Development of Tracheoesophageal Fistula after the Use of Sorafenib in Locally Advanced Papillary Thyroid Carcinoma: a Case Report

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Sorafenib, an oral multi-kinase inhibitor, is used for the treatment of patients with radioactive iodine (RAI) refractory differentiated thyroid carcinoma (DTC) with favorable outcomes. Some unusual but fatal adverse effects are known for this drug and tracheoesophageal fistula (TEF) is one of them, which has never been reported in thyroid cancer patients. We present a successfully treated patient who had developed TEF associated with rapid tumor regression during sorafenib treatment for locally advanced papillary thyroid carcinoma (PTC). Sorafenib was discontinued and feeding jejunostomy tube was placed for nutritional support. 3 months later, the TEF had successfully healed and there was no visible fistula track or interval change of the viable tumor during 15 months of follow-up. Identifying patients at high risk for this potential complication and paying special attention when prescribing anti-angiogenics to these patients are crucial to prevent associated morbidity and mortality.

Key Words: Tracheoesophageal fistula, Sorafenib, Thyroid cancer, Papillary

Introduction

The prognosis of differentiated thyroid carcinoma (DTC) is known to be excellent after surgical treatment and radioactive iodine (RAI) followed by thyrotropin suppressive therapy. However, approximately half of locally advanced or metastatic DTCs are refractory to RAI therapy and have a very poor prognosis. Sorafenib, an oral multi-kinase inhibitor that affects both tumor cell proliferation and angiogenesis, has emerged as an effective therapeutic option for patients with advanced RAI-refractory DTC. It has a relatively well-tolerated toxicity profile compared with conventional cytotoxic chemotherapy. However, rare but fatal adverse events, such as hemorrhage, myocardial infarction, sepsis, and sudden death, have been reported. Tracheoesophageal fistula (TEF), which is one of them, is a life threatening complication in malignancy such as lung, esophagus, or head and neck cancer. TEF formation because of DTC is extremely rare and there have been no previous reports of this phenomenon as a complication of using sorafenib. Herein, we report a patient with TEF associated with rapid tumor regression of locally advanced papillary thyroid carcinoma (PTC) after treatment with sorafenib.

Case Report

A 71-year-old woman presented with a 1-week history of hemoptysis and progressive dyspnea...
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(modified Medical Research Council grade 4). 15 years ago, she had undergone total thyroidectomy and subsequent RAI ablation for the treatment of PTC. After 10 years of disease-free period, a single metastatic PTC in brain was found and surgical mass excision was done. There was no evidence of disease in other lesions at that time.

4 years later, she was admitted to a local hospital because of recurrent hemoptysis and dyspnea. On neck computed tomography (CT) and bronchoscopy, there was a 5.0–cm–sized mass in her right tracheoesophageal groove that invaded into the cervical esophagus and mid-trachea causing near total obstruction of the trachea (Fig. 1A, B). Several cervical lymph nodes were enlarged and core needle biopsy confirmed metastatic PTC. She underwent an 8 Gy single dose of external beam radiotherapy and subsequent high dose steroid therapy for the metastatic mass. However, her symptoms did not improve and she was referred to our hospital.

To treat the endotracheal metastatic mass, a twice daily regimen of 400 mg sorafenib was initiated, 28 days after the initial radiotherapy. After 1 month of sorafenib administration, the mass had decreased by 50% of its initial size on follow-up CT and bronchoscopy (partial response according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria, Fig. 1C, D). Accordingly, her symptoms were much improved.

However, after 4 months of sorafenib treatment, she returned to our clinic with a complaint of recurrent aspiration. A tracheobronchial CT scan revealed newly developed TEF at the level of the metastatic tumor (Fig. 2A, B). The fistula opening was right below the upper esophageal sphincter and esophageal stent insertion was not feasible. She underwent insertion of a feeding jejunostomy tube (Fig. 2C) and sorafenib was discontinued. She was followed by TSH suppression by thyroxine supplementation.

