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Case Report

A Case of Pneumothorax Required Surgical Treatment as a Complication of Paclitaxel with Bevacizumab Treatment

Yumi Moriya[a] Tomohiro Oshino[a] Mitsuchika Hosoda[a] Karin Shikishima[a] Shun Miura[b] Jun Muto[c] Tatsuya Kato[c] Masato Takahashi[a]

[a]Department of Breast Surgery, Hokkaido University Hospital, Sapporo, Japan; [b]Department of Respiratory Medicine, Hokkaido University Hospital, Sapporo, Japan; [c]Department of Thoracic Surgery, Hokkaido University Hospital, Sapporo, Japan

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Bevacizumab · Pneumothorax · Complication · Surgery

Abstract
A 63-year-old woman had a history of neoadjuvant chemotherapy, mastectomy, and adjuvant endocrine therapy for 5 years before being diagnosed with recurrent lesions involving the right anterior chest wall, multiple lymph nodes, and pulmonary metastases. The patient was subsequently initiated on a paclitaxel and bevacizumab regimen. During this treatment, the patient complained of palpitations and malaise. Chest radiography revealed a left pneumothorax. Despite attempts at conservative treatment, the pneumothorax did not improve and a thoracoscopic approach was required. One of the metastatic tumors in the left lower lobe appeared to rupture, and this area was estimated to be the cause of air leak. The tumor was covered with a tissue seal sheet, and the patient's condition improved with no recurrence of pneumothorax. This case highlights the importance of early conversion to surgical treatment when conservative treatment for pneumothorax is unresponsive due to the potential side effects of bevacizumab. The findings of this case report may be of interest to oncologists, pulmonologists, and other healthcare professionals involved in the care of patients with breast cancer and pulmonary metastases who are undergoing bevacizumab chemotherapy.

Correspondence to:
Masato Takahashi, masato.takahashi0725@gmail.com

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Introduction

Bevacizumab is a monoclonal antibody that binds and inactivates VEGF, thus inducing tumor microvessel regression and inhibiting neovascularization, resulting in potent antitumor effects [1]. It is commonly used to treat a variety of carcinomas, including breast, lung, and colorectal cancer. However, inhibition of vascular endothelial cell function can also cause negative side effects such as hypertension, proteinuria, ischemia, and impaired wound healing. Severe cases can lead to gastrointestinal perforation and tumor bleeding [2].

We encountered a case of breast cancer with pulmonary metastases that manifested as pneumothorax during bevacizumab chemotherapy and required surgical intervention. This event was considered secondary pneumothorax caused by bevacizumab. Although pneumothorax during bevacizumab treatment has been reported in other types of carcinomas, relatively few cases have been reported in breast cancer [3]. We consider this a serious adverse event that should be reported. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533440).

Case Report

We present the case of a 63-year-old patient with metastatic breast cancer who successfully underwent surgical treatment for a pneumothorax that developed during bevacizumab therapy. Eleven years before this episode, she was diagnosed with invasive ductal carcinoma of the right breast and metastasis to the axillary lymph nodes, classified as cT2N2M0 cStage IIIA. Pathological examination revealed estrogen receptor (ER)-positive, progesterone receptor (PgR)-negative, and human epidermal growth factor receptor 2 (HER2)-negative. We administered fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel as neoadjuvant chemotherapy, which resulted in mild tumor shrinkage. Subsequently, right mastectomy with axillary dissection was performed. Postoperative pathological examination revealed invasive ductal carcinoma, ypT1cN1a (n 2/12), nuclear grade 2, without lymphovascular invasion, ER-positive (20%), PgR-negative, and HER2-negative. Tamoxifen was initiated as an adjuvant treatment, and after a 2-year period, tamoxifen was switched to an aromatase inhibitor. However, owing to adverse events, we switched to tamoxifen again after 4 months and continued administering tamoxifen for a total of 5 years.

Approximately 5 years after the completion of treatment at the age of 63 years, ultrasound revealed a resurgence of lymph node metastasis in the subclavian region. Computed tomography was used to diagnose multiple lymph node metastases, multiple lung metastases, and recurrence of lesions in the right anterior chest wall. A needle biopsy was performed on the chest wall lesion, with a pathological diagnosis of recurrent breast cancer, ER-negative, PgR-negative, HER2-negative, and a Ki67 proliferation index of 37.9%. The BRCA genetic test and PD-L1 test were both negative. Systemic therapy was initiated with a combination of paclitaxel and bevacizumab. Following the 14th course, the patient complained of palpitations and malaise, and chest radiography and computed tomography revealed a collapsed left lung (Fig. 1, 2a, b). She had smoked 10 cigarettes per day since the age of 25 years and had a Brinkman index of 380. She also had a history of inflammation in her lungs at the time of pneumothorax.

A chest tube was inserted into the chest cavity and continuous suction was performed. Although pleural drainage was continued, the air leak persisted. A blood patch was placed on the second and ninth days after intubation, but the air leak persisted. We decided to use a thoracoscopic approach for healing.

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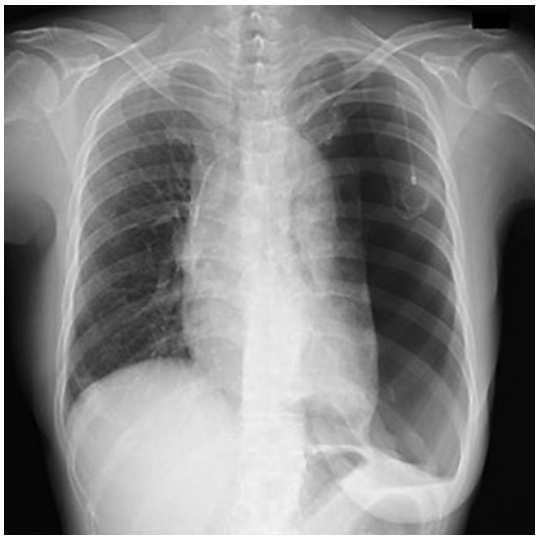

Fig. 1. Chest X-ray: Pulmonary patterns in the left lung field have disappeared, and the left diaphragm has been pushed down. This is considered to be a finding of severe lung collapse.

Thoracoscopic observation under general anesthesia revealed multiple nodules on the lung surface (Fig. 3a), suggesting lung metastasis from breast cancer. Although the site of the air leak could not be identified, a tumor in the left lower lobe appeared to rupture, and that area was estimated to be the cause of the air leak (Fig. 3b). Complete resection of the tumor would require a left lower lobectomy, but it was too invasive and not indicated. The tumor was covered with a TachoSil® tissue-sealