Simultaneous chylous ascites and chylothorax during ramucirumab plus docetaxel chemotherapy in a patient with non-small lung cell cancer

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Abstract

A 69-year-old woman was diagnosed as having non-small cell lung cancer (adenocarcinoma, T1aN3M1b). She had no history of surgery or abdominal trauma. She was treated with ramucirumab (10 mg/kg) plus docetaxel (60 mg/m²) intravenously (RAM + DTX) every 3 weeks. Although an enhanced CT examination showed a partial tumor response after eight courses of RAM + DTX, she gradually began to experience abdominal fullness with severe peripheral pitching edema. Her body weight increased by 18 kg in 2 months and RAM + DTX chemotherapy was discontinued. An enhanced CT examination showed a large amount of ascites and pleural effusion, with no obstructions of the central vein or lymphatic ducts. The ascites were white and milky in appearance and contained 527 mg/dL of triglyceride. In addition, her pleural effusion was also white and milky in appearance. No further increases in ascites and pleural effusion were observed thereafter. Four months after her last RAM + DTX chemotherapy, she continued to exhibit a partial response and no increases in ascites or pleural effusion were present. The chylous effusion might have been caused by the RAM + DTX chemotherapy.

Keywords Ramucirumab · Docetaxel · Chylous ascites · Chylothorax

Abbreviations

NSCLC	Non-small cell lung cancer
RAM	Ramucirumab
DTX	Docetaxel
VEGFR	Vascular endothelial growth factor receptor
LECs	Lymphatic endothelial cells

Introduction

Ramucirumab is a human immunoglobulin G1 monoclonal antibody receptor antagonist against vascular endothelial growth factor receptor (VEGFR) 2 and has been approved for the treatment of gastric cancer, colorectal cancer, and NSCLC [1]. Ramucirumab inhibits angiogenesis by binding

specifically to the extracellular domain of VEGFR-2 inhibiting binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D [2]. Inhibition of the VEGF pathway has an anti-cancer effect but can cause adverse events, possibly attributable to the VEGF pathway (hypertension, proteinuria, hemorrhage/bleeding, gastrointestinal perforation, arterial thromboembolic events and venous thromboembolic events). Although the mechanisms underlying these adverse events are not clear, previous reports have raised the possibility that damage to endothelial cells in the capillaries, caused by inhibition of the VEGF pathway by ramucirumab, may lead to these adverse events.

In this case, we report a patient who showed simultaneous chylous ascites and chylothorax during ramucirumab and docetaxel chemotherapy with NSCLC.

Case presentation

A 69-year-old woman was diagnosed as having non-small cell lung cancer (NSCLC) (adenocarcinoma, T1aN3M1b). She had no history of surgery or abdominal trauma. She underwent four courses of chemotherapy consisting of carboplatin/paclitaxel/bevacizumab and then received 38 courses

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of bevacizumab as a maintenance therapy. Her disease progressed, and she was treated with ramucirumab (10 mg/kg) plus docetaxel (60 mg/m²) intravenously (RAM + DTX) every 3 weeks. After eight courses of RAM + DTX, an enhanced CT examination showed a partial tumor response, but grade 2 proteinuria was observed. The administration interval was subsequently adjusted to 4 weeks. Four weeks thereafter, she gradually began to experience abdominal fullness with severe peripheral pitching edema. Her body weight increased by 18 kg in 2 months. An abdominal ultrasonography examination showed massive ascites and lymphedema, and severe erosions were observed on her legs; consequently, the patient was hospitalized, and RAM + DTX chemotherapy was discontinued. An enhanced CT examination showed a large amount of ascites and pleural effusion, with no obstructions of the central vein or lymphatic ducts (Fig. 1). We aspirated the ascites three times (2.8, 2.0, and 1.4 L) as well as the pleural effusion (0.7 L). The ascites were white and milky in appearance and contained 527 mg/

dL of triglyceride (TG) (Table 1; Fig. 2). In addition, her pleural effusion was also white and milky in appearance. Cytological examinations failed to detect malignant cells in the ascites or pleural effusion. No further increases in ascites and pleural effusion were observed thereafter. She

Table 1 Characteristics of ascites

Laboratory data	
Triglyceride (mg/dL)	527
Cell count ($\times 10^{-3}/\mu\text{L}$)	200
Total protein (g/dL)	0.6
Serum to ascites albumin gradient (g/dL)	1.9
Total cholesterol (mg/dL)	32
Ascites/serum ratio of total cholesterol	0.21
Lactate dehydrogenase (IU/L)	49
Culture	Negative
Cytology	Class I

Fig. 1 Enhanced CT obtained **a** 1 month before admission, **b** at the time of admission, and **c** 2 months after admission

Fig. 2 Appearance of ascites

was discharged on the 17th day of her hospital stay. Four months after her last RAM + DTX chemotherapy, she continued to exhibit a partial response and no increases in ascites or pleural effusion were present.

