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CASE REPORT

Bronchial Typical Carcinoid with Carcinoid Syndrome Successfully Treated with Everolimus and Octreotide: a Case Report

Hirokazu Tokuyasu[1]; Yuriko Sueda[1]; Hiromitsu Sakai[1];
Natsumi Omura-Tanaka[1]; Hiroshi Miura[2]; Akira Yamasaki[3]

ABSTRACT —— ***Background.*** Bronchopulmonary typical carcinoid tumors with distant metastasis and carcinoid syndrome are rare. ***Case.*** We report the case of a 77-year-old woman diagnosed with a bronchial typical carcinoid in the right middle lobe bronchus and multiple liver metastases. The patient presented with facial flushing and diarrhea, and the serotonin blood levels were elevated, indicative of carcinoid syndrome. Combination therapy with everolimus and octreotide maintained the patient in a healthy condition for approximately two years until she died in 2019. ***Conclusion.*** Bronchial typical carcinoids with multiple liver metastases and carcinoid syndrome in our patient was well-managed by combination therapy with everolimus and long-acting release octreotide.

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KEY WORDS —— Bronchial typical carcinoid, Carcinoid syndrome, Everolimus, Long-acting release octreotide, Serotonin

INTRODUCTION

Bronchopulmonary carcinoid tumors are rare, accounting for approximately 1-2% of primary lung tumors.[1] These tumors are classified as typical or atypical based on their histopathology.[2,3] Carcinoid tumors may produce various humoral factors, resulting in carcinoid syndrome, which is often characterized by facial flushing, diarrhea, and bronchospasms. However, somatostatin analogues, such as octreotide, can improve these symptoms by suppressing the production of humoral factors. Additionally, the mammalian target of rapamycin (mTOR) pathway is a central regulator of cellular proliferation and angiogenesis, and is inhibited by everolimus, which has been shown to have antitumor activity in the pulmonary and gastrointestinal tract carcinoid tumors.[4]

We herein report the case of a patient with a bronchial typical carcinoid (TC) with carcinoid syndrome who was treated with everolimus and octreotide.

CASE REPORT

In the beginning of June 2017, a 77-year-old woman with no history of smoking was referred to our hospital because she had been experiencing episodic face edema, facial flushing, and diarrhea for one month. Upon physical examination, redness of the face, precordial area, and palms of both hands was observed. Additionally, the neuron-specific enolase level was slightly elevated at 18.9 ng/ml (normal range, 0-16.3 ng/ml). Further, her blood level of serotonin was elevated to 625 ng/ml (normal range, 57-230 ng/ml). Computed tomography (CT) showed atelectasis in the middle lobe of the right lung, multiple low-density areas in the liver, and multiple osteosclerotic lesions in the vertebral bodies and pelvic bones (Figure 1). Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography/CT images revealed intense FDG accumulation, proximal to the site of right pulmonary atelectasis, in the liver, and in the vertebral bodies. A bronchoscopic examination revealed that the

[1]Department of Respiratory Medicine, [2]Department of Pathology, Matsue Red Cross Hospital, Japan; [3]Division of Respiratory Medicine and Rheumatology, Department of Multidisciplinary Internal Medicine, School of Medicine, Faculty of Medicine, Tottori University, Japan.
Corresponding author: Hirokazu Tokuyasu.
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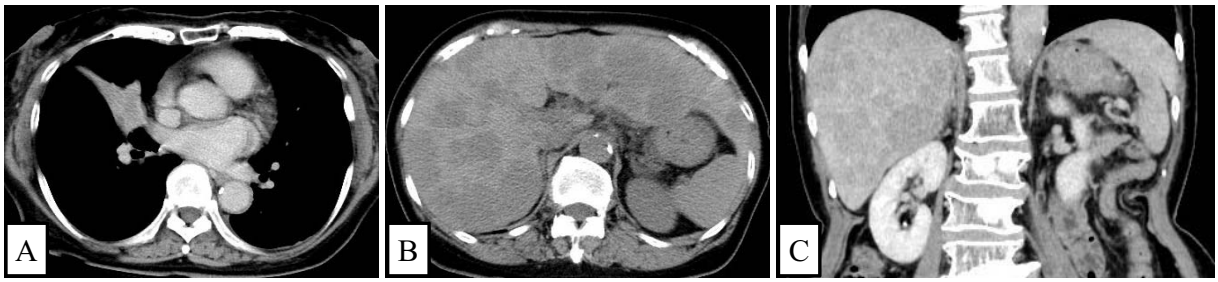

Figure 1. Chest computed tomography images at the initial presentation showing atelectasis in the middle lobe of the right lung **(A)**, multiple low-density areas in the liver **(B, C)**, and multiple osteosclerotic lesions in the vertebral bodies **(C)**.

