Cell Lung Cancer Treated With Etoposide-containing Chemotherapy

SHINICHIRO OKAUCHI1, SOU HATTORI1, GEN OHARA1, NORIO TAKAYASHIKI2 and HIROAKI SATOH1

Divisions of 1Respiratory Medicine, and 2Pathology, Mito Medical Center, University of Tsukuba, Mito, Japan

Abstract. Background/Aim: Long-term survival of patients with small cell lung cancer (SCLC) is rare, and, to the best of our knowledge, there has been no SCLC patient who developed second malignancy after long-term survival. Case Report: A 66-year-old woman with a history of smoking was admitted to our hospital with a nodule in her right lung. She was diagnosed with cT2aN3M0 localized-SCLC. Chest irradiation and chemotherapy including etoposide was performed. A new nodule appeared in the right lung more than 7 years after the end of treatment for SCLC. A specimen obtained by bronchoscopic biopsy was pathologically confirmed to be a non-SCLC malignancy. Conclusion: There is a possibility of tumor development associated with etoposide, which is known to be carcinogenic, or residual tumor development from combined type SCLC. We could not confirm whether it was second malignancy or recurrence after long-term interval. The number of long-term survivors of SCLC is likely to increase in the future. The clinical course of this patient is interesting from the perspective of long-term survival of SCLC patients and might have implications for the treatment of patients with similar clinical course in the future.

Although it is difficult to obtain long-term control for small cell lung cancer (SCLC), expectations for cure are increasing due to the development of multidisciplinary therapies such as chemoradiotherapy and the addition of immune checkpoint inhibitors to the treatment (1, 2). Among the chemotherapeutic drugs for SCLC, etoposide, a topoisomerase type I antitumor drug, is still considered to be a key antitumor drug (1, 2). However, etoposide is evaluated to have a high incidence of secondary hematological malignancies (3, 4). With SCLC treatment, the carcinogenicity of etoposide has not been an issue because there had been no long-term survivors, but it may become a problem if the prognosis improves in the future. In addition, transformation to SCLC after treatment for non-small cell lung cancer (NSCLC) has been reported (5-7). However, this transformation was observed in NSCLC patients treated with EGFR-TKI, ALK-TKI, or ICI (5-7).

We report herein a patient who developed non-SCLC malignancy after 7 years disease-free interval from the initiation of etoposide-containing chemotherapy. Regarding the development of the second malignancy other than SCLC in our patient, there was a possibility of secondary carcinogenesis due to etoposide, transformation from SCLC to other malignant tumor, or recurrence after a long period of time from residual components other than SCLC.

Case Report

A 66-year-old woman with a history of smoking 40 pack-years referred to our hospital due to abnormal opacities detected by chest radiograph taken at annual check-up in mass-screening. Physical examination was unremarkable. Chest radiography and CT scan revealed a mass in the right middle lobe with ipsilateral mediastinal lymph node swelling (Figure 1). A transbronchial biopsy of the lesion in the right middle lobe revealed small-sized tumor of cells possessing minimal cytoplasm and hyperchromatic indistinct nuclei with abnormal mitosis. Immunohistochemical staining for CD56 and synaptophysin was positive (Figure 2). Imaging studies including brain magnetic resonance imaging (MRI), abdominal computed tomography (CT), and bone scan revealed no distant metastasis. Together with histopathological findings, the patient was diagnosed as having limited disease (LD)-SCLC. She was treated with 6 courses of chemotherapy with carboplatin and
etoposide and 45 Gy irradiation to the primary lesion and mediastinum. The response to the chemotherapy was evaluated as complete response. Thereafter, the presence or absence of recurrence was monitored by periodic image evaluation, but there was no recurrence for more than 7 years. Chest CT performed 7 years and 7 months after the end of SCLC treatment revealed small nodules in both lungs and swelling of the lymph nodes in the ipsilateral mediastinum (Figure 3).

