Pyopneumothorax during bevacizumab-containing chemotherapy in a patient with metastatic breast cancer

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Abstract Pyopneumothorax is a rare but troubling complication of bevacizumab. We herein report a case of pyopneumothorax in a patient with metastatic breast cancer during bevacizumab treatment. A 60-year-old female who was diagnosed with metastatic breast cancer (ER+, PgR+, HER2-, Ki67 <14 %, metastasized to lung, pleural, brain, subcutaneous tissue, and bone) was started on bevacizumab plus paclitaxel chemotherapy. Although the disease was well-controlled, pyopneumothorax was noted after 3 months of treatment and the chemotherapy was therefore stopped immediately. The pyopneumothorax was so intractable that no conservative treatment could successfully manage it. The patient underwent a radical operation using the technique of latissimus dorsi muscle transfer. The operation improved her general condition and lead to hormonal therapy. Our case indicates the successful management of a severe side effect of bevacizumab for a breast cancer patient.

Keywords Bevacizumab · Breast cancer · Pyopneumothorax · Pyothorax

Introduction

Bevacizumab (BEV) has been increasingly used for the treatment of advanced breast cancers since 2011 in Japan. Various adverse events in association with the use of BEV need to be managed. We herein report on a patient with metastatic breast cancer who developed pyopneumothorax during BEV treatment.

Case report

A 60-year-old female was presented with dyspnea and a large mass in the right breast. Computed tomography (CT) scan revealed a large tumor in the right breast, large pleural effusion in the right pleural cavity, and collapse in the right lung. Multiple metastases were also found in auxiliary lymph nodes, lung, bone, brain, and subcutaneous tissue (Fig. 1). A needle biopsy was performed and the tumor was determined as an invasive ductal carcinoma (estrogen receptor: highly positive (80 %), progesterone receptor: highly positive (60 %), HER2 1+, Ki67 labeling index <14 %). Since the patient's condition was considered life-threatening, the pleural effusion was controlled with thoracic drainage, followed by the administration of BEV (10 mg/kg/biweekly) plus paclitaxel (90 mg/m² weekly) and zoledronic acid (4 mg/body/monthly). Brain metastases were treated by gamma knife and were well-controlled. Chemotherapy on the tumor yielded a partial response but the patient subsequently developed a fever and increased inflammation after 3 months of chemotherapy. Chest X-ray indicated fluid accumulation in the right pleural cavity. Chemotherapy and any systemic therapy for breast cancer were stopped immediately and drainage of the pleural cavity was performed. Green-whitish pus was observed, which was cultured and identified as

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Fig. 1 Enhanced CT images at the initial visit. A large tumor with ulcer in the right breast and the right pleural effusion were observed (a). Multiple metastases to subcutaneous tissue (b), lung (c), bone (d), brain (e, f) were identified

pasteurella multocida and *candida glabrata* (Fig. 2). The conservative treatment including antibiotics (piperacillin and tazobactam) and thoracic drainage could not successfully manage it. The formation of dead space, pus discharge, and air leak in the lower area of the right pleural cavity persisted even after the administration of third time thoracic drainage. It was determined as intractable pyopneumothorax. Since there was no indication of other metastases to the brain or distant organs, a radical surgery was performed for pyopneumothorax (curettage of empyema in the right pleural cavity, closure of air leaks, and reconstruction of the 7th intercostals muscle and the latissimus dorsi muscle) on the 70th day after cessation of the chemotherapy. The leakage occurred in one spot at the wide range of inflammatory, fibrotic change in the right thoracic cavity (Fig. 3). The right breast tumor was

removed at the same time. After the operation, recurrence of air leaks was observed. The patient underwent another operation 16 days after the initial surgery, and closure of same site with the 7th intercostals muscle was performed once again. The chest drain was removed 7 days later. The operation improved her general condition, and the administration of an aromatase inhibitor (Letrozole) was initiated 20 days after the last operation. The patient's disease responded well to the multidisciplinary treatment including hormonal therapy, and her quality of life was maintained. She has been followed as an outpatient for over 2 years after the diagnosis and her chest condition remains stable (Fig. 4). Gamma knife treatment has been effective; no new lesions have been found and no other local or distant lesions have been identified either.