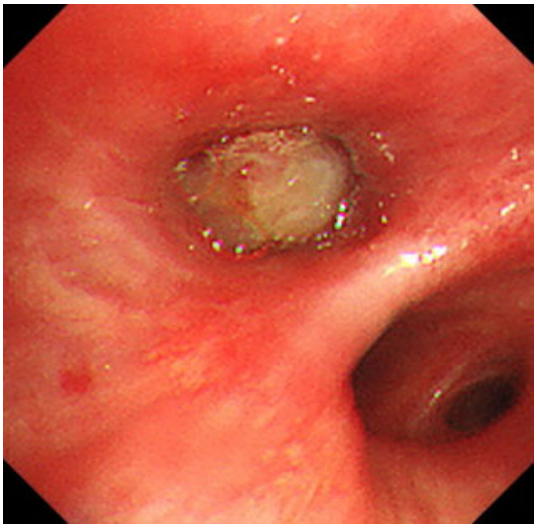

Figure 2. Bronchoscopy findings showing that the tumor nearly occluded the orifice of the right B^5 bronchus.

tumor nearly occluded the orifice of the right B^5 bronchus (Figure 2). Furthermore, a histological examination of transbronchial biopsy specimens obtained from the mass revealed a TC tumor with a trabecular pattern, without necrosis (Figure 3A). Additionally, <2 mitoses/2 mm^2 were observed in the primary tumor and liver metastases. Immunohistochemistry was highly positive for synaptophysin and chromogranin (Figure 3B, 3C), while the Ki-67 labeling index was approximately 6.4% (66/1029).

In July 2017, the patient was diagnosed with a right bronchial TC (cT2aN1M1c, stage IV) and carcinoid syndrome. Subcutaneous octreotide therapy was initiated at a dose of 100 μg/day, and the symptoms of carcinoid syndrome improved. Five days later, the patient underwent chemotherapy with carboplatin (area under the curve = 5, day 1) and etoposide (100 mg/m^2, days 1-3). At three weeks after chemotherapy, CT showed radiologic reductions of the pulmonary atelectasis and liver metastases. However, temporary aggravation of facial flushing and diarrhea occurred as adverse effects of chemotherapy and the patient opted to discontinue chemotherapy. In the beginning of August, she transitioned to second-line treatment with everolimus (10 mg, daily) and in the middle of August, she began treatment with 20 mg of long-acting release (LAR) octreotide via intramuscular injection every four weeks. The patient was well controlled with minimal symptoms, and the level of serotonin remained in the normal range for approximately two years. At the end of July 2019, aggravation of facial flushing and diarrhea recurred, and her blood level of serotonin increased to 300 ng/ml. CT revealed no change in the atelectasis in the middle lobe of the right lung, while the metastatic lesions in the liver showed slight enlargement. The patient died at the end of September 2019. Everolimus and octreotide were both finished two weeks and two days before death.

DISCUSSION

Lung neuroendocrine tumors (NETs) can be classified according to grade: TC, low grade; atypical carcinoid (AC), intermediate grade; and neuroendocrine carcinoma/small cell lung carcinoma, high grade. These classifications are based on histological factors, including the cell size, cell morphology, mitotic index, architectural growth patterns, and the presence of necrosis, but not the Ki-67 index.[2,3] In this case, TC was diagnosed due to the occurrence of <2 mitoses/2 mm^2 and the absence of necrosis.

Systemic chemotherapy should be considered in patients with advanced unresectable progressive pulmo-

