CASE REPORT

The First Case Report of Effective Treatment With Sotorasib for Metastatic Atypical Lung Carcinoid Harboring KRAS G12C Mutation and Aggressive Disseminated Lung Metastasis: A Case Report

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ABSTRACT

Pulmonary neuroendocrine tumors are rare, accounting for approximately 1% to 2% of lung cancers. Atypical carcinoids account for approximately 10% of pulmonary neuroendocrine tumors and are categorized as moderately malignant. Treatment options for advanced-stage atypical carcinoids include everolimus, cytotoxic anticancer agents, and peptide receptor radionuclide therapy. In this report, we present the first case of KRAS G12C mutation-positive atypical carcinoid that was successfully treated with sotorasib. Therapeutically important mutations observed in non-small cell lung cancer are seldom found in atypical carcinoid tumors. Nonetheless, it is worthwhile to search for genetic mutations in atypical carcinoid tumors, considering the potential for molecular targeted therapy to be effective in their treatment as well.

Keywords: Sotorasib; Atypical carcinoid; KRAS G12C mutation; Comprehensive genome profiling

Introduction

Lung neuroendocrine tumors are rare, well-differentiated tumors that account for 1% to 2% of lung cancer in adults. The incidence rate is less than two per 100,000 people in the population. Within lung neuroendocrine tumors, 90% are typical carcinoids (TCs) and 10% are atypical carcinoids (ACs). TC is considered low-grade malignancy, whereas AC displays intermediate-grade malignancy. Patients with NSCLC often harbor treatable driver gene mutations, whereas those with neuroendocrine tumors rarely do, and there have been only a few reported cases thus far.[1]

KRAS gene mutations are found in approximately 30% of Western and 10% of Japanese lung adenocarcinomas. Sotorasib, a molecular-targeted drug that specifically targets the KRAS G12C mutation, was developed and received approval from the U.S. Food and Drug Administration in May 2021. It has now become the standard secondary treatment for KRAS G12C mutation-positive NSCLC.

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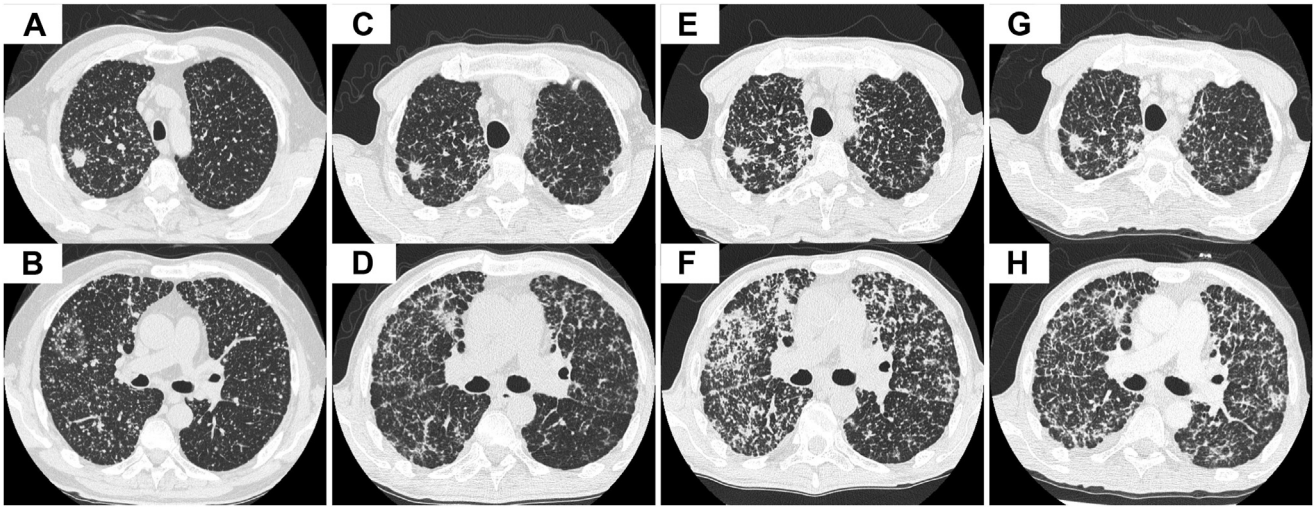

