CANCER DIAGNOSIS & PROGNOSIS
2: 716-719 (2022) doi: 10.21873/cdp.10166

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

SHINICHIRO OKAUCHI[1], SOU HATTORI[1], GEN OHARA[1], NORIO TAKAYASHIKI[2] and HIROAKI SATOH[1]

Divisions of [1]Respiratory Medicine, and [2]Pathology, 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 nucleoli 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

Correspondence to: Hiroaki Satoh, MD, Ph.D., Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Miya-machi 3-2-7, Mito-city, Ibaraki, 310-0015, Japan. Tel: +81 292312371, Fax: +81 292215371, e-mail: hirosato@md.tsukuba.ac.jp

Key Words: Etoposide, small cell lung cancer, second malignancy, recurrence, chemotherapy.

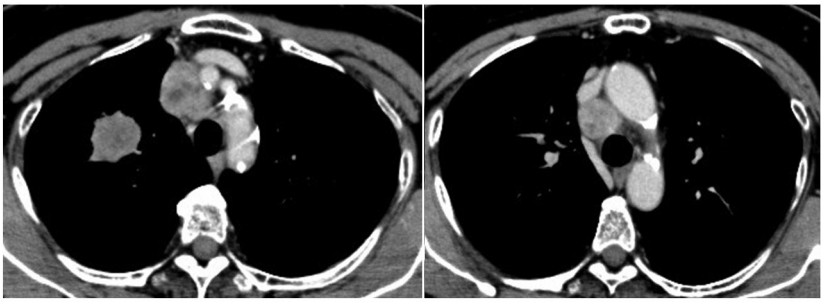

Figure 1. *Chest computed tomography scan taken at the time of reference revealed a mass in the right middle lobe with ipsilateral mediastinal lymph node swelling.*

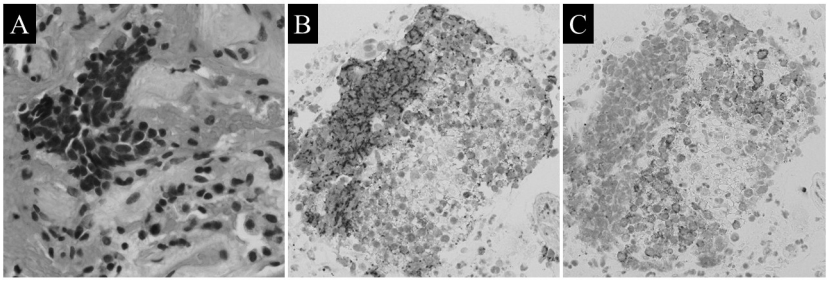

Figure 2. *Biopsy specimens from the nodule in the right lung obtained by fiberoptic bronchoscopy revealed a small-sized tumor with cells possessing minimal cytoplasm and hyperchromatic indistinct nucleoli with abnormal mitosis (A: H-E staining), Immunohistochemical staining for CD56 (B) and synaptophysin (C) are positive.*

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-

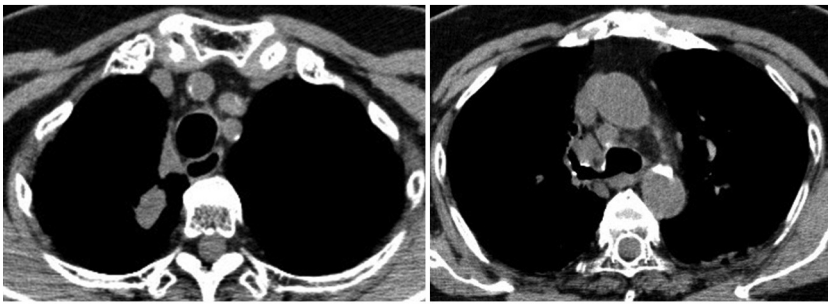

Figure 3. *Chest computed tomography taken 7 years and 7 months after the start of small cell lung carcinoma treatment revealed small nodules in both lungs and swelling of the lymph nodes in the ipsilateral mediastinum.*

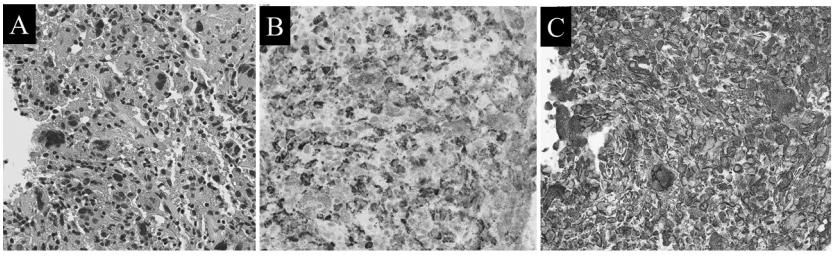

Figure 4. *Biopsy specimens taken 7 years and 7 months after the start of small cell lung carcinoma treatment from the nodule in the right lung (A: HE staining). Positive staining for CD68 (C) and vimentin (B). Proliferation of giant cells with histiocytic traits was confirmed.*

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 a10-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.