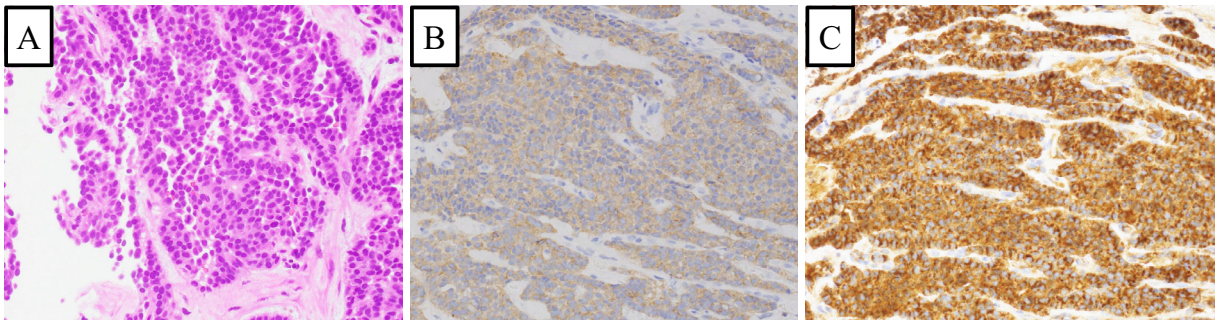

Figure 3. The histological examination of transbronchial lung biopsy specimens obtained from the right middle bronchial mass revealed a typical carcinoid tumor with a trabecular pattern, uniform cells, and no necrosis **(A)**. Immunohistochemical staining of synaptophysin **(B)** and chromogranin **(C)** was highly positive.

nary carcinoid. Forde et al reported that radiologic responses occurred in 4 of 17 patients with advanced pulmonary carcinoid (23.5%) who received etoposide and platinum combination with a median progression-free survival (PFS) of seven months.[5] The cytotoxic regimen has demonstrated some effects in patients with advanced pulmonary carcinoid.

Carcinoid tumors can secrete a myriad of bioactive substances, among which serotonin is the most common. In patients with extensive liver metastases, a high proportion of tumor-secreted substances are not completely metabolized by hepatic or pulmonary cells. These substances enter the systemic circulation system, causing carcinoid symptoms. Increased serotonin levels can cause facial flushing, diarrhea, and bronchospasms, which are consistent with the main symptoms of carcinoid syndrome. In a previous study of 9512 patients with NET, 1784 (19%) experienced carcinoid symptoms, and the proportion of patients with pulmonary NETs with carcinoid syndrome was reported to be 7.6%.[6] In this case, chemotherapy with carboplatin and etoposide resulted in the temporary aggravation of facial flushing and diarrhea. It is possible that the secretion of serotonin was stimulated by the initiation of chemotherapy.

Most NETs contain a high density of somatostatin receptors (SSTRs).[7] SSTR subtypes 2 and 5 are the most important for carcinoid symptom control, and subtype 2 is most frequently expressed in lung carcinoids.[8] Somatostatin analogues such as octreotide suppresses the production of bioactive substances that cause carcinoid symptoms by binding to the somatostatin receptors on tumor cells.[9] Furthermore, octreotide is expected to have somatostatin receptor-mediated and antiangiogenic antiproliferative effects.[10] The randomized PROMID study of LAR octreotide (30 mg) versus placebo in patients with midgut NET demonstrated a significantly longer median time to progression in the LAR octreotide group in comparison to the placebo group, (14.3 months vs. 6 months, respectively).[11] In the present case, the patient's carcinoid syndrome was well-managed for two years with LAR octreotide.

The mTOR pathway has been identified as a kinase-activated part of the phosphatidylinositol-3-kinase (PI3K) signaling pathway, which regulates key cell functions involved in cell survival, proliferation, and metabolism. Recently, oncogenic mutations of the PI3K catalytic subunit α (PIK3CA) that result in the continuous activation of PI3K have been reported in TC and AC.[12] Everolimus is an oral selective inhibitor of mTOR and has shown antitumor activity in patients with advanced NETs.[13,14] The randomized phase III RADIANT-4 trial, which assessed everolimus 10 mg versus placebo in patients with a functioning lung and gastrointestinal NET showed a median PFS of 11.0 months in the everolimus arm and 3.9 months in the placebo arm.[4] Moreover, a positive treatment effect was observed irrespective of the extent of liver metastasis. Additionally, the RADIANT-4 lung subgroup analysis showed everolimus to be consistently effective and safe in the overall study.[15] In the RADIANT-4 study, the median PFS was 9.2 months in the everolimus arm and 3.6 months in the placebo arm. Thus, everolimus is a feasible therapeutic option for TC and AC. In the present case, the patient was treated with everolimus and LAR octreotide combination treatment. The randomized phase III trial, RADIANT-2, assessed everolimus (10 mg) plus LAR octreotide versus placebo plus LAR octreotide in 429 patients with non-pancreatic NETs and carcinoid syn-

drome; 44 of the NETs were of bronchial origin. The study revealed a median PFS of 16.4 months in the everolimus arm versus 11.3 months in the placebo arm.[13,16] Thus, this combination therapy may further improve patient outcomes.

In conclusion, bronchial TC with multiple liver metastases and carcinoid syndrome in our patient was well-managed by combination therapy with everolimus and LAR octreotide.

本論文内容に関連する著者の利益相反：山﨑　章［日当・講演料］アストラゼネカ株式会社

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