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Case report

Bevacizumab helped resolve pericardial and pleural effusion that was associated with malignant ovarian clear cell carcinoma

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1. Introduction

Pericardial effusion is an uncommon fatal complication of advanced or recurrent ovarian cancer. Dauplat et al. reported that its incidence was 2.4%, and all 6 patients in that series also had pleural effusion (Dauplat et al., 1987). A PubMed search reveals 12 case reports of cardiac tamponade that was associated with ovarian carcinoma, and the median overall survival (OS) among these cases was <2 months (Feferkorn et al., 2014). In this report, we describe a patient with ovarian clear cell carcinoma who ultimately developed pericardial and pleural effusion, which were successfully managed using bevacizumab (Bev). To our best knowledge, this is the first report of using Bev to treat pericardial effusion that was associated with ovarian cancer.

2. Case report

A 52-year-old nulliparous woman initially visited our hospital with an ovarian tumor of 19 cm in diameter in 2010. After primary debulking surgery, she was diagnosed with stage IC ovarian clear cell carcinoma with positive cytology of ascites and the rupture of the left ovarian tumor during surgery. She underwent 6 cycles of adjuvant chemotherapy with paclitaxel and carboplatin. Three years later, she developed multiple lung metastases (maximum diameter: 20 mm) and subsequently underwent 6 cycles of paclitaxel and carboplatin, which resulted in complete remission. However, she developed malignant ascites with lung metastases (maximum diameter: 10 mm) and deep vein thrombosis after 14 months. We initiated treatment using warfarin and she underwent 2 cycles of carboplatin therapy, which induced anaphylaxis, and then underwent 3 cycles of pegylated liposomal doxorubicin (40 mg/m^2), which induced interstitial pneumonia. Although the interstitial pneumonia improved with prednisolone treatment, she subsequently presented with minor chest pain, a cough, and dyspnea in February 2015 (Fig. 1).

Her blood pressure and heart rate were normal at the February 2015 presentation, although computed tomography (CT) revealed lung metastases (maximum diameter: 11 mm), minor right-side pleural effusion, and pericardial effusion. Echocardiography revealed an echo-free space of 20 mm and diastolic collapse of the right atrium. We performed pericardiocentesis, drained 700 mL of bloody fluid, and performed cytology, which revealed clear cell adenocarcinoma. The patient refused combination chemotherapy with Bev due to the risk of gastrointestinal perforation (GIP), and underwent 3 months of weekly treatment with paclitaxel (wPTX, 80 mg/m^2). Unfortunately, she developed a cough and dyspnea due to the right-side pleural effusion, and refused hospitalization for talc pleurodesis; therefore, we performed outpatient thoracocentesis. The interval between thoracocentesis was reduced, and she received an oral etoposide (50 mg daily). However, she required weekly thoracocentesis, and her dyspnea was exaggerated. Her oxygen saturation was 82–86% in room air, with a blood pressure of 119/75 mm Hg and a heart rate of 124 bpm.

In May 2015, the patient was admitted to our emergency department, where echocardiography revealed 25 mm of pericardial effusion and diastolic collapse of the right atrium and ventricle. Her oxygen saturation improved to 95% with an oxygen mask. As CT revealed pulmonary embolism, despite her use of warfarin, we decided to place an inferior vena cava filter, and administered heparin in addition to the warfarin. The patient exhibited bilateral pleural effusion and pericardial effusion (Fig. 2), and her Eastern Cooperative Oncology Group performance status (PS) was 3. Furthermore, she had mild ascites, underwent right-side thoracocentesis, and 1450 mL of bloody pleural effusion was drained, although her dyspnea and cough persisted. Her symptoms improved after

