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Accelerated Disease Progression after Discontinuation of Sorafenib in a Patient with Metastatic Papillary Thyroid Cancer

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Distant metastases from papillary thyroid carcinoma (PTC) are rare and are associated with a poor prognosis. Here, we describe a patient with metastatic PTC who was treated with a tyrosine kinase inhibitor (TKI, sorafenib) for several months that was acutely exacerbated by discontinuation. A 43-year-old male was diagnosed with PTC in February 2004 and underwent total thyroidectomy followed by two courses of high-dose radioactive iodine (RAI) therapy. Despite two additional courses of high-dose RAI therapy, lung and muscle metastases were developed. Treatment with sorafenib was begun in September 2010. After 11 months treatment of sorafenib, newly developed metastatic lesions were found in mediastinal lymph nodes, liver, and bones. Considered as treatment failure, the administration of sorafenib was discontinued. Two weeks after sorafenib treatment was stopped, the disease progressed abruptly and caused death of the patient by respiratory failure. In our patient, PTC progressed rapidly after the cessation of sorafenib treatment. Patients with several other types of cancer have also experienced such rapid disease progression, termed "flare-ups." Physicians should be aware that flare-ups may occur in advanced PTC patients following the cessation of TKI therapy.

Keywords: Thyroid neoplasms; Papillary; Neoplasm metastasis; Sorafenib

INTRODUCTION

Distant metastases from papillary thyroid carcinoma (PTC) are rare and are associated with a poor prognosis [1]. In general, the progression of metastatic PTC is unlikely to be rapid despite a low overall survival rate, especially among young patients [2]. The conventional therapy for metastatic PTC include total thyroidectomy, the removal of resectable metastatic lesions, radioactive iodine (RAI) and/or external beam radiation at the sites of metastases [3]. If the disease does not respond to these conventional therapies, the use of targeted therapeutic agents such as tyrosine kinase inhibitors (TKIs) is recommended based on the results of clinical trials [3].

Sorafenib (Nexavar, Onyx Pharmaceuticals, Emeryville, CA, USA; and Bayer Healthcare, Wayne, NJ, USA) is a multiple TKI used in the treatment of renal cell carcinoma and hepatocellular carcinoma. By inhibiting both cell surface tyrosine kinase receptors (e.g., vascular endothelial growth factor

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[VEGF] receptors) and intracellular serine/threonine kinases (e.g., BRAF), sorafenib produces antiproliferative and antiangiogenic effects [4]. Because differentiated thyroid cancers have been well documented to exhibit genetic alterations in the mitogen-activated protein kinase (MAPK) pathway, including BRAF mutations [5] and VEGF overexpression [6], sorafenib has been proposed as a good candidate therapy for refractory thyroid cancers. Recently, several reports have demonstrated substantial efficacy of sorafenib in the treatment of refractory thyroid cancers [2,7].

Here, we report sorafenib therapy for a patient with RAI-refractory metastatic PTC. Despite the use of sorafenib and the maintenance of a partial response for several months, the disease progressed, producing new metastatic lesions in the lymph nodes, liver, and bone. After the cessation of sorafenib treatment due to disease progression, the growth of the disease, including lesions stabilized under sorafenib use, was further accelerated. The objective of this report is to highlight the rapid progression of PTC after the cessation of sorafenib treatment.

CASE REPORT

A 43-year-old male patient presented with metastatic PTC. He had been diagnosed with PTC in February 2004 and underwent total thyroidectomy at another hospital. High-dose (150 mCi) RAI therapy was performed twice in May 2004 and July 2006. In April 2007, right neck lymph node dissection was performed due to the discovery of recurrent PTC in cervical lymph nodes. Despite the application of additional high-dose RAI therapy in August 2007, hematogenous lung metastasis was observed in April 2009, and a fourth course of RAI therapy was performed in July 2009.

