CASE REPORT
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A Case of Adjuvant Treatment with Sorafenib after Radiotherapy for Brain Metastasis from Poorly Differentiated Thyroid Carcinoma

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Sorafenib is an emerging therapeutic option for radioactive iodine (RAI)-refractory differentiated thyroid carcinoma. However, the effects of sorafenib as an adjuvant treatment following surgery or radiation on brain metastases from poorly differentiated thyroid carcinoma (PDTC) have never been reported. A 52-year-old patient underwent total thyroidectomy for follicular thyroid carcinoma. Despite high-dose RAI therapy, a neck mass and lung metastases were developed. PDTC was diagnosed by neck mass removal. During adjuvant external beam radiation therapy (EBRT) to the neck, brain metastases developed. After palliative EBRT for brain metastases, the brain tumor size decreased but lung metastases markedly progressed. Off-label sorafenib was used to treat progressive multiple metastatic lesions. Over five months of sorafenib treatment, the sum of the longest diameters for target lesions was decreased by 45% in brain and 13% in lung. Sorafenib can be considered a new adjuvant therapeutic option for metastatic brain lesions from PDTC after EBRT.

Key Words: Thyroid carcinoma, Brain, Sorafenib

Introduction

Brain metastases occur in approximately 1% of all differentiated thyroid carcinoma (DTC). Despite a low overall incidence and an indolent nature, 4.5–18% of patients with distant metastases from thyroid carcinoma develop brain metastases, resulting in poor mean survival.[1)] As only relatively few cases have been described in the literature, management of patients with brain metastases of DTC origin is unclear.[2)] Poorly differentiated thyroid carcinoma (PDTC) has a propensity to metastasize distantly (36–85%), most commonly to the lung (14–54%) and bones (18–33%);[3)] however, incidence of brain metastases from PDTC has not been previously described. Patients with PDTC often have a high incidence of recurrence despite appropriate treatment. Although there have been multiple publications over the years, controversies regarding optimal management of these patients still exist.[4)]

Sorafenib is an oral, tyrosine kinase inhibitor of the RAF protein kinase receptor, VEGFR2 and PDGF-β and displays strong anti-angiogenic activity.[5)] Because DTC has been well documented to exhibit genetic alterations in the mitogen-activated protein kinase (MAPK) pathway, including BRAF mutations[6)] and VEGF overexpression,[7)] sorafenib has been proposed as a good candidate therapy for refractory DTC.[8)] We treated one patient with rapidly progressive PDTC metastases to brain with radiation therapy and sub-

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sequent adjuvant sorafenib. After five months of sorafenib treatment, the best overall response was progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The objective of this report is to highlight the comparable response of brain metastasis with pulmonary metastasis in a PDTC patient during sorafenib administration.

Case Report

A 52-year-old female patient with thyroid cancer was referred to our clinic for radioactive iodine (RAI) therapy. She had undergone total thyroidectomy in March 2010 at another hospital, and postoperative pathology showed a 4.5-cm follicular carcinoma with extracapsular and vascular invasion but no lymph node metastasis (0 of 14). After six days of high-dose (150 mCi) RAI therapy, only therapeutic dose of radioiodine trapped in remnant thyroid tissue in the anterior neck. In January 2011, six months after RAI therapy, the levels of thyroid stimulating hormone (TSH), thyroglobulin (Tg), and anti-thyroglobulin antibody (anti-Tg-Ab) were 0.34 (0.17-4.05) mIU/L, 32.37 (0.00-35.00) ng/mL, and 8.03 (0.00- 70.00) IU/mL, respectively. We reviewed the thyroid tissue from surgery at another hospital showed focal suspicious lesions with histopathology of poorly differentiated carcinoma. ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan demonstrated tumor recurrence in the left thyroid bed and extensive lung metastases. An anterior neck mass measuring 2.5 cm and multiple variable sized lung metastases were observed on neck and chest CT. Neck mass removal was performed in February 2011, and the histopathology of poorly differentiated insular-type thyroid cancer was supported by immunohistochemical staining: galectin-3 (-), Cd45RB (-), P53 (+), TTF-1 (+), pancytokeratin (+) (Fig. 1A, B).

After two weeks, she received adjuvant external beam radiation therapy (EBRT) to the neck with a total dose of 55 Gy over 22 days. She complained of progressive headache, nausea, and vomiting at the completion of EBRT. The levels of TSH, Tg, and anti-Tg-Ab were 0.05 mIU/L, 150.49 ng/mL, and 0.14 IU/mL, respectively. Brain magnetic resonance imaging (MRI) showed a 4.4-cm lesion in the right frontal lobe with another small metastatic nodule in the left parietal lobe (Fig. 2A). Chest CT showed increased size and number of multiple metastatic pulmonary nodules without mediastinal lymphadenopathy (Fig. 3A, C). In March 2011, she underwent EBRT for brain metastases with a total dose of 45 Gy over 22 days and her headache and nausea were much relieved.

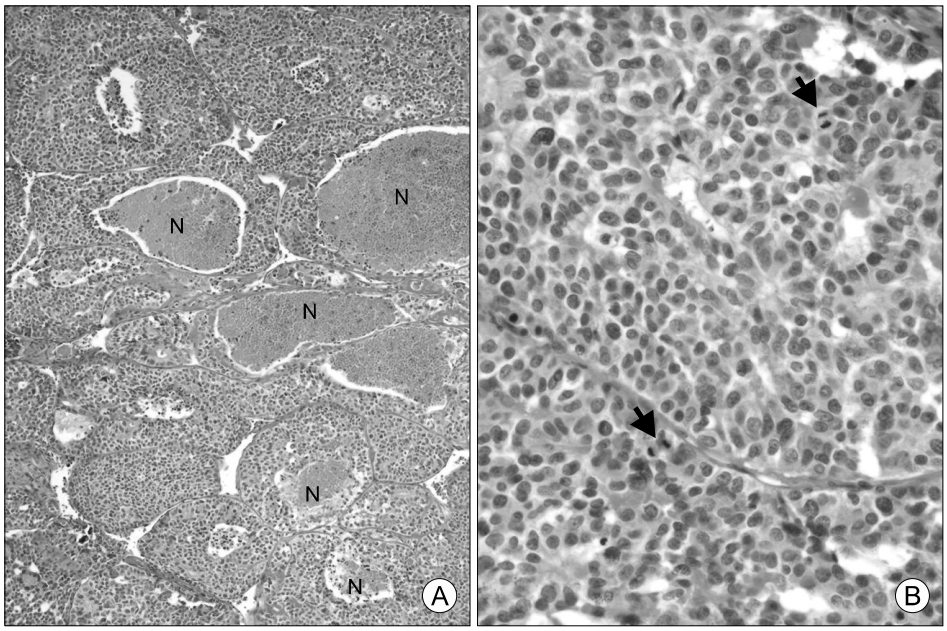

Fig. 1. Microscopic imaging of anterior neck mass. (A) The tumor shows a solid trabecular growth pattern and frequent necrosis (N) (H-E stain, ×40). (B) The tumor cells are monotonous and show small round nuclei with dark chromatin and frequent mitoses (arrows) (H-E stain, ×40).

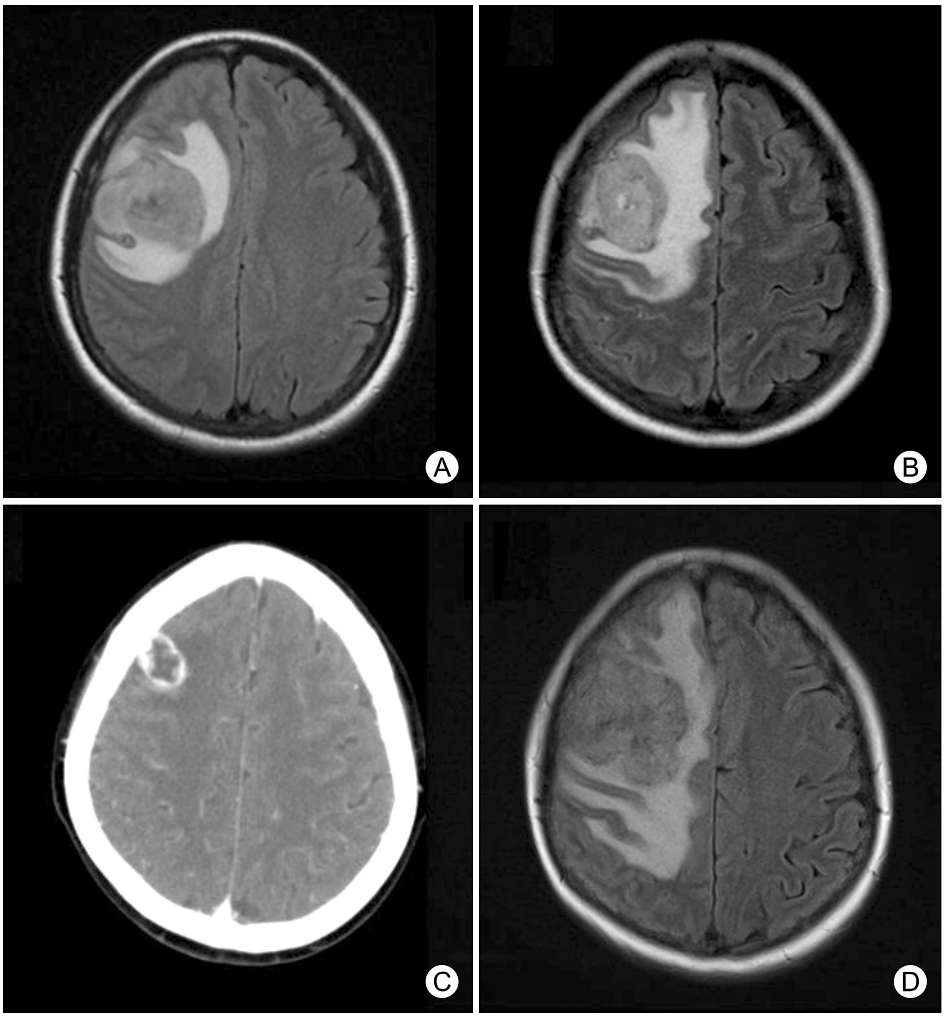

Fig. 2. Radiologic imaging of brain. (A) Brain metastases were diagnosed by MR imaging, showing a 3.8×4.4 cm mass with central necrosis in the right frontal lobe. (B) Shortly after EBRT for brain metastases. The dimensions of the mass had decreased to 3.8×2.7 cm. (C) Five months after sorafenib treatment. Brain CT showed decrease in size of the mass (2.0×1.5 cm). (D) Two months after sorafenib discontinuation. Brain MRI showed marked progression of the mass (5.4×3.7 cm).

One month after the end of brain EBRT, the metastatic mass in the right frontal lobe decreased to 3.8 cm and small metastatic nodule in the left parietal lobe was no longer visible on brain MRI (Fig. 2B). In May 2011, off-label sorafenib was used to treat progressive pulmonary metastatic lesions. Two weeks after sorafenib administration (800 mg per day), grade 3 hand-foot syndrome occurred, and the dose was subsequently reduced to 600 mg per day. One month after the start of sorafenib treatment, biochemical improvement was achieved (Fig. 4) and the hand-foot syndrome was relieved to grade 1. The levels of TSH, Tg Ag, and anti-Tg-Ab were 0.02 mIU/L, 86.24 ng/mL, and 0.12 IU/mL, respectively. Chest CT showed significant decreases in metastatic lung nodules but increases in the sizes of mediastinal lymph nodes. Brain CT showed a marked decrease in the right frontal lobe mass to 2.3 cm. After five months of sorafenib treatment, the best tumor responses, calculated as percentage change in sum of target lesions compared with baseline, were 45% decrease in brain (Fig. 2C) and 13% decrease in lung (Fig. 3B). Unfortunately, mediastinal lymph nodes had progressed over one month of therapy (Fig. 3D). Sorafenib was discontinued in October 2011 because of personal issues and financial problems. During the whole sorafenib administration period afterwards, the dose 600 mg per day was maintained and the best overall response by RECIST criteria was PD. Two months after sorafenib discontinuation, the patient was admitted to the emergency room complaining of severe headache and dizziness. Left hemiplegia with grade 1 muscle strength in the left arm and leg developed. Subsequent brain MRI revealed a marked increase in size of the right frontal lesion from

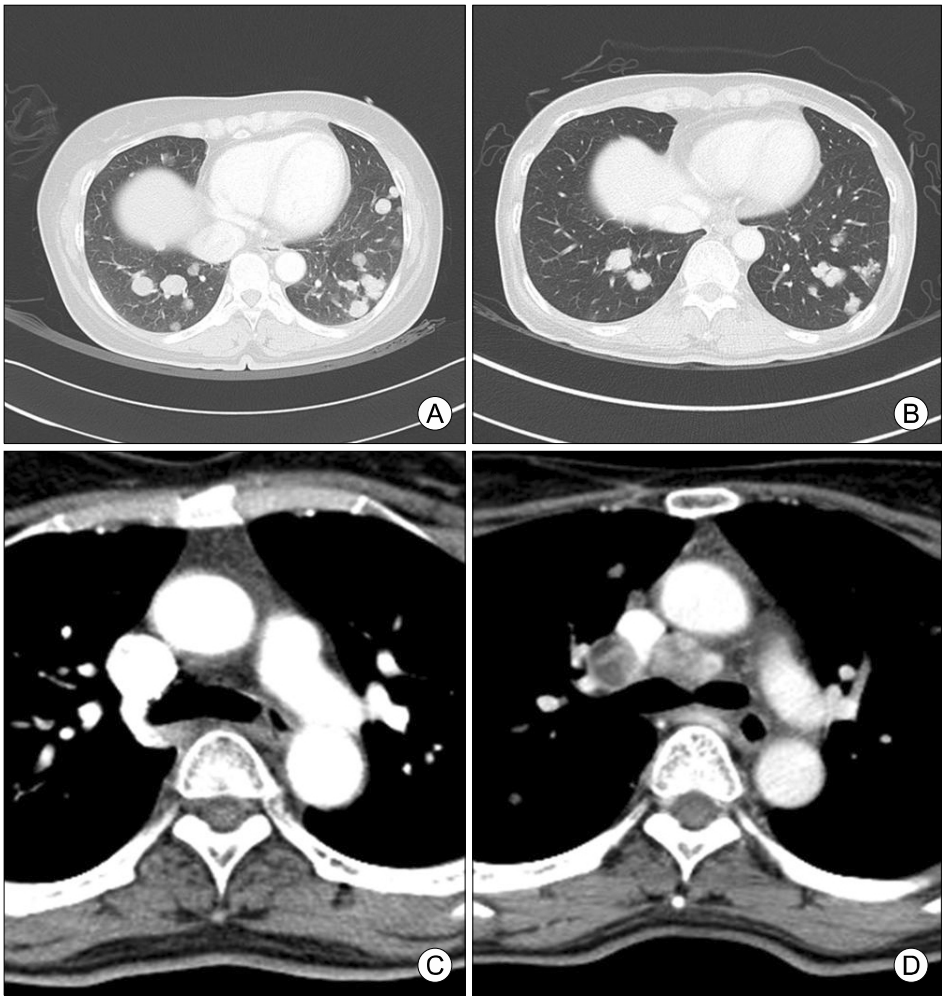

Fig. 3. CT scan of the chest. (A) At the end of EBRT on thyroid bed. Chest CT images showed multiple metastatic nodules in both lungs. (B) Five months after sorafenib initiation. Sum of the longest diameters of two nodules decreased by 13%. (C) At the end of EBRT on thyroid bed. Chest CT images showed no mediastinal lymph node enlargement. (D) Five months after sorafenib initiation. Mediastinal lymph nodes were extensively enlarged.

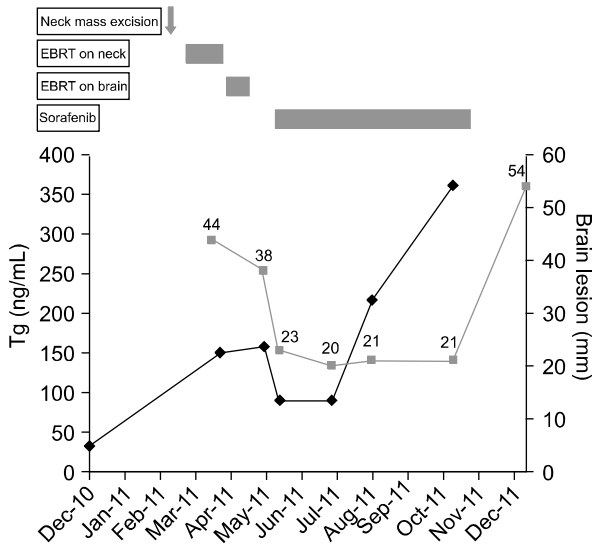

Fig. 4. Clinical course. Neck mass excision, EBRT on neck and brain, and sorafenib therapy were performed. Line graphs show time course of suppressed serum thyroglobulin (Tg) level (black line) and the diameter of metastatic brain lesion (grey line).

2.3 cm to 5.4 cm (Fig. 2D). Although EBRT was recommended for this progressive metastatic brain lesion, she refused further treatment and was transferred to a local palliative and hospice care hospital.

Discussion

Our patient had progressive metastatic lesions from PDTC in brain and lungs after surgery and RAI therapy, indicating a highly aggressive disease requiring urgent therapy. PDTC is a clinically aggressive tumor representing the main cause of death from nonanaplastic follicular cell-derived thyroid cancer.[9] Postoperative treatment options such as RAI therapy, EBRT, and chemotherapy remain poorly established.[10] Brain metastases from DTC occur in approximately 1% of patients,[1] and management of these patients remains difficult.[2] Previous reports suggested stereotactic ra-

diosurgery or EBRT for effective control of brain metastases from advanced thyroid cancer.[11,12] We chose EBRT rather than radiosurgery because of the large brain mass size and unstable extra-cranial metastases. Because the progression-free survival of DTC patients treated with EBRT alone for brain metastases is not known, we chose sorafenib treatment for not only progressive lung metastases, but also the brain metastasis in this patient.

Sorafenib is the only tyrosine kinase inhibitor able to target the MAPK pathway and with demonstrated inhibitory activity against VEGFR, PDGFR, and RAF kinases.[5] It is an emerging therapeutic option in the treatment of RAI-refractory advanced or metastatic DTC, especially when there are multiple pulmonary metastases.[13] Since metastatic brain lesions can cause acute life-threatening complications, appropriate management is crucial. However, to the best of our knowledge, there are only two case reports involving treatment of brain metastasis with sorafenib in thyroid cancer patients. One case of a patient with follicular thyroid cancer demonstrated partial response (PR) in the brain metastasis and stable disease (SD) in lung metastatic lesions.[14] Although sorafenib therapy was only given for 16 weeks in another report, no progression occurred in the metastatic brain lesion of a papillary thyroid cancer patient.[15]

We chose sorafenib to treat RAI refractory progressive lung metastases. Similar to the response of brain metastases in the previous two reports,[14,15] radiological examination confirmed good response over five months of sorafenib treatment in not only lung lesions but also brain lesion of our patient. Because the brain accumulation of sorafenib is restricted primarily by ABCG2 (breast cancer resistance protein) and partly by P-gp (P-glycoprotein),[16] this substantial effect on a brain lesion might be due to preceding EBRT. However, considering marked progression (increased by 234%) after cessation of sorafenib treatment, this drug might have penetrated the blood brain barrier through cerebral capillaries damaged by radiotherapy.[17] The rationale to combine radiotherapy with sorafenib is the following: (a) to target RAS-RAF-MAPK and VEGFR signaling pathways, which are specifically activated after exposure to radiation and are responsible for radio-resistance phenomenon; (b) to enhance the oxygen effect through normalization of the surviving tumor vasculature; and (c) to synchronize the cell cycle. Sorafenib and radiotherapy represent complementary strategies. Radiotherapy may be useful to prolong the effect of sorafenib through control of macroscopic disease, while sorafenib may target latent microscopic disease.[18] Therefore, sorafenib is reasonably well-tolerated with clinical and biological antitumor activity for metastatic brain lesion after EBRT.

Unlike brain metastasis, thyroglobulin levels increased during sorafenib treatment presumably due to mediastinal lymphadenopathy progression. Prior studies also showed varying responses to sorafenib treatment in different organs. Lung metastases respond more favorably compared to lymph nodes,[19] bone, or pleural lesions.[20] The pathophysiological mechanism underlying this variable response has been rarely clarified. It remains to be determined whether organ-specific responses are derived from different expressions of various VEGFRs or non-VEGF-mediated mechanisms, such as differences in drug concentrations among tissues.[19] Similar to previous reports,[14,19,20] sorafenib effectiveness was highest in the brain of our patient, followed by lung and lymph nodes. This suggests that sorafenib treatment be considered a novel adjuvant therapy for massive brain metastasis after EBRT in PDTC patients.

In conclusion, sorafenib can be considered a new adjuvant therapeutic option for metastatic brain lesions in PDTC after EBRT. Further clinical trials are needed to completely elucidate the potential adjuvant role of sorafenib in brain metastases from DTC after surgery or other radiotherapy.

Conflicts of Interest

The authors declare that they had no competing interests.

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this study. A portion of these results was presented in abstract form at 2014 American Thyroid Association annual meeting in Coronado, CA.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal. This report is in compliance with the institutional review board regulations of the College of Medicine, The Catholic University of Korea.

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