References

1 Reddy HG, Qin A and Kalemkerian GP: Emerging drugs for small cell lung cancer: a focused review on immune checkpoint inhibitors. Expert Opin Emerg Drugs *25(3)*: 353-366, 2020. PMID: 32683991. DOI: 10.1080/14728214.2020.1798929

2 Remon J, Passiglia F, Ahn MJ, Barlesi F, Forde PM, Garon EB, Gettinger S, Goldberg SB, Herbst RS, Horn L, Kubota K, Lu S, Mezquita L, Paz-Ares L, Popat S, Schalper KA, Skoulidis F, Reck M, Adjei AA and Scagliotti GV: Immune checkpoint inhibitors in thoracic malignancies: review of the existing evidence by an IASLC expert panel and recommendations. J Thorac Oncol *15(6)*: 914-947, 2020. PMID: 32179179. DOI: 10.1016/j.jtho.2020.03.006

3 Sneha LM, Arockia J, Suman FR and Khethan V: Secondary acute myeloid leukemia in a child treated for retinoblastoma: A case report with review of literature. J Family Med Prim Care *9(11)*: 5796-5798, 2020. PMID: 33532438. DOI: 10.4103/jfmpc.jfmpc_1538_20

4 Pendleton M, Lindsey RH Jr, Felix CA, Grimwade D and Osheroff N: Topoisomerase II and leukemia. Ann N Y Acad Sci *1310*: 98-110, 2014. PMID: 24495080. DOI: 10.1111/nyas.12358

5 Zhang K and Yuan Q: Current mechanism of acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors and updated therapy strategies in human nonsmall cell lung cancer. J Cancer Res Ther *12(Supplement)*: C131-C137, 2016. PMID: 28230005. DOI: 10.4103/0973-1482.200613

6 Kondoh C, Horio Y, Hayashi Y, Ebi H, Hida T, Hasegawa Y and Yatabe Y: Anaplastic lymphoma kinase expression in small-cell lung cancer. Histopathology *75(1)*: 20-28, 2019. PMID: 30790327. DOI: 10.1111/his.13842

7 Bar J, Ofek E, Barshack I, Gottfried T, Zadok O, Kamer I, Urban D, Perelman M and Onn A: Transformation to small cell lung cancer as a mechanism of resistance to immunotherapy in non-small cell lung cancer. Lung Cancer *138*: 109-115, 2019. PMID: 31683093. DOI: 10.1016/j.lungcan.2019.09.025

8 Ishibashi Y, Tokuchi Y, Kamachi M, Harada M and Isobe H: A case of a long-term survivor of small cell lung cancer developing triple second primary malignancies. Haigan *42(2)*: 129-133, 2002.

9 Tartarone A, Lerose R, Ardito R, Troiani L, Tedesco B, Bozza G, Cangiano R and Aieta M: Long-term survival in small cell lung cancer: a case report and review of the literature. Future Oncol *10(4)*: 523-528, 2014. PMID: 24754583. DOI: 10.2217/fon.13.213

10 Al-Ajam M, Seymour A, Mooty M and Leaf A: Ten years of disease-free survival between two diagnoses of small-cell lung cancer: a case report and a literature review. Med Oncol *22(1)*: 89-97, 2005. PMID: 15750201. DOI: 10.1385/MO:22:1:089

11 He Y, Song L, Wang H, Chen P, Liu Y, Sun H, Li X, Dang S, Liu G, Liu X, Chen S, Zhang X, Hofman P, Uchino J, Park HS, Pacheco JM, Tabbò F, Xu M, Dai J, He K, Yang Y, Zhou C and written on behalf of the AME Lung Cancer Collaborative Group: Mutational profile evaluates response and survival to first-line chemotherapy in lung cancer. Adv Sci (Weinh) *8(4)*: 2003263, 2020. PMID: 33643802. DOI: 10.1002/advs.202003263

12 Kalemkerian GP: Small cell lung cancer. Semin Respir Crit Care Med *37(5)*: 783-796, 2016. PMID: 27732999. DOI: 10.1055/s-0036-1592116

13 Kurishima K, Watanabe H, Ishikawa H, Satoh H and Hizawa N: Modified glasgow prognostic score in patients with small-cell lung cancer. Mol Clin Oncol *7(1)*: 121-124, 2017. PMID: 28685088. DOI: 10.3892/mco.2017.1261

14 Bianco A, D'Agnano V, Matera MG, Della Gravara L, Perrotta F and Rocco D: Immune checkpoint inhibitors: a new landscape for extensive stage small cell lung cancer treatment. Expert Rev Respir Med *15(11)*: 1415-1425, 2021. PMID: 34374626. DOI: 10.1080/17476348.2021.1964362

Received August 14, 2022
Revised September 5, 2022
Accepted September 6, 2022