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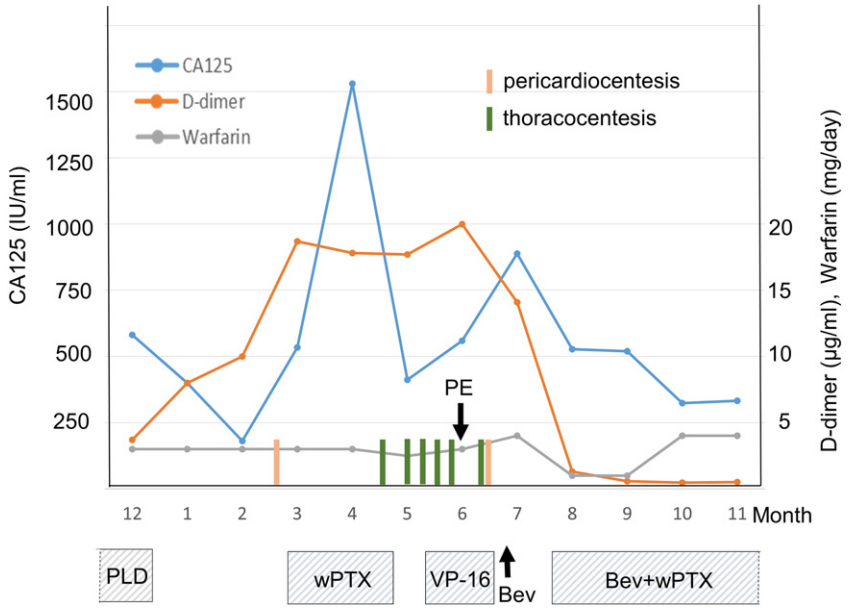

Fig. 1. Treatment course for a patient with ovarian clear cell carcinoma (December 2014 to November 2015). PLD, pegylated liposomal doxorubicin at 40 mg/m^2 every 28 days; wPTX, weekly paclitaxel at 80 mg/m^2; VP-16, 50 mg of oral etoposide daily; Bev, 15 mg/kg of bevacizumab; Bev + wPTX, 15 mg/kg of bevacizumab every 21 days and weekly paclitaxel at 80 mg/m^2; PE, pulmonary embolization.

750 mL of pericardial effusion was drained via pericardiocentesis, and she agreed to receive Bev therapy. After intravenous administration of 15 mg/kg of Bev, she was discharged. After 3 weeks, chest radiography and echocardiography revealed no increase of pleural or pericardial effusion, and her PS was improved to 1. She began a combination regimen of Bev (15 mg/kg, triweekly) and wPTX (80 mg/m^2). She has not required pericardiocentesis or thoracocentesis for 18 weeks after the initiation of Bev therapy.

3. Discussion

Malignant pericardial effusion or cardiac tamponade reduces patients' quality of life and can lead to a life-threatening condition. Approximately one-half of these cases are comprised of patients with lung cancer and breast cancer, and when malignant cells are detected in the pericardial effusion, the patients' median OS is 7.3 months (Gornik et al., 2005). This is consistent with the findings from the 12 cases of patients with ovarian cancer. In addition to repeated pericardiocentesis, various treatments have been reported, such as surgical or percutaneous balloon pericardiostomy, sclerotherapy, intrapericardial chemotherapy, and radiation therapy (Gornik et al., 2005). In the present case, we treated the patient using anticoagulation therapy for the pulmonary embolism and deep vein thrombosis, which was likely due to the activation of her clear cell carcinoma (Matsuura et al., 2007). Unfortunately, the surgical or invasive approach increases the risk of bleeding, and sclerotherapy increases the risk of constrictive pericarditis, although Petersen et al. have reported successfully treating a patient with ovarian cancer using intrapericardial administration of thiotepa (Petersen et al., 2009). Chen et al. have recently reported intrapericardial administration of Bev for a patient with lung cancer and pericardial effusion (Chen et al., 2015). Although most cases of malignant pericardial effusion or cardiac tamponade with advanced or recurrent ovarian cancer exhibit pleural effusion (Dauplat et al., 1987), local treatment appears to provide minimal benefit.

The etiology of pericardial effusion appears similar to that of malignant effusion in the peritoneal and pleural cavities via metastases to