Fig. 2 X-ray image following the 5th course of bevacizumab plus paclitaxel (a), CT image while receiving thoracic drainage (b), *pasteurella multocida* and *candida glabrata* (c)

Fig. 3 Thoracoscopy during surgery. Dead space in the right lower pleural cavity and air leak (arrow) (a), curettage of serous membrane using thoracoscopy (b), closure of air leaks using the 7th intercostals muscle cutaneous flap (c)

Discussion

BEV is a recombinant humanized monoclonal IgG1 antibody that binds to the human vascular endothelial growth factor and inhibits its biologic activity. It was approved by the Japanese Ministry of Health, Labour, and Welfare for the treatment of colorectal cancer in April 2007, followed

by approval for the treatment of advanced breast cancer in September 2011.

The E2100 study demonstrated a significant improvement in progression-free survival (PFS) with paclitaxel plus bevacizumab for patients with advanced breast cancer [1]. In addition, results from phase III trials, AVADO [2], and RIBBON-1 [3], demonstrated a significantly improved

Fig. 4 Chest X-ray after surgery

PFS using BEV as a first-line treatment. However, no study trials have been conducted to suggest an improvement in overall survival rate for breast cancer patients. In our case, the patient's life-threatening condition due to malignant pleural effusion led to our decision to opt for BEV plus paclitaxel as a first-line treatment. Various adverse events in association with the use of BEV have been reported such as hypertension, albuminuria, delayed wound healing, and hemorrhage. The use of BEV combined with paclitaxel is known to cause frequent developments of neutropenia [2, 3]. Furthermore, BEV could induce rapid tumor necrosis. Perforations and abscesses are frequently observed in the gastrointestinal tract. Adverse events occurring in the thoracic portions are occasional [4–6]. If pyopneumothorax is not manageable by thoracic drainage, it would be appropriate to consider surgical intervention immediately after it is diagnosed intractable. Adjuvant hormonal therapy or chemotherapy can be offered to patients with hormone receptor-positive breast cancers in the expectation of a long-term prognosis. Initially, we were reluctant to operate on the patient with an invasive treatment involving thoracotomy and muscle flap construction. The surgery turned out to be effective and the patient was able to continue receiving further treatment for breast cancer.

We found 7 articles using the combined keywords “bevacizumab and pneumothorax,” “bevacizumab and empyema,” and “bevacizumab and pyothorax” in PubMed and the database of Japan Medical Abstracts Society (ICHUSHI). Two surgery reports were found in Japanese literature. One of them reported on a patient with stage IV lung adenocarcinoma that developed intractable pyopneumothorax during BEV administration. The patient underwent salvage lobectomy of the right lower lobe but

developed a bronchopleural fistula, and another surgery was performed to fill the pleural cavity with omentum [7]. The other article reported on a patient with metastatic lung tumors derived from sigmoid colon cancer. The patient developed intractable pneumothorax while receiving bevacizumab-containing chemotherapy, which was successfully treated with an anterior serratus muscle digitation flap [8]. In both cases, the patients underwent multiple surgeries. It is presumed that the delayed wound healing time of BEV is a contributing factor, thus indicating the BEV should be initiated carefully after its half-life (20 days) and even 28 days following surgery [9]. The other searched articles were on conservative treatment; 1 follow-up observation [10], 3 cases with drainage [11–13], and 1 pleurodesis [14]. While most reported the cessation of BEV use after pyopneumothorax developed and was treated, there is a reported case in which BEV continued to be administered without any recurrences of pneumothorax until the patient started suffering from disease progression [11]. Therefore, this is the first case report in English literature that presents a patient with breast cancer who developed pyopneumothorax as a possible adverse event from BEV administration.

We also performed a resection of the primary tumor followed by pyopneumothorax treatment. As for tumor resections in stage IV breast cancers, the guidelines of the Japanese Breast Cancer Society mention that “resection of a local breast tumor with distant metastasis could achieve long-term local control. Although the prolonged survival rate is unknown, the resection of local tumors should be performed with extreme care. Only those who would benefit from local tumor control in their postoperative life should be selected” [15]. There is no doubt that the emotionally distressed patient who previously suffered from an ulcerated, malodorous breast tumor was relieved by the local tumor resection. Of course, the treatment strategies should be decided after carefully controlling any brain metastases. In our case, pyothorax was not observed in the drainage of effusions before chemotherapy. It is presumed that BEV caused necrotic changes in the pleural cavity lesion and the pleura gradually hardened to form a dead space. The occurrence of pneumothorax made it even more difficult to control infection. It is reasonable to conclude that the adverse event of BEV caused the occurrence of pyopneumothorax.

Conclusion

We herein reported a patient with advanced breast cancer who developed pyopneumothorax during BEV administration.

Conflict of interest All authors declare that they have no conflict of interest.

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