Discussion

Chylous ascites and/or pleural effusion is rare and is defined as a triglyceride-rich peritoneal fluid with a milky appearance, characterized by the presence of thoracic or intestinal lymph in the abdominal cavity [3]. Chylous ascites is caused by the thoracic duct obstruction or disruption (trauma/surgery, infections, radiotherapy, autoimmune disease) or increased lymph production (cirrhosis, cardiovascular disease). Invasion and disruption of the normal lymph flow (lymphomas, neuroendocrine tumors, sarcomas, leukemia, solid organ malignancies) is also the cause of chylous ascites.

Because a cell culture and a cytological examination of the ascites were negative in the present case, there is a low probability that infection or peritoneal dissemination of the lung cancer had occurred. In addition, her liver function was normal, and she had not undergone surgery or been injured. After the discontinuation of the chemotherapy, the ascites and pleural effusion did not increase in volume again, suggesting that the chylous effusion might have been caused by the RAM + DTX chemotherapy. Although the mechanism by which the RAM + DTX chemotherapy caused the chylous effusion is uncertain, we speculate that the ramucirumab might have damaged the lymphatic endothelial cells and,

consequently, obstructed the lymphatic ducts. Although VEGFR3 has been reported to be expressed in lymphatic endothelial cells (LECs), VEGFR2 also plays an important role in controlling the development of the lymphatic vascular system [4]. However, the situation may differ in diseased tissues; the amount of VEGFR2 protein in lysates of LECs derived from lymphangioma patients was significantly greater than that from human umbilical vein endothelial cells [5]. Therefore, ramucirumab might cause chylous ascites and chylothorax by blocking VEGFR2 in LECs. It is unclear whether ramucirumab could occlude a thick lymphatic duct. A direct effect of ramucirumab would be a reduction in blood vessel sprouting and formation and a moderate destruction of existing tumor vasculature. Dynamic contrast-enhanced magnetic resonance imaging revealed that the perfusion and permeability in a liver metastasis decreased after treatment with ramucirumab [5]. We speculated that the accumulation of obstruction of small lymphatic ducts might result in the obstruction of lymphatic flow.

Docetaxel was used in this case. Docetaxel has been one of the most important chemotherapeutic drugs for cancer treatment. Currently, docetaxel is widely used for treatment of breast, non-small cell lung, gastric, head and neck, ovary, esophageal, uterus body and prostate cancers. There was a case report that a patient with prostate adenocarcinoma showed the chylothorax and chylous ascites with vertebral metastases after docetaxel chemotherapy [6]. Therefore, in our case, there was the possibility that the effect of DTX in combination with RAM might be related to the chylothorax and chylous ascites. But, it is difficult to speculate the mechanism of the chylothorax and chylous ascites by docetaxel.

Bevacizumab is a humanized monoclonal antibody directed against VEGF165 and RAM is a monoclonal antibody receptor antagonist against VEGFR 2. The mechanisms of Bevacizumab and RAM may resemble. In addition, she underwent bevacizumab treatment for a long period of time. Therefore, there is the possibility that bevacizumab might influence the chylous ascites and chylothorax. Pleural effusion is one of the major adverse events of bevacizumab, but there was the case with the chylothorax during bevacizumab treatment who underwent surgical treatment [7].

This is the first report of chylous ascites and chylothorax during ramucirumab plus docetaxel chemotherapy in a patient with no history of surgery or trauma.

Compliance with ethical standards

Conflict of interest There is no competing interest.

Ethical statement In Chiba University hospital, we announce that clinical studies are performed in this hospital and that their results are published. We explained her and got the written informed consent in accordance with the Declaration of Helsinki.

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