Nevertheless, chest computed tomography (CT) in February 2010 showed interval increase in the size of multiple hematogeneous metastasis in both lungs. For the further treatment, he was transferred to our hospital. On the basis of chest CT scans (Fig. 1A) performed in August 2010, the disease was classified as progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Additionally, two measurable lesions in the right gluteus muscle (Fig. 1B) were confirmed to be metastatic PTCs by ultrasound-guided needle biopsies (Fig. 2). Increase in serum thyroglobulin (Tg) level was also noted after he was transferred to our institution. Considering changes in both imaging studies and serum Tg level after four cycles of RAI therapy, the disease was considered as refractory to RAI therapy. Therefore, the patient was recruited for an investigational study of sorafenib, which had been approved by the institutional review board, and received his first medication in September 2010.

After 2 months of sorafenib administration (800 mg per day), a follow-up chest CT scan showed slight decreases in metastatic lung and muscle lesions compared with previous examinations (Fig. 1C, D). Because there was no evidence of disease progression or newly developed lesions revealed by imaging studies, which were repeated every 2 months, sorafenib was maintained at a full dose.

Until August 2011, after 11 months of sorafenib administration, multiple metastatic lesions in lung parenchyma and in the right gluteus muscle showed little interval change. However, chest CT scan revealed marked increase in the size of the subcarinal and right interlobar nodes, which had previously been stable, and a newly enlarged right paratracheal lymph node. In follow-up chest and abdominal CT in October 2011, though multiple metastatic nodules in both lungs showed stabilization in size, progression of mediastinal lymph nodes and multiple new hepatic metastatic masses were identified. In addition, a lumbar spine magnetic resonance imaging scan, obtained due to back pain, revealed extensive metastatic lesions of thoracic spine, lumbar spine, sacrum, and pelvis, which were not identified in previous chest or abdominal CT scans. Because the disease had progressed, palliative treatments, such as external beam radiation of the lumbar spine, were planned.

On October 8, 2011, radiotherapy of the metastatic lesions of the lumbar spine and the sacrum was initiated. In addition, sorafenib was discontinued on October 17, 2011. After the first fraction of radiotherapy, the patient visited an emergency room for dyspnea and fever on November 2011, after 17 days sorafenib discontinuation. A chest CT showed marked progression of metastatic lesions in the lungs, which had been stable under sorafenib, and the development of pleural metastasis with bilateral effusion (Fig. 1E). To relieve the symptoms, the pleural effusions were drained using a pigtail catheter. On the 12th day of hospitalization, a liver biopsy was performed for further evaluation and management. The histopathology, which was supported by immunohistochemical staining (Fig. 3), was consistent with the anaplastic transformation of follicular cell-derived carcinoma [8]. In addition, BRAF V600E mutation was found in the tissue.

CT pulmonary angiography performed on the 13th hospital day revealed marked progression of lung, pleural, and mediastinal metastases compared with a chest CT scan obtained 2 weeks prior. No pulmonary thromboembolism was identified.

