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Case Report

A Case of Lung Adenocarcinoma with Marked Improvement of Pulmonary Lymphangitic Carcinomatosis by Adding Bevacizumab to Cisplatin and Pemetrexed

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Keywords
Bevacizumab · Lung cancer · Pulmonary lymphangitic carcinomatosis

Abstract
A 40-year-old man with a diagnosis of lung adenocarcinoma (cT4N3M1c, stage IVB) experienced worsening of lymphangitic carcinomatosis in the right lung and right pleural effusion after receiving 1 cycle of first-line chemotherapy consisting of cisplatin and pemetrexed. Bevacizumab was thus added from the second cycle of the cisplatin-pemetrexed regimen, leading to a marked improvement in pulmonary lymphangitic carcinomatosis and a decrease in pleural effusion. Subsequently, maintenance therapy consisting of pemetrexed and bevacizumab was continued, successfully leading to long-term progression-free survival. Generally, pulmonary lymphangitic carcinomatosis shows poor prognosis because of poor response to chemotherapy. However, recent studies have been elucidating the role of the vascular endothelial growth factor A (VEGF-A)/VEGF receptor-2 pathway in pulmonary lymphangitic carcinomatosis. Therefore, bevacizumab is expected to be beneficial in the treatment of this pathological condition.

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Introduction

Pulmonary lymphangitic carcinomatosis is a form of lung metastasis of malignancy, accounting for 6–8% of all cases of lung metastases [1]. Generally, pulmonary lymphangitic carcinomatosis responds poorly to chemotherapy and shows poor prognosis, and it is well known that approximately 50% of the patients die within 3 months after its diagnosis [1]. We recently encountered a case of pulmonary lymphangitic carcinomatosis that markedly improved in response to bevacizumab added to a chemotherapy regimen after progressive disease was shown as the best response to the chemotherapy alone, and here we report the case.

Case Report

A 40-year-old man, with unremarkable medical history and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, was found to have abnormal chest X-ray findings at medical checkup and referred to our hospital. Chest X-ray at our hospital showed nodular opacity in the right upper lung field, reticular opacity in the entire right lung field, and right pleural effusion. Computed tomography (CT) of the chest showed a 38-mm nodule in the right upper lobe, increased bronchovascular markings and shaggy appearance in the entire right lung, and right pleural effusion (Fig. 1a). A bronchoscopic biopsy of the lung tumor tissue led to the diagnosis of lung adenocarcinoma with surrounding lymphangitic carcinomatosis. After detailed examination of the whole body, the disease was staged as cT4N3 (with metastases to the right supraclavicular and right mediastinal-hilar lymph nodes), M1c (BRA), stage IVB. Genetic testing of the cancer tissue specimens showed negative results for EGFR mutation and ALK translocation. The brain metastasis was initially treated with whole-brain irradiation, followed by systemic chemotherapy consisting of cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2) every 3 weeks. However, before the second cycle of the chemotherapy, cough and dyspnea developed. CT showed no worsening of the primary lesion, but showed worsening of pulmonary lymphangitic carcinomatosis in the right lung and right pleural effusion (Fig. 1b). These findings were attributed to an inadequate effect of cisplatin and pemetrexed rather than complication by cardiac failure, because the patient had no decrease in cardiac function or any abnormal left lung findings. Thus, from the second cycle, cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), and bevacizumab (7.5 kg/m^2) were to be given every 3 weeks, in the hope that bevacizumab, an angiogenesis inhibitor effective in controlling cancerous pleural effusion, would exert its efficacy on pulmonary lymphangitic carcinomatosis as well. After 1 cycle of the combined use of bevacizumab and chemotherapy, CT showed a marked improvement of pulmonary lymphangitic carcinomatosis and a reduction of pleural effusion (Fig. 1c). Then, stable disease was finally achieved after 4 cycles of the regimen of cisplatin and pemetrexed plus bevacizumab. Consequently, subsequent maintenance therapy consisting of pemetrexed and bevacizumab was continued up to 16 cycles, successfully leading to long-term progression-free survival.

