

Effective combined therapy with ramucirumab for advanced pulmonary pleomorphic carcinoma

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Abstract

Pulmonary pleomorphic carcinoma (PPC) is a rare disease with a poor prognosis. Most patients with PPC are refractory to chemotherapy, whereas good responses to platinum-based chemotherapy in combination with the anti-angiogenesis agent bevacizumab have been reported. An 82-year-old man was diagnosed with PPC with a clinical stage of T3N0M0, coincident with primary lung adenocarcinoma in an early stage. We chose single-agent chemotherapy with docetaxel as an initial treatment, but both the primary adenocarcinoma and two PPC lesions in the right lung were enlarged after one treatment cycle. We subsequently started treatment with ramucirumab and docetaxel, and thereafter, the disease showed a good partial response. Here, we report the first case of advanced PPC that was effectively treated with chemotherapy and the anti-VEGFR-2 antibody ramucirumab. These observations suggest a potential therapeutic strategy for patients with PPC.

Introduction

Pulmonary pleomorphic carcinoma (PPC) is a rare disease that accounts for <1% of all lung tumours and carries a poor prognosis. PPC is known to be refractory to chemotherapy among non-small cell lung cancers. Recently, several cases have been reported in which chemotherapy with bevacizumab exerted a tumour reduction [1]. These observations suggest that anti-vascular endothelial growth factor (VEGF) agents may be promising for controlling PPC progression.

Ramucirumab is an anti-VEGF Receptor 2 (VEGFR2) antibody that blocks the binding of VEGF to VEGFR2. Here, we report an effective combined therapy with ramucirumab for patients with PPC.

Case Report

An 82-year-old man had been observed for 12 years after undergoing nephrectomy for left renal cell carcinoma, with pathological stage 1 pT1aN0M0. He underwent periodic computed tomography (CT) to detect metastasis, and CT found that there were a few nodules in his right lung.

A small subpleural nodule on the right upper lung (RUL) had not changed much for at least 3 years, but two other lesions in the right lower lobe (RLL) had enlarged rapidly. We subsequently performed CT-guided biopsies of these nodules, and they were diagnosed as primary lung adenocarcinoma on the RUL pleura and PPCs with spindle cells in the RLL (Fig. 1).

The patient was diagnosed with T1aN0M0 stage IA primary lung adenocarcinoma in the RUL and T3N0M0 stage IIB PPC in the RLL. We decided to treat him with systemic chemotherapy due to his poor pulmonary function and choose a single-agent therapy with docetaxel (60 mg/m², tri-weekly) as an initial treatment owing to his advanced age. After one cycle of this regimen, CT revealed that the two PPC lesions in the RLL had progressed rapidly, and some new lesions had also appeared, while the adenocarcinoma in the RUL had not been affected. We subsequently added ramucirumab (600 mg/m²) to docetaxel in his treatment regimen, and thereafter, the PPC lesions were markedly decreased in size after only one cycle of this treatment, showing partial remission according to the Response Evaluation Criteria in Solid Tumours (Fig. 2). Furthermore, the size of the adenocarcinoma in the RUL was slightly reduced. After four cycles, while the

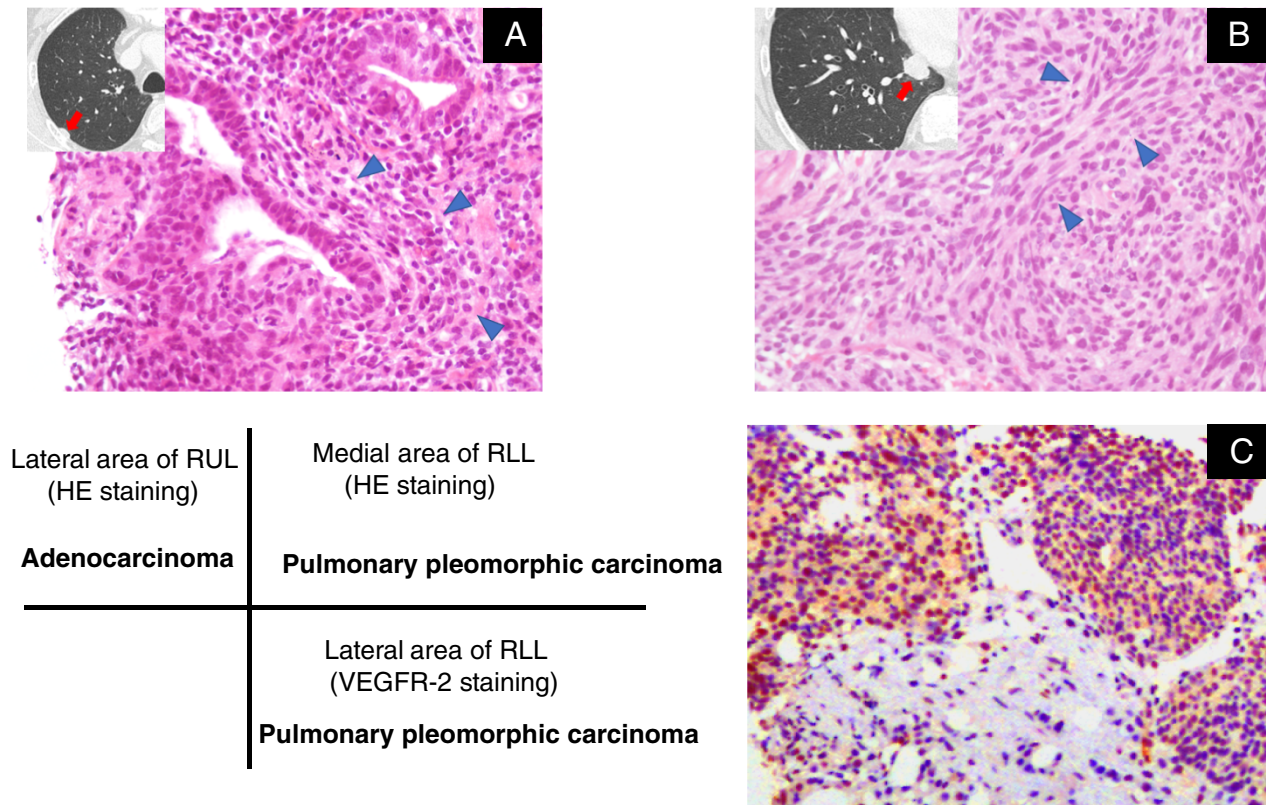


Figure 1. Histological findings of the lung. The right upper lung (RUL) pleura nodule exhibited adenocarcinoma (A), while the right lower lobe (RLL) showed many spindle cells spread into a bundle (B). Immunohistochemistry showed positive cytoplasmic staining for VEGFR2. H&E, $\times 200$; immunostaining of VEGFR2, $\times 200$ (C).

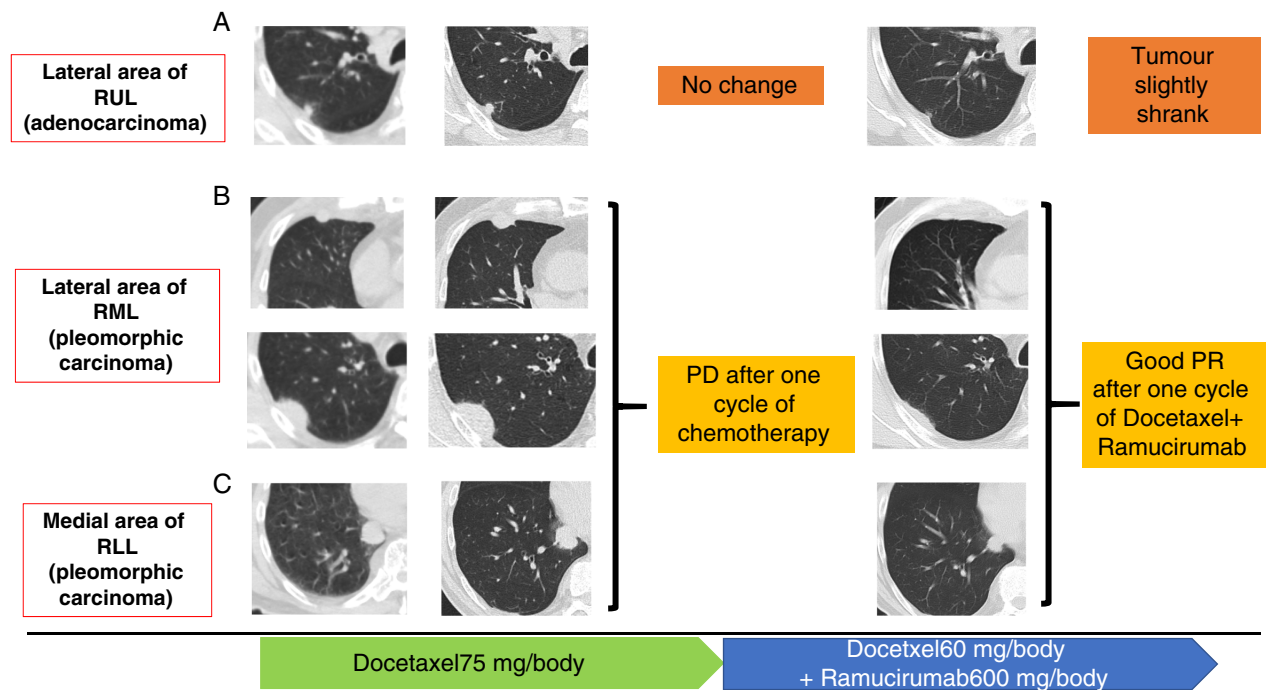


Figure 2. Clinical course of chemotherapy. (A) Adenocarcinoma in the right upper lobe (RUL). (B) PPC of the right middle lobe (RML). (C) PPC of the right lower lobe (RLL).

tumour lesions in lung were well controlled, a new small brain metastasis was detected. He is currently continuing the new immune checkpoint inhibitors (pembrolizumab 200mg/body tri-weekly) regimen, and the disease is well controlled.

Discussion

According to the 2015 WHO classification of Lung Tumours, PPC is defined as a malignancy composed of spindle cells or giant cells that account for more than 10% of patient's entire tumour. Only 0.1–0.3% of all lung cancer is PPC, and this cancer generally progresses rapidly [2]. Advanced PPC has been found to respond poorly to both platinum- and non-platinum-based systemic chemotherapy. Therefore, standard therapeutic strategy for advanced PPC remains unclear.

Previous reports have shown good response to treatment with combined bevacizumab and chemotherapy [3], while the mechanism of action of bevacizumab against PPC is still unknown. Several studies have reported that PPC induces a high level of VEGF expression in the tumour, and these findings may indicate a microenvironment with enriched angiogenesis in PPC compared to tumours of typical non-small lung cancer (NSCLC). Therefore, using bevacizumab may be a useful strategy for controlling PPC because it binds to soluble VEGF-A and inhibits vessel formation, resulting in inhibition of tumour progression [4].

Ramucirumab is a receptor antagonist that binds to VEGF Receptor 2 (VEGFR2), and it blocks the interaction between VEGFs (including VEGF-A, VEGF-C, and VEGF-D) and VEGFR2 [5]. Therefore, it is possible that ramucirumab is a useful choice to treat PPC, like bevacizumab.

Our case of PPC expressed VEGFR2 in the cytoplasm as shown by immunohistochemical staining with anti-VEGFR2 antibodies (Fig. 1C), and ramucirumab therapy in addition to docetaxel had a remarkable effect on the patient's tumour. Moreover, this case also showed that single-agent docetaxel did not result in tumour reduction.

In conclusion, we encountered a patient with PPC that showed remarkable response to ramucirumab combined with docetaxel, and a further study with ramucirumab in combination with chemotherapy in patients with PPC is warranted.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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