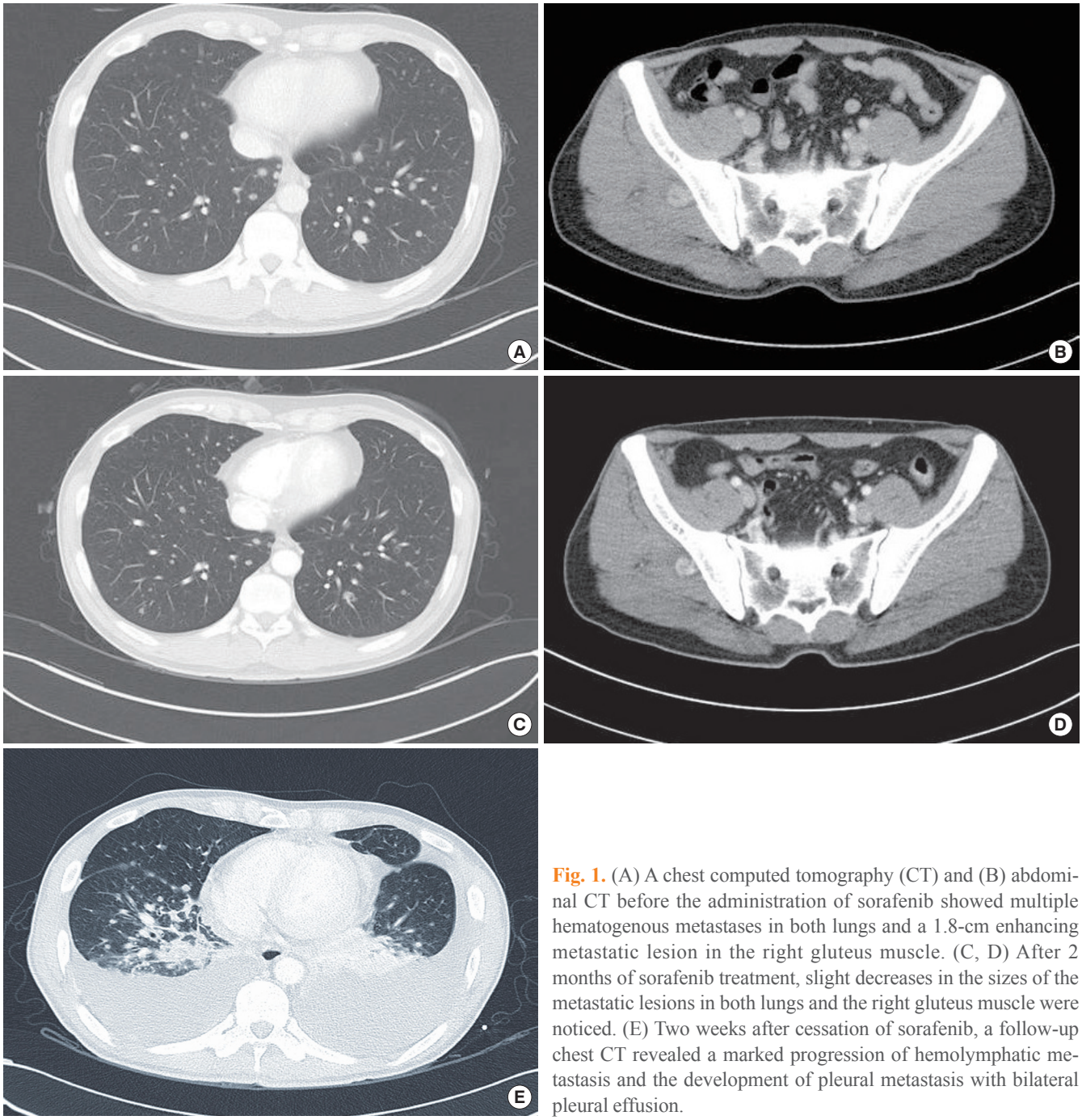

Fig. 1. (A) A chest computed tomography (CT) and (B) abdominal CT before the administration of sorafenib showed multiple hematogenous metastases in both lungs and a 1.8-cm enhancing metastatic lesion in the right gluteus muscle. (C, D) After 2 months of sorafenib treatment, slight decreases in the sizes of the metastatic lesions in both lungs and the right gluteus muscle were noticed. (E) Two weeks after cessation of sorafenib, a follow-up chest CT revealed a marked progression of hemolymphatic metastasis and the development of pleural metastasis with bilateral pleural effusion.

The patient died on the 14th day of hospitalization due to respiratory failure.

DISCUSSION

PTC has been reported to initially present with distant metastases in approximately 4% of cases [9]. According to the 2009 American Thyroid Association guidelines [3], the removal of resectable metastatic disease and repeated RAI therapy are the mainstay of further management in cases of RAI-avid lesions.

There are insufficient data showing the efficacy of RAI therapy for metastatic thyroid cancers. It has been reported that a substantial number of metastatic thyroid carcinomas would not be responsive to RAI therapy because 20% to 50% lose the

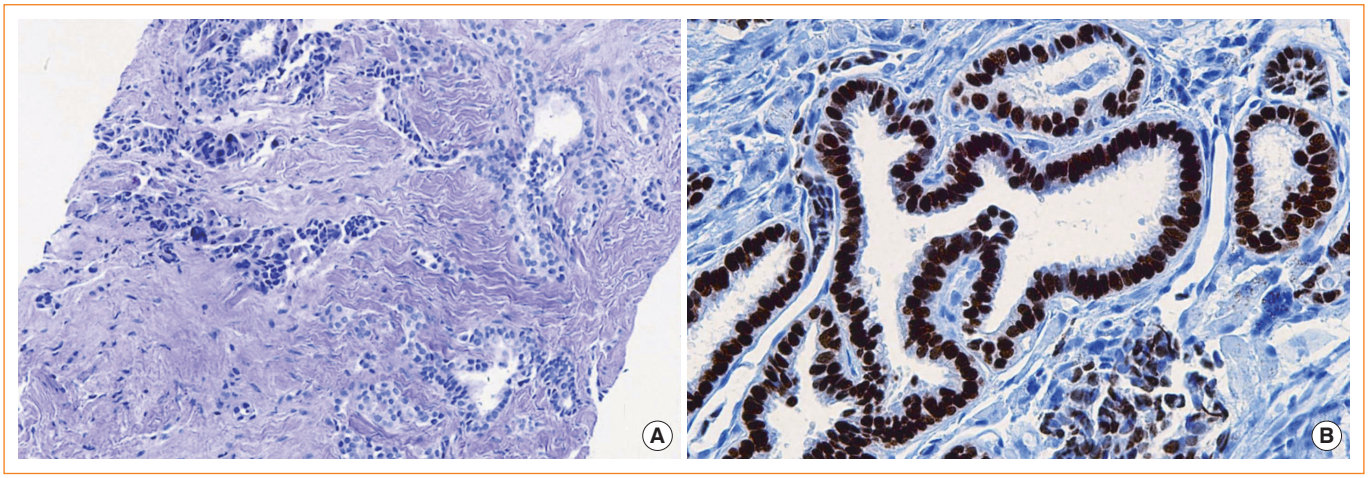

Fig. 2. (A) A histopathological examination of the right gluteus muscle lesion showed papillary architecture (H&E stain, ×200). (B) Immunohistochemical staining showed strong thyroid transcription factor-1 immunoreactivity (×400).

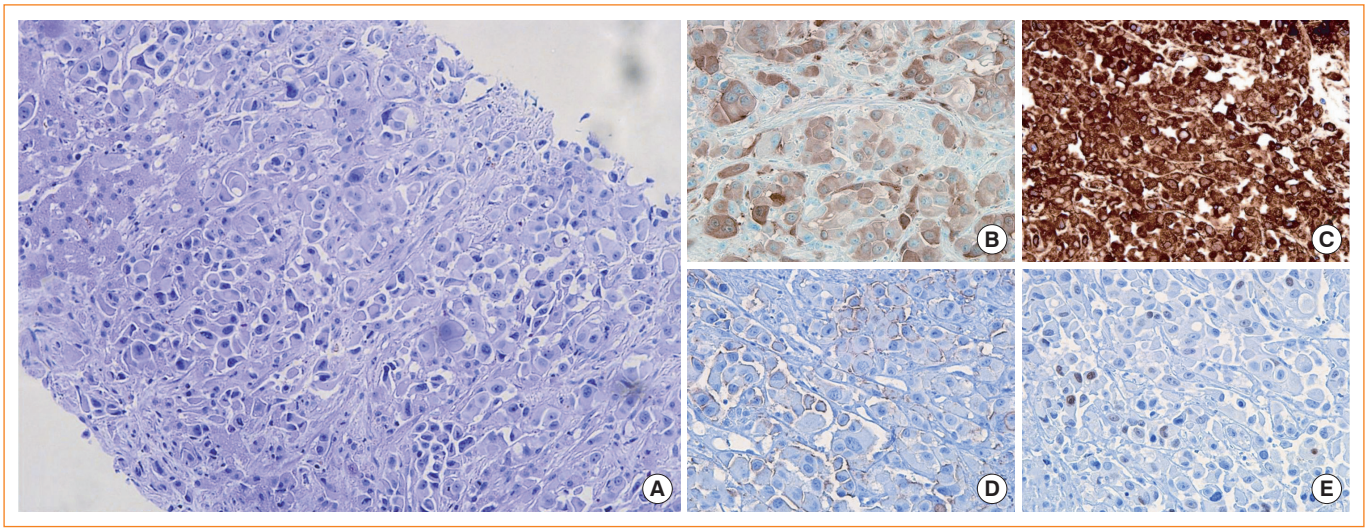

Fig. 3. (A) A histopathological examination of the liver revealed the anaplastic transformation of follicular cell-derived thyroid carcinoma (H&E stain, ×200). (B) Immunohistochemical staining showed strong immunoreactivity with CK-7 (×400), (C) galectin-3 (×400), (D) human mesothelial cell-1 (×400), and (E) thyroid transcription factor-1 (×400).

ability to concentrate iodine [10]. In addition, it is known that thyroid carcinomas lose RAI avidity during dedifferentiation [11]. The current recommendation for patients with PTC who do not respond to conventional therapy is participation in a clinical trial using targeted therapy agents such as TKIs.

Our patient, whose disease was refractory to RAI therapy, was a good candidate for TKI therapy. Treating the patient with sorafenib for 2 months achieved 13.1% reduction in the total sum size of measurable lesions (stable disease according to the RECIST criteria). Furthermore, after the initial partial response, no significant changes in the lesions were found for 9 months.

However, sorafenib was stopped 13 months later because newly developed liver and bone metastases and the progression of existing lesions in lymph nodes were observed. As soon as sorafenib was discontinued, the disease progressed rapidly. Prior studies of patients with several advanced cancers showed the cessation of TKI therapy was followed by the rapid progression of disease or mortality [12,13]. Several reports described this as "flare-ups" [12-14]. No definite mechanism for this phenomenon has yet been elucidated. One possible mechanism is the rapid growth of TKI-sensitive clones following the discontinuation of the drug [12,13]. In our case, as shown in Table 1, stabilized lesions in the lungs and the right gluteus

Table 1. Size Changes of Metastatic Lesions according to Location

	2 mo after sorafenib use	13 mo after sorafenib use	2 wk after sorafenib discontinuation
Lung (parenchymal)	Decreased	Stable	Increased
Lymph node (mediastinal, interlobar)	Stable	Increased	Increased
Right gluteus muscle	Decreased	Stable	Increased
Liver	Not detected	Detected	Increased
Spine	Not detected	Detected	Increased

muscle under TKI treatment, which were considered as TKI-sensitive, showed rapid progression after cessation of the drug. Therefore, rapid growth of TKI-sensitive clones might play a role in abrupt exacerbation of disease after discontinuation of the drug. Another possible explanation is that cessation of therapy could result in removal of the residual inhibitory effect of the antiangiogenics, regardless of the TKI sensitivity of the lesion in each tissue (lung, lymph node, muscle, liver, or bone), as suggested by another study [14].

Another interesting finding of the patient was the presence of metastatic lesions in the liver, which indicated the anaplastic transformation of thyroid carcinoma. There have been several reports of the anaplastic transformation of PTC in metastatic lesions [15,16], most of which were discovered after RAI therapy. However, the anaplastic transformation in our patient developed 27 months after the final RAI treatment. Thus, considering the time interval between the final RAI treatment and development of liver metastasis, the role of RAI therapy in transformation is not clear in this case. Because the patient was treated with sorafenib, unlike the previous cases, the role of TKIs in anaplastic changes should be considered. Because sorafenib inhibits the MAPK pathway, it is possible that an alternative pathway, such as the AKT pathway, might be activated instead. Activation of the AKT pathway is known to be associated with anaplastic carcinoma [17].

In this context, a multitargeted therapy directed at the inhibition of multiple signaling pathways, including escape and alternate pathways, should be considered not only for effective treatment, but also for the reduction of drug resistance [18]. A therapy to block dual cell proliferation pathways would be promising, such as the combination of a pan-RAF inhibitor and BEZ235 (a dual phosphatidylinositol-4,5-bisphosphate 3-kinase/mammalian target of rapamycin [mTOR] inhibitor) or the combination of mTOR and MEK inhibitors for treating thyroid cancer [19,20].

In conclusion, doctors should be aware of the possibility of flare-ups after the cessation of sorafenib. Additionally, considering the oncogenic variability and complex positive and negative feedback regulation involved in the signal pathways of cancer cells, the activation of an alternative pathway should be taken into account when targeted therapies are administered to RAI-refractory patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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