Discussion

We encountered a case in which the combination of bevacizumab with chemotherapy led not only to an improvement of malignant pleural effusion but also to a marked improve-

ment of pulmonary lymphangitic carcinomatosis. Generally, pulmonary lymphangitic carcinomatosis is a sign of poor prognosis, seen in 6–8% of all cases of lung metastases [1]. In addition to lung cancer, breast and stomach cancers are the common primary tumors causing pulmonary lymphangitic carcinomatosis [1]. A suggested mechanism of the onset of pulmonary lymphangitic carcinomatosis is retrograde lymphatic spread of tumor cells from the mediastinal and hilar lymph node metastases into the pulmonary lymphatics [2]. As for the molecular mechanism, it has been suggested that vascular endothelial growth factor (VEGF) produced by tumor cells binds to VEGF receptor (VEGFR) on the lymphatic endothelial cells, which promotes lymphangiogenesis, thereby accelerating the lymphatic spread of tumor cells [3].

Bevacizumab is a humanized IgG1 monoclonal antibody that specifically binds to VEGF-A, and inhibits its binding to VEGFR-1 and VEGFR-2, thereby inhibiting tumor angiogenesis. Currently, bevacizumab combined with chemotherapy is positioned as one of the standard therapies in patients with advanced non-small cell lung cancer based on a study (ECOG4599) that showed prolongation of overall survival [4].

Bevacizumab is known to exert the efficacy on malignant pleural effusion by reducing the activity of VEGF-A expressed in pleural effusion [5, 6]. For pulmonary lymphangitic carcinomatosis, on the other hand, the effectiveness of bevacizumab is currently considered to be unclear. This is because, in lymphangiogenesis, a significant role of the signaling pathway involving VEGF-C and VEGF-D binding to VEGFR-3, among other members of the VEGF family, has been shown [7, 8], while evidence has been limited regarding the role of the signaling pathway involving VEGF-A, which is targeted by bevacizumab.

However, in recent years, increasing evidence has been accumulating about the significance of the VEGF-A signaling pathway in lymphangiogenesis and lymphangitic carcinomatosis. Specifically, an in vitro study showed that VEGF-A promoted lymphatic endothelial cell proliferation and the VEGF-A-induced proliferation was inhibited by blockage of VEGFR-2, indicating a possible contribution of VEGF-A to lymphangiogenesis via VEGFR-2 [9]. An in vivo study in VEGF-A-overexpressing mice reported the promoted formation of lymphatic vessels in the wound-healing process [10]. Similarly, in VEGF-A-overexpressing mice bearing skin cancer, VEGF-A promoted active expression of VEGFR-2 in tumor-associated lymphatic vessels and induced tumor metastasis to lymph nodes [11]. Furthermore, in mice with delayed hypersensitivity reactions, inflammation-induced lymphangiogenesis was potently blocked by systemic administration of a VEGF-A neutralizing antibody [12]. Thus, these studies suggest that VEGF-A is potentially involved not only in angiogenesis but also in lymphangiogenesis via VEGFR-2, in the processes of tumor growth and metastasis. In fact, there has been a clinical case report describing a patient with diffuse pulmonary lymphangiomatosis, who had VEGF-A overexpression in diseased lymphatic vessels and was successfully treated with bevacizumab [13].

In summary, this report presented a case of advanced lung adenocarcinoma that poorly responded to chemotherapy alone but showed long-term improvement in response to adding bevacizumab to the chemotherapy regimen. As recent studies have been elucidating the role of the VEGF-A/VEGFR-2 pathway in lymphangitic carcinomatosis, bevacizumab is expected to be beneficial in the treatment of this pathological condition.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no relevant financial interests.