Figure 1. Chest computed tomography images (*A*, *B*) at first visit, (*C*, *D*) after 4 cycles of first-line treatment, (*E*, *F*) after two cycles of maintenance therapy, and (*G*, *H*) 1 month after sotorasib initiation.

Here, we report a case of AC harboring the KRAS G12C mutation, where sotorasib proved effective against rapid progression.

Case Presentation

A 62-year-old man with 38 pack-year smoking history and underlying hypertension was referred to our hospital due to abnormalities on chest computed tomography scan. The chest computed scan revealed a nodule in the right upper lobe and bilateral miliary metastasis (Fig. 1*A* and *B*). Laboratory findings indicated an increase in progastrin-releasing peptide level. Bronchoscopy-guided transbronchial lung biopsy resulted in a combined pathologic diagnosis of AC and adenocarcinoma (Fig. 2*A*). Most biopsy samples consisted of the AC component. The AC component exhibited three to four mitoses per 2 mm^2 and lacked necrosis (Fig. 2*B* and *C*). Immunohistochemical studies revealed that the adenocarcinoma component was positive for TTF-1 (Fig. 2*D*), whereas the AC component was positive for synaptophysin (Fig. 2*E*). The Ki-67 was positive in an average of 15% and 30% in hotspot in each component (Fig. 2*F*). Molecular analyses revealed that the tumors containing both components were positive for KRAS G12C mutation and that less than 1% of the tumor cells expressed programmed death-ligand 1 (PD-L1). During the course of these investigations in 1 month, his disease rapidly progressed, leading to respiratory failure and deteriorated performance status.

Initially, we thought that the rapid progression of the disease was atypical for AC; thus, we decided to treat it as NSCLC. He was treated with combination of carboplatin, nab-paclitaxel, and atezolizumab. After completing 4 cycles of chemotherapy, the response was categorized as stable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria (Fig. 1*C* and *D*), and there was a tendency for progastrin-releasing peptide level to decrease. There was no exacerbation of respiratory failure observed. Subsequently, he commenced atezolizumab maintenance therapy. Nevertheless, after the administration of two cycles of atezolizumab, there was a deterioration in his condition, marked by worsening bilateral miliary metastases (Fig. 1*E* and *F*). This was accompanied by metastasis to the mediastinal lymph node and the liver. Only AC components were detected in the liver biopsy samples (Fig. 3*A*). These samples exhibited one to two mitoses per 2 mm^2 and had no signs of necrosis (Fig. 3*B* and *C*). Immunohistochemical studies revealed that they were negative for TTF-1 (Fig. 3*D*) but positive for synaptophysin (Fig. 3*E*). The Ki-67 was positive in an average of 20% of the samples and 30% in hotspots (Fig. 3*F*). Molecular analyses revealed that the liver biopsy sample had a positive result for KRAS G12C mutation. Comprehensive genome profiling (CGP) using liquid biopsy was also carried out through Foundation One Liquid CDx, Roche. The CGP revealed STK11 and KEAP1 mutations in addition to KRAS G12C mutation. Nevertheless, TP53 and RB1 mutations were not detected. Tumor mutation burden (TMB) was 9 mutations per megabase, and microsatellite instability—high was not detected. He was treated with sotorasib as second line 3 weeks after the last dose of atezolizumab. At the time of treatment start, his respiratory failure worsened, needing supporting for high-flow nasal cannula therapy. After the commencement of treatment with sotorasib, there was rapid improvement in his respiratory failure and bilateral miliary metastases within 1 month (Fig. 1*G*

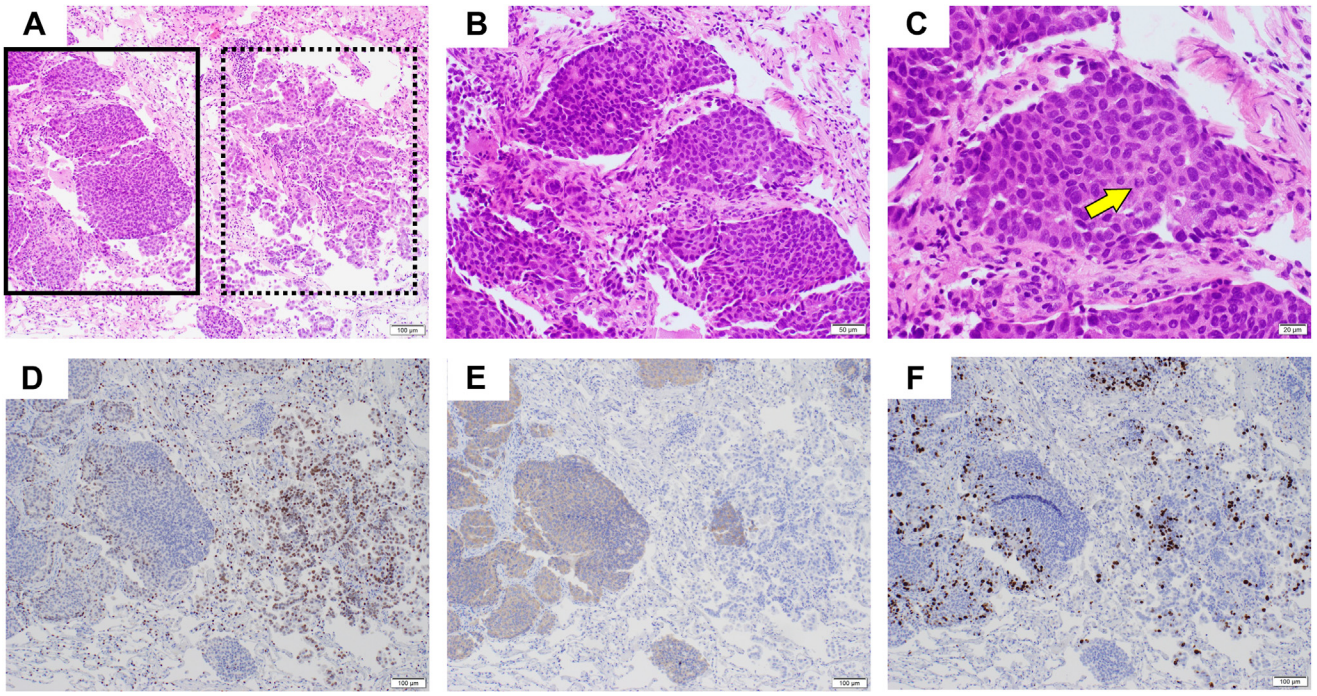

Figure 2. Histologic features of bronchoscopy-guided transbronchial biopsy samples. (*A*) Hematoxylin and eosin staining differentiated between AC (indicated by a square) and adenocarcinoma components (indicated by a dotted square). The AC component exhibited three to four mitoses per 2 mm^2 and lacked necrosis (*B*; 20×, *C*; 40× magnification, with arrows indicating mitosis). (*D*) Immunostaining revealed TTF-1 positivity exclusively in the adenocarcinoma components, (*E*) whereas only the AC component was positive for synaptophysin. (*F*) The Ki-67 staining indicated an average positivity of 15% and 30% in hotspots in each component. AC, atypical carcinoid.

and *H*). The liver metastasis had a slight reduction. The response was categorized as stable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria. Nevertheless, he experienced grade 2 to 3 hepatic dysfunction, leading to the discontinuation of sotorasib. Once his hepatic function improved to grade 1, sotorasib was reintroduced at a lower dose. Unfortunately, he encountered grade 3 liver failure once again, resulting in the cessation of sotorasib. Subsequently, his condition swiftly deteriorated during the treatment interruption, and he passed away 2 months after initiating sotorasib.

Discussion

We described the first case of effective treatment with sotorasib for metastatic AC harboring the KRAS G12C mutation, to our knowledge.

Carcinoid can exhibit various growth patterns including organoid, trabecular, rosette, insular, pseudoglandular, and solid. The tumor cells are typically uniform and can feature round to oval or spindled nuclei. These nuclei have finely granular chromatin. In addition, the cells often have moderate to abundant eosinophilin cytoplasm and inconspicuous nucleoli. In 2021 WHO classification, AC has two to ten mitoses/2 mm^2 or may have necrosis, which is usually focal and punctate. In the immunohistochemical studies, carcinoid was positive for synaptophysin, chromogranin A, and CD56. TC will have a Ki-67 expression of less than 5%, whereas AC has 5% to 30%. In this case, the lung biopsy revealed the presence of an adenocarcinoma component, whereas most consisted of the AC component. In a subsequent biopsy obtained from a liver metastasis, only the AC component harboring the KRAS G12C mutation was detected. On the basis of these findings, the diagnosis of KRAS G12C mutation-positive AC was established.

Several reports have been published regarding CGP in neuroendocrine tumors thus far.[2–4] These studies have consistently revealed a reduced occurrence of TP53 or RB1 mutations in carcinoids when contrasted with high-grade neuroendocrine tumors. Regarding the mutations of TP53 and RB1, it is reported that they are observed in 81% to 89% and 26% to 42% of large cell neuroendocrine carcinoma (LCNEC) cases, whereas in carcinoids, they are observed in only 5% to 29% and 2% to 29%, respectively. Similarly, the incidence of targeted gene mutations was found to be notably infrequent in carcinoids. Comparatively, the TMB was considerably lower in carcinoids as opposed to high-grade neuroendocrine tumors, and it is a common