An endobronchial ultrasound-guided transbronchial needle aspiration from the nodule revealed that it was a malignant tumor other than SCLC. The results of immunostaining of the tumor were as follows: positive for vimentin and CD68, negative for thyroid transcription factor-1, pancytokeratin, CD56, synaptophysin, chromogranin A, S-100, desmin, and alpha-SMA. Proliferation of giant cells with histiocytic traits was confirmed (Figure 4). Chemotherapy with carboplatin and etoposide, and then with carboplatin and paclitaxel were administered, and good response was obtained. Therefore, she received supportive care. Two years after diagnosis, the patient died of the non-SCLC malignancy.

This study was approved by the institutional ethics committee of our institute (NO16-66). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Discussion

In recent years, multidisciplinary therapies have increased the number of long-term survivors of SCLC (8-10). Factors such as low tumor volume, localized lesions in the thorax, and good response to first-line treatment are important for long-term survival of SCLC patients (11, 12). Good nutrition and no systemic inflammation at the start of treatment are also considered prognostic factors (13). Immune checkpoint inhibitors (ICIs) can also be administered, and further improvement in prognosis is expected (14). As a chemotherapeutic agent to be used in combination with ICI, etoposide has been one of the key drugs for treatment of SCLC (1, 2). Although etoposide still has been a key drug for SCLC, cases of secondary carcinogenesis have been reported (4). In addition, secondary malignancies after administration of etoposide for the treatment of pediatric malignancies have been reported (3, 4). Recently, in contrast, changes from EGFR and ALK mutation-positive NSCLC to SCLC after TKI treatment have been reported (5, 6). Similar transformation has also been reported in patients treated with immune checkpoint inhibitors (7). However, there has been no report of transformation of SCLC into other malignancies. The present patient with SCLC, who had been treated with etoposide-

Figure 1. Chest computed tomography scan taken at the time of reference revealed a mass in the right middle lobe with ipsilateral mediastinal lymph node swelling.

Figure 2. Biopsy specimens from the nodule in the right lung obtained by fiberoptic bronchoscopy revealed a small-sized tumor with cells possessing minimal cytoplasm and hyperchromatic indistinct nucleoli with abnormal mitosis (A: H-E staining). Immunohistochemical staining for CD56 (B) and synaptophysin (C) are positive.
containing chemotherapy, developed malignant tumor derived from histiocytes after a 7-year disease free period.

It is well known that the majority of patients with SCLC smoke. Therefore, when a malignant tumor of the lung develops in SCLC patients at different times, it might be necessary to consider the effects of smoking more than etoposide treatment. There are few SCLC patients who have survived for a long time at this time, so it is not a clinical problem, but it might be a problem in the future. To our best knowledge, some reports of lung cancer developed after long-term SCLC control were found (8, 10). Ishibashi et al. reported an SCLC patient with three malignant diseases 5 years after etoposide administration to SCLC (8). In this patient, there might be a possibility of development of second malignancy after etoposide therapy, or recurrence from non-SCLC components mixed in SCLC. Al-Ajam et al. presented a case of a patient with a 10-year disease-free survival between two diagnoses of SCLC (10). This patient had LD-SCLC at the time of the initial diagnosis, but did not receive etoposide (10). In that patient, the possibility of SCLC recurrence and that of second SCLC might be considered. In our patient, it was not clear whether the non-SCLC malignancy should be considered as a second malignancy developed after etoposide treatment. It can be envisioned that SCLS changes to other malignancies after long-term management. It could not be ruled out that original malignancies mixed with SCLC regrew after a long management period. At present, ICIs are already available for ED-SCLC, and transformation of SCLC into other carcinomas might be reported in the future.

**Conclusion**

We reported this case as a clinical experience that gives suggestions for the treatment of cases that may have a similar course in the future. The accumulation of cases and the development of biological approaches are awaited.

**Conflicts of Interest**

The Authors have no conflicts of interest to declare in relation to this study.

**Authors’ Contributions**

SO and HS designed the study. SO, SH, GO, NT and HS collected the data. SO and HS analyzed the data and prepared the manuscript. All Authors approved the final version of the article.
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