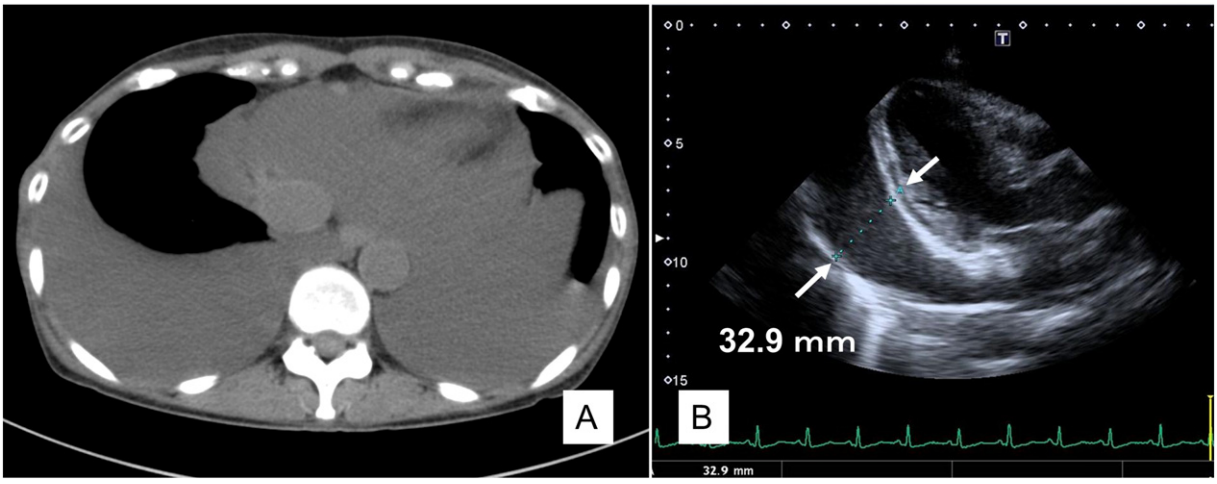

Fig. 2. Computed tomography and echocardiography findings. (A) Computed tomography reveals bilateral pleural effusion. (B) An echocardiogram reveals pericardial effusion (width: 32.9 mm). The patient underwent treatment with bevacizumab (15 mg/kg, every 21 days) after thoracocentesis and pericardiocentesis.

the serosal membranes. Furthermore, vascular endothelial growth factor (VEGF)-A is considered a key molecule in the development of malignant ascites and pleural effusion. In this context, Bev is a human monoclonal antibody to VEGF-A that preclinical and clinical studies have demonstrated and is effective for controlling malignant ascites in ovarian cancer, and pleural effusion in lung cancer (Pujade-Lauraine et al., 2014; Bradshaw et al., 2013). At the last hospitalization in the present case (May 2015), our patient complained of dyspnea and exhibited tachycardia, hypoxia, pulmonary embolism, and pericardial and pleural effusion. Anticoagulation therapy and placement of an inferior vena cava filter for her acute pulmonary embolism, and drainage of the pleural effusion via thoracocentesis, did not resolve her dyspnea. However, drainage of the pericardial effusion and Bev monotherapy improved her dyspnea and cough, which resulted in her discharge and a sustained response for 3 weeks. She then underwent combination therapy using Bev and wPTX, did not require pericardiocentesis or thoracocentesis, and was not hospitalized for >4 months. Therefore, we believe that the Bev therapy helped relieve her symptoms and improve her quality of life during the late stage of ovarian cancer.

The patient in the present case was not classified as platinum-resistant, although she had a history of anaphylaxis to platinum. She experienced interstitial pneumonia that was induced by pegylated liposomal doxorubicin, and did not respond to wPTX and etoposide. The patient initially refused Bev therapy, as GIP is a known adverse effect of this therapy. Cannistra et al. have reported that the incidence of GIP is only 11.4% and that the number of previous regimens is a risk factor (Cannistra et al., 2007). Furthermore, the AURELIA trial (a randomized phase 3 trial) evaluated patients with platinum-resistant ovarian cancer, and reported that the incidence of GIP was only 2.2% among Bev-treated patients, although that study excluded patients with a history of ≥3 previous regimens (Pujade-Lauraine et al., 2014). In contrast, other reports have denied any relationship between the number of previous regimens and the incidence of GIP.

When the patient eventually decided to accept Bev therapy, we initially administered it as a monotherapy, as she had complained of weakness. The patient was subsequently discharged, and received a combination of Bev and wPTX in our outpatient clinic once her condition had improved. A recent retrospective study that compared Bev monotherapy and combination chemotherapy revealed that the combination chemotherapy provided longer OS (hazard ratio: 0.51, $p < 0.01$) in the multivariate analysis, with similar adverse events for both treatments (Fuh et al., 2015). Furthermore, analysis according to chemotherapy in the AURELIA trial revealed that wPTX and Bev were a promising combination. In the present case, the patient's cancer progressed after she had received wPTX monotherapy, although it has remained stable during the treatment using Bev and wPTX.

In conclusion, pericardial effusion or cardiac tamponade is a rare, but fatal, complication of ovarian cancer. Furthermore, patients with pericardial effusion can also experience pleural effusion. Given the poor prognosis that is associated with malignant pericardial effusion, symptom relief and cancer stabilization are the main goals of treatment, and the efficacy and mild toxicities of Bev may indicate that it is a promising treatment.

Disclosure

Written informed consent for this report was obtained from the patient. The authors have no conflicts of interest to declare.

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