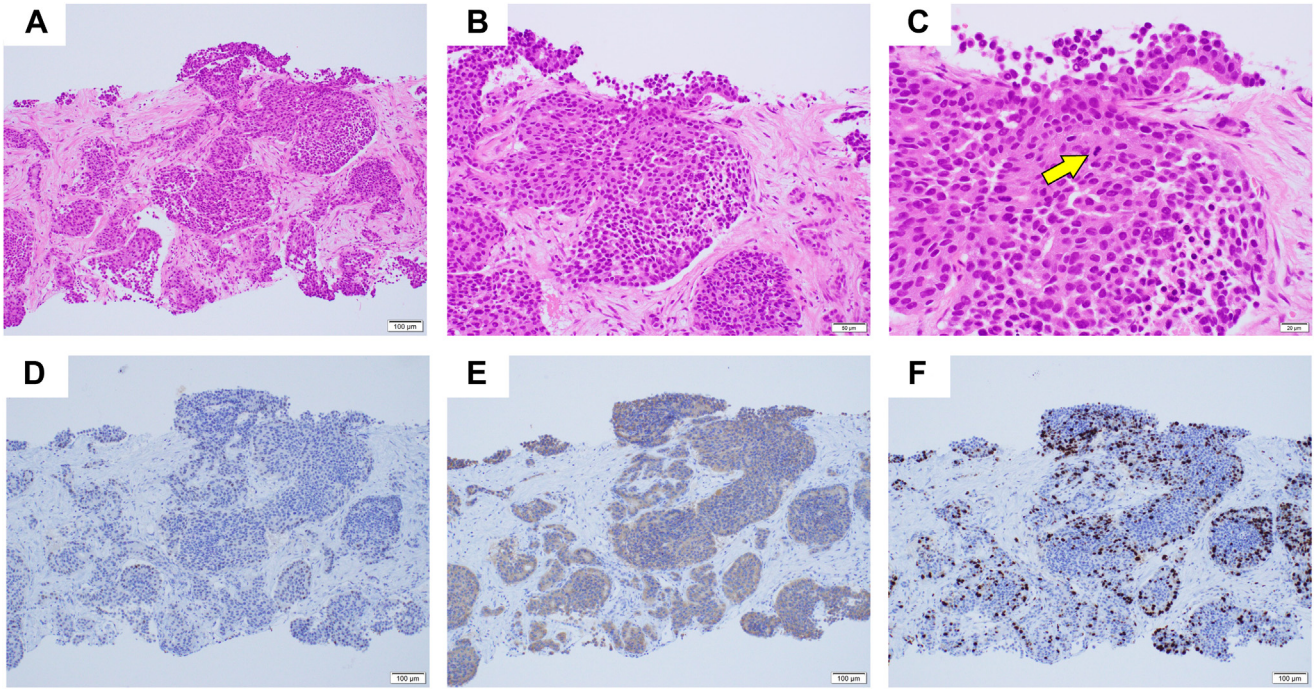

Figure 3. Histologic findings of liver biopsy samples. (*A*) Hematoxylin and eosin staining revealed only the atypical carcinoid components. The liver biopsy samples exhibited one to two mitoses per 2 mm^2 and lacked necrosis (*B*; 20×, *C*; 40×, magnification, with arrows indicating mitosis). Immunostaining was (*D*) negative for TTF-1 but (*E*) positive for synaptophysin. (*F*) Ki-67 staining indicated an average positivity of 20% and 30% in hotspots.

observation for PD-L1 expression to be negative in carcinoids. These findings collectively align with the diagnosis of the current case as an AC. Nevertheless, the low levels of microsatellite instability and TMB, in conjunction with negative PD-L1 expression, further compounded by the presence of mutations in KEAP1 and STK11 in addition to KRAS G12C, were regarded as contributing factors to the ineffectiveness of atezolizumab in this case.

In general, carcinoids are considered to progress slowly, with 5-year survival rates of 91% for TC and 68.5% for AC.[5] In this case, a rapid deterioration was observed during the initial 1-month period, clinically suggesting the possibility of LCNEC rather than AC. In WHO 2021 classification, however, the diagnosis of LCNEC is based on the presence of mitotic figures of 11 greater than 2 mm^2, and necrosis is often marked, with Ki-67 exceeding 30% and usually 40% to 80%. Furthermore, the absence of TP53 and RB1 mutations, which are frequently observed in LCNEC, was considered to more strongly suggest that the diagnosis in this case is AC. There is also report of disseminated grade 2 neuroendocrine tumor, which is considered to be AC, with an acute clinical course.[6] This case reveals monthly progression, and it is plausible that certain instances of AC might exhibit an aggressive trajectory. Given the effectiveness of sotorasib, the KRAS G12C mutation was deemed a driver mutation in his tumor, potentially contributing to the aggressive nature of the disease progression.

Conclusions

We described the first case of effective treatment with sotorasib for metastatic AC harboring the KRAS G12C mutation. Although carcinoid tumors infrequently possess driver mutations, it remains valuable to investigate genetic mutations, particularly in cases displaying an aggressive nature. This exploration is justified by the potential efficacy of molecular targeted therapy in their treatment.

CRediT Authorship Contribution Statement

Masafumi Saiki: Investigation, Writing—original draft.

Chisa Omori: Writing—review and editing.
Honami Morikawa: Writing—review and editing.
Ken Shinohara: Writing—review and editing.
So Shimamura: Writing—review and editing.
Hiroki Ohkoshi: Writing—review and editing.
Yoshinori Uchida: Writing—review and editing.
Tomohiro Inoue: Writing—review and editing.
Tetsuo Kondo: Writing—review and editing.
Shinnosuke Ikemura: Writing—review and editing.

Kenzo Soejima: Writing—review and editing, Project administration.

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