Fig. 1. Locally advanced papillary thyroid carcinoma in the tracheoesophageal groove with esophagus and tracheal invasion before sorafenib treatment (A, B). (A) Neck CT image, (B) Bronchoscopic image. After 1 month of treatment with sorafenib, the metastatic tumor significantly decreased in size (C, D). (C) Neck CT image, (D) Bronchoscopic image.
Follow up CT image was performed every 1 month after feeding through the jejunostomy tube to evaluate the change in TEF and its size. After 3 months, esophagography showed no extraluminal leakage of contrast media (Fig. 2D) and TEF was found to be in a healing state on tracheobronchial CT (Fig. 2E, F). She started oral feeding and jejunostomy tube was removed.

Our patient remains alive without signs of recurrent TEF, and the tumor remains stable at 15 months after the discontinuation of sorafenib. She underwent radiofrequency ablation for a right level II cervical lymph node metastasis after withdrawal of sorafenib and this lesion has also been stable up to the most recent follow-up.

Discussion

Patients with RAI refractory DTC have a poor prognosis and a long-term overall survival of only 10%.

No definite therapeutic option was available until sorafenib was first approved by Food and Drug Administration (FDA) for these patients. Sorafenib, a multi-kinase inhibitor that mainly targets angiogenesis, significantly improved progression-free survival for 5 months compared with placebo group.

Hand-foot syndrome, diarrhea, alopecia, and rash are some of the most common adverse effects of sorafenib. TEF formation is very rare and direct cancer invasion of the trachea or esophagus, prior radiation therapy, and instrumentation of the trachea or esophagus are known to be high risk factors for its development. A previous study reported three cases of aerodigestive fistula formation after the treatment of thyroid cancer with antiangiogenic tyrosine kinase inhibitors (TKI), including TEF after 3 months of cabozantinib, trachea–tumor fistula after 6 weeks of...
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sunitib, and esophago–tumor fistula after 6 months of lenvatinib.\(^{13}\) All of the three cases had progressive thyroid cancer that directly invaded the esophagus or trachea. Two cases had a history of external beam radiation, both a total dose of 66 Gy in 33 daily fractions over 48 days and 46 days respectively. Our patient also had a progressive, locally advanced PTC with direct invasion of the endotracheal space and a previous history of external radiation therapy which are all relevant to risk factors of TEF formation. Notably, the TEF occurrence in our current case was associated with tumor regression after sorafenib treatment and not with tumor progression. During the first month of treatment with sorafenib, her tumor size decreased dramatically. This suggests that a good response to sorafenib treatment could also be a risk factor for TEF formation when the tumor directly invades to the trachea or esophagus.

Optimal treatment for TEF associated with malignancy is not established – esophageal stent or gas-trotromy/jejunostomy is generally performed although it should be carefully chosen considering patient’s performance status and the location of TEF. Surgical intervention is not preferred in terms of advanced malignancy and poor performance status of the patients.\(^{6,14}\)

The prognosis of a patient who develops TEF as a complication of a malignancy is very poor. In the previously reported cases by Blevins et al.\(^{13}\) all of the patients died within 2 months of the formation of aero-digestive fistulas that resulted from hemorrhage, infection, or respiratory distress. Our present case suggests that early diagnosis of TEF and immediate therapeutic interventions for enteric feeding to prevent life threatening complications, such as aspiration pneumonia, are critical to improve the survival outcomes and quality of life.

In conclusion, TEF formation can be a progressively deteriorating complication in patients administered antiangiogenic agents with tumors directly invading vital organs including esophagus and trachea, previous radiation therapy, and instrumentation of the trachea or esophagus. As sorafenib grows in importance in the treatment of RAI refractory DTC and more anti-angiogenic TKIs are being developed, greater awareness when using these drugs in high risk patients should be made for this potential complication.

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