References

1 Bruce DM, Heys SD, Eremin O: Lymphangitis carcinomatosa: a literature review. J R Coll Surg Edinb 1996;41:7–13.
2 Chandler GN, Telling M: Lymphangitis carcinomatosa. Br Med J 1952;2:639–641.
3 Shimizu K, Kubo H, Yamaguchi K, Kawashima K, Ueda Y, Matsuo K, Awane M, Shimahara Y, Takabayashi A, Yamaoka Y, Satoh S: Suppression of VEGFR-3 signaling inhibits lymph node metastasis in gastric cancer. Cancer Sci 2004;95:328–333.
4 Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–2550.
5 Tamiya M, Tamiya A, Yamadori T, Nakao K, Asami K, Yasue T, Otsuka T, Shiroyama T, Morishita N, Suzuki H, Okamoto N, Okishio K, Kawaguchi T, Atagi S, Kawase I, Hirashima T: Phase 2 study of bevacizumab with carboplatin-paclitaxel for non-small cell lung cancer with malignant pleural effusion. Med Oncol 2013;30:676.
6 Du N, Li X, Li F, Zhao H, Fan Z, Ma J, Fu Y, Kang H: Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. Oncol Rep 2013;29:2332–2340.
7 Stacker SA, Baldwin ME, Achen MG: The role of tumor lymphangiogenesis in metastatic spread. FASEB J 2002;16:922–934.
8 He Y, Rajantie I, Pajusola K, Jeltsch M, Holopainen T, Yla-Herttuala S, Harding T, Jooss K, Takahashi T, Alitalo K: Vascular endothelial cell growth factor receptor 3-mediated activation of lymphatic endothelium is crucial for tumor cell entry and spread via lymphatic vessels. Cancer Res 2005;65:4739–4746.
9 Satoshi H, Young-Kwon H, Natasha H, Vivien S, Kant M, Towia L: Identification of vascular lineage-specific genes by transcriptional profiling of isolated blood vascular and lymphatic endothelial cells. Am J Pathol 2003;162:575–586.
10 Hong YK, Lange-Asschenfeldt B, Velasco P, Hirakawa S, Kunstfeld R, Brown LF, Bohlen P, Senger DR, Detmar M: VEGF-A promotes tissue repair-associated lymphatic vessel formation via VEGFR-2 and the alpha1beta1 and alpha2beta1 integrins. FASEB J 2004;18:1111–1113.
11 Hirakawa S, Kodama S, Kunstfeld R, Kajiya K, Brown LF, Detmar M: VEGF-A induces tumor and sentinel lymph node lymphangiogenesis and promotes lymphatic metastasis. J Exp Med 2005;201:1089–1099.
12 Halin C, Tobler NE, Vigl B, Brown LF, Detmar M: VEGF-A produced by chronically inflamed tissue induces lymphangiogenesis in draining lymph nodes. Blood 2007;110:3158–3167.
13 Aman J, Thunnissen E, Paul MA, van Nieuw Amerongen GP, Vonk-Noordegraaf A: Successful treatment of diffuse pulmonary lymphagiomatosis with bevacizumab. Ann Intern Med 2012;156:839–840.

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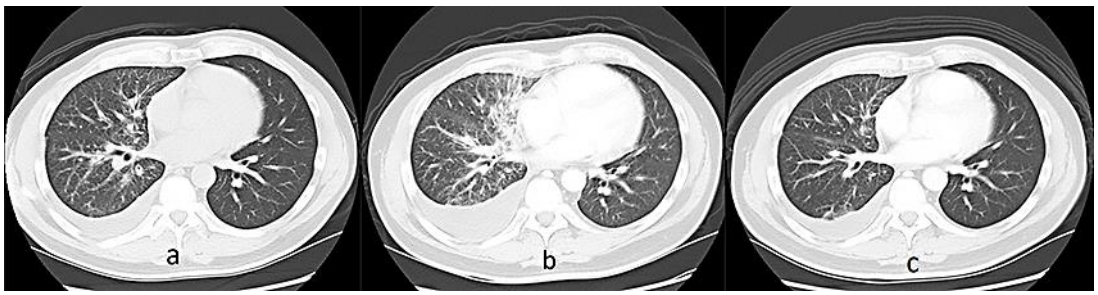

Fig. 1. Sequential chest CT scans showing the changes in right pulmonary lymphangitic carcinomatosis and right pleural effusion. **a** Before treatment. **b** After 1 cycle of first-line therapy with cisplatin and pemetrexed. **c** After 1 cycle of bevacizumab plus cisplatin and pemetrexed.