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【 CASE REPORT 】

Secondary Brain Neoplasm after Stereotactic Radiosurgery in Patients with Metastatic Non-small Cell Lung Cancer

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Abstract:
Stereotactic radiosurgery (SRS) using the Gamma Knife (GK) is now being increasingly utilized for the treatment of brain metastases. However, there are a few reported cases of SRS-induced brain neoplasms. We herein report the case of a Japanese woman with metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor (EGFR)-mutations who was treated four times with a GK for brain metastases. She developed glioblastoma 5.7 years after the initial GK surgery. Radiation-induced secondary neoplasms generally appear after a latency period of several years. Advances in cancer therapy have improved the survival of patients with NSCLC, providing enough time for secondary neoplasms to appear after SRS.

Key words: non-small cell lung cancer, stereotactic radiosurgery, brain metastases, radiosurgery induced brain neoplasm

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Introduction

New molecular targeted agents for lung cancer have recently been developed such as the epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI) and anaplastic lymphoma kinase (ALK) inhibitor. These agents have shown dramatic antitumor effects in patients with specific driver mutations. Though these agents have helped to increase patient survival, a worsening of brain metastases will sometimes occur while keeping the extracranial disease under control. Radiation therapy plays a critical role in such situations, especially, stereotactic radiosurgery (SRS) using a Gamma Knife (GK), which is being increasingly utilized for the treatment of a limited number of brain metastases. SRS has been shown to achieve excellent local tumor control and it is considered to be a relatively safe procedure. However, there are a few reported cases of SRS-induced brain neoplasms. We herein present a case of glioblastoma, which developed after multiple rounds of GK treatment for brain metastases in a patient with non-small cell lung cancer (NSCLC), which was successfully treated by surgery.

Case Report

A 66-year-old Japanese woman who was a non-smoker was diagnosed with stage 4, EGFR exon21 L858R mutation-positive NSCLC with a right upper lobe tumor and malignant pleural effusion in May 2007. She was treated with gefitinib for 14 months as the first-line treatment, followed by four cycles of carboplatin and docetaxel as a second-line treatment, and then underwent a rechallenge with gefitinib as the third-line treatment. After two months of the gefitinib rechallenge, magnetic resonance imaging (MRI) of her brain showed brain metastases in the right cerebellum and the right temporal lobe. She underwent GK treatment for these lesions for the first time in January 2010 followed by gemcitabine and vinorelbine as a fourth-line treatment for a total of 13 cycles (Fig. 1A). In May 2013, she underwent radiotherapy for the local control of a residual upper right lobe lesion of the lung, after which the extracranial lesions had elapsed without recurrence. From July 2014 to May 2015, GK treatment was performed thrice for cerebellar lesions that repeatedly recurred (Fig. 1B-D). How-

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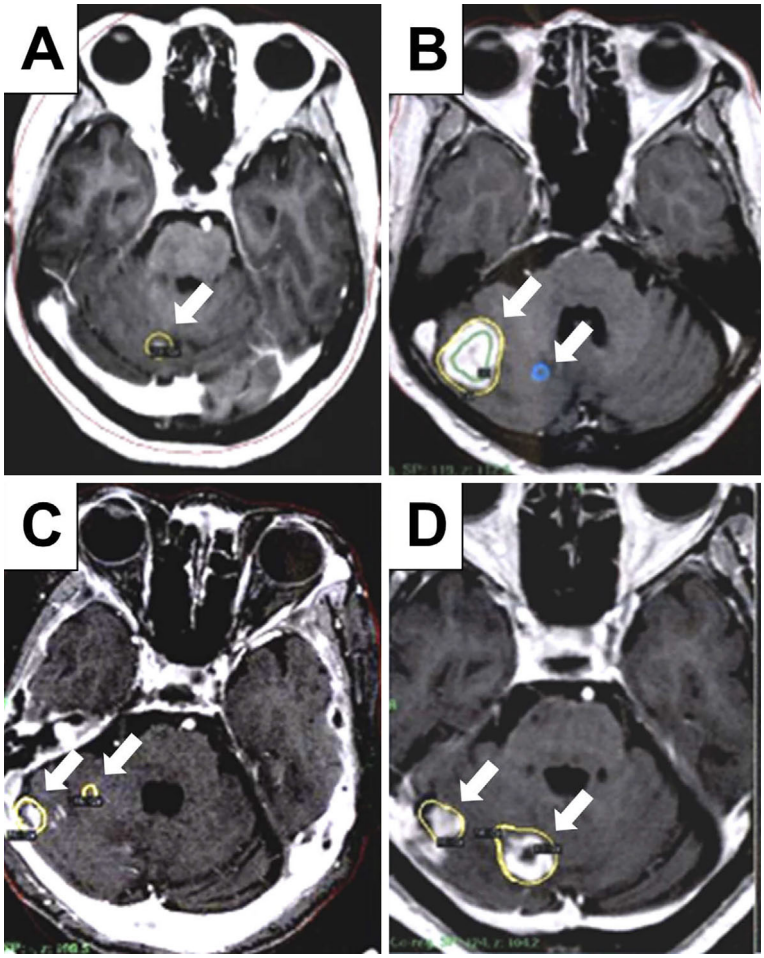

Figure 1. **Axial MRIs of the brain. The irradiation site is indicated by the arrow. (A) The first lesion was irradiated with 16 Gy administered to the 50% isodose line in January 2010. (B) The second lesion was irradiated with 16 Gy administered to the 50% isodose line in July 2014. (C) The third lesion was irradiated with 16 Gy administered to the 50% isodose line in February 2015. (D) The fourth lesion was irradiated with 16-18 Gy administered to the 50% isodose line in May 2015.**

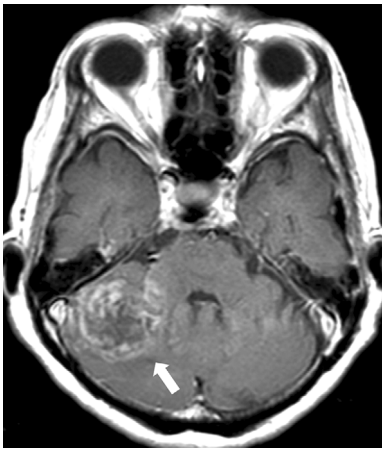

Figure 2. **A gadolinium MRI scan 5.7 years after the initial GK treatment demonstrating a tumor with peripheral enhancement and central necrosis in the cerebellum. The tumor location is indicated by the arrow.**

ever, as multiple cerebellar lesions appeared and treatment with a GK became difficult, she was given erlotinib from July 2015. After one month on erlotinib, she developed nausea and general malaise. Although there were no changes in most of the multiple cerebellar lesions on MRI, one of these lesions grew rapidly (Fig. 2). Whole-body computed tomography (CT) showed no evidence of recurrence. Because the brain stem was pressed by the right cerebellar lesion, she underwent surgical resection. A histological examination of this specimen demonstrated glioblastoma with no evidence of brain metastasis (Fig. 3). She started adjuvant oral temozolomide with radiotherapy for glioblastoma. The residual cerebellar lesions were located within the irradiation field. Therefore, these lesions disappeared after postoperative radiotherapy. She is still alive 22 months after diagnosis of glioblastoma without a recurrence of NSCLC.

Discussion

Brain metastases are a common and lethal complication of NSCLC. Approximately 25% to 40% of patients with NSCLC will develop brain metastases during the course of their disease (1). The frequency of metastatic brain tumors

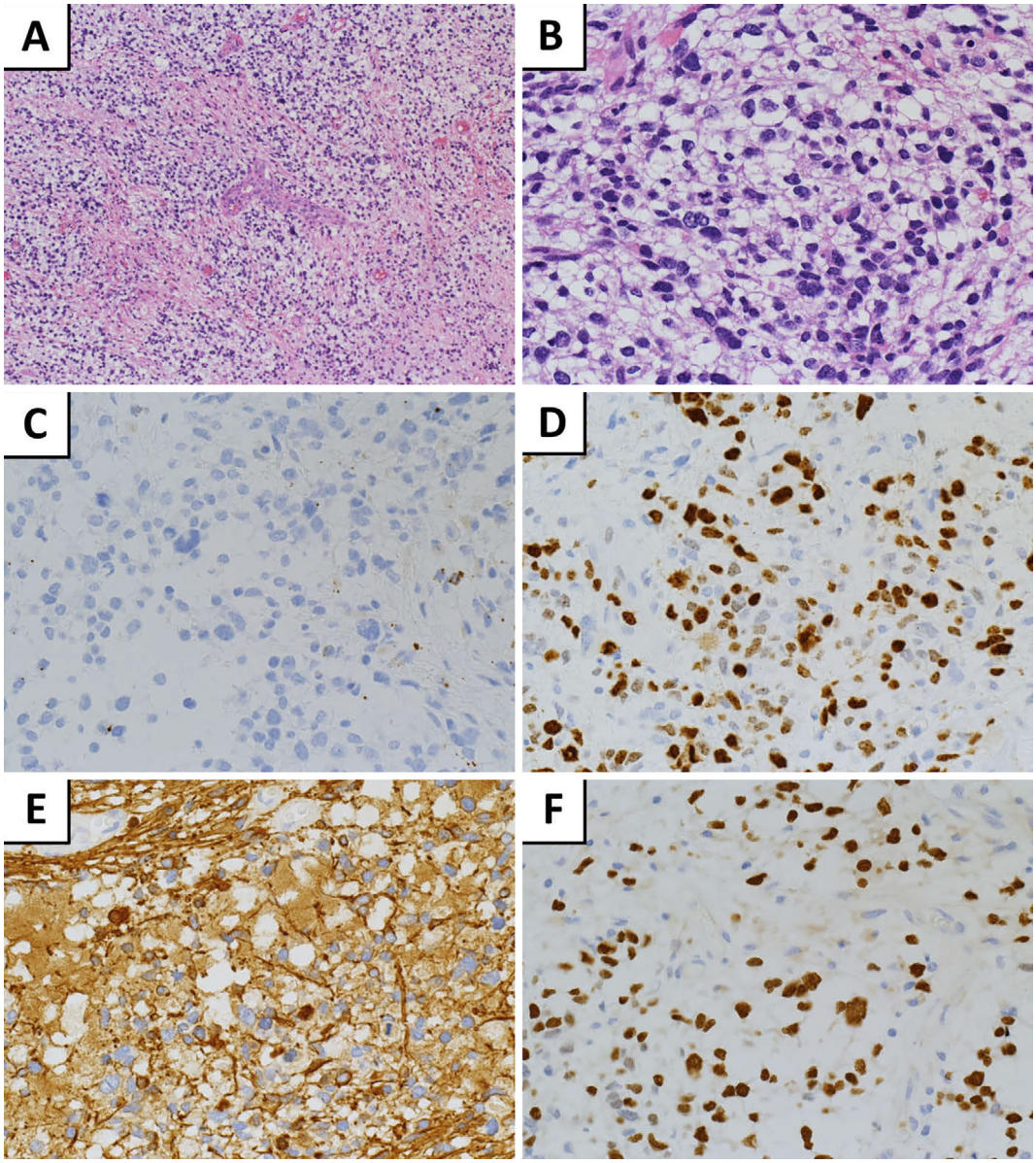

Figure 3. **Histopathology of the brain tumor demonstrating glioblastoma. (A) Hematoxylin and Eosin (H&E) staining at 10×magnification. (B) H&E staining at 40×magnification. (C) Keratin staining at 40×magnification. (D) Ki-67 staining at 40×magnification. The molecular immunology Borstel-1 (MIB-1) proliferation index was found to be 50%. (E) GFAP staining at 40×magnification. (F) Olig2 staining at 40×magnification.**

being diagnosed seems to be increasing because of patients living longer as a result of effective systemic therapies (2). Especially, the development of molecular targeted therapies has significantly improved the prognosis of patients with NSCLC harboring specific driver oncogenes including EGFR-mutations. The 5-year survival among EGFR-mutant metastatic lung adenocarcinoma patients treated with an EGFR-TKI has improved to 14.6%, in contrast to the <5% that was previously reported for unselected metastatic patients with NSCLC treated with chemotherapy and not exposed to an EGFR-TKI (3). However, patients often experience a worsening of brain metastases while their extracranial disease remains under control thanks to the administration of systemic therapies (4). The prolonged survival of patients due to controlled extracranial disease makes it even more important to manage the brain metastases. In these situations, SRS using GK is widely used for the control of brain metastases and it has been shown to achieve excellent local tumor control. The local tumor control with SRS in patients with NSCLC has been reported to consistently exceed 80% (5, 6); therefore, its use for brain metastases has increased significantly since the turn of the century (7). SRS is generally considered a relatively safe procedure because it allows the delivery of high doses of radiation with high precision to treat brain metastasis with having a minimal effect on the surrounding normal tissue. However, as a late complication of brain radiotherapy, secondary neoplasms, including glioblastomas, have been reported (8-16). It has been es-

Table. Reported Cases and Present Case of SRS-induced Secondary Neoplasm Which Occurred from the Site of Metastatic Brain Tumor.

Patient	Primary	Modality	Secondary neoplasm	Location	Latency period	Reference
37 F	Melanoma	Gamma Knife	Glioblastoma	Cerebellum	5.3 years	(9)
43 F	RCC	Cyber Knife	High-grade astrocytoma (probably glioblastoma)	Cerebellum	4.5 years	(10)
66 F	NSCLC	Gamma Knife	Glioblastoma	Cerebellum	5.7 years	Present case

F: female, RCC: renal cell carcinoma, NSCLC: non-small cell lung cancer

tablished that exposure to radiation can cause DNA damage-inducing oncogenic mutations (11). Experimental studies have shown that low nonlethal-dose radiation is more carcinogenic than higher dose radiation (17). Although the influence of SRS on the normal tissue surrounding brain metastases is very low, it can still cause carcinogenesis. Cahan's criteria are widely used for diagnosing secondary neoplasms due to radiation exposure. Cahan's criteria include: 1) the second tumor must occur within the field of radiation, 2) a latency period is required between exposure to radiation and development of the second tumor, 3) the histology of the second tumor must be unique and different from the original tumor, and 4) the patient cannot have a genetic syndrome that causes multiple primary cancers (18). In our case, the glioblastoma occurred within the irradiation field of the GK (Fig. 1, 2), and the patient was diagnosed with glioblastoma 5.7 years after her initial GK surgery. However, the possibility that the glioblastoma was a concurrence with NSCLC must also be considered. Previous studies have reported that only 0.4-3.4% of all glioblastomas occur in the cerebellum, while the majority of them occur in the cerebral hemispheres (19, 20). Because her glioblastoma occurred in an atypical location, the concurrence of NSCLC and primary cerebellum glioblastoma is unlikely. In addition, she had no family history of genetic syndromes. For these reasons, although no histological information was obtained before irradiation, this patient was diagnosed with GK-induced glioblastoma. There are two reported cases of SRS-induced secondary neoplasms, which occurred at the site of a metastatic brain tumor (Table). This case is the first report showing a secondary brain neoplasm after stereotactic radiosurgery for metastatic NSCLC. The mean latency period before the development of an SRS-induced neoplasm is reported to be 7.9 years (range 0.7-19 years) (8). Therefore, primary lesions before SRS are mostly benign diseases with a good prognosis; more than half of the cases had an initial diagnosis of vestibular schwannoma (8). However, advances in cancer therapy have so dramatically improved the survival of patients with NSCLC that there is now a sufficient amount of time for secondary neoplasms to occur after SRS. As in our patient, Kempf et al. reported a case of a metastatic EGFR-mutated lung adenocarcinoma patient who achieved a prolonged survival of 10 years through various therapies including EGFR-TKI and local therapy (21). The risk of radiation-induced neoplasms after SRS is very low. The incidence rates of secondary neoplasms induced by SRS and conventional fractionated radiotherapy are estimated to be 0.04-2.6% at 15 years and 1-3% at 10-20 years, respectively (8, 22). The incidence of SRS-induced neoplasms may be lower than that observed with conventional fractionated radiotherapy. However, optimal treatments for metastatic brain tumors and secondary brain neoplasms differ greatly. Therefore, it is important for clinicians to follow up such patients while keeping the possibility of a secondary neoplasm in mind after SRS. In addition, brain metastases often recur repeatedly during the long-term treatment of NSCLC. In such cases, repeated SRS for recurrent brain metastases may increase the chances of a secondary neoplasm.

Conclusion

Due to the development of various new systemic therapies and the increasing utilization of SRS, more SRS-induced neoplasms may be identified in patients with NSCLC. Clinicians should therefore be careful to look for secondary neoplasms when a brain tumor reappears in patients with NSCLC after receiving SRS. An early diagnosis of secondary neoplasms can make it possible to administer the appropriate treatment in a timely manner to improve the patient's prognosis.

The authors state that they have no Conflict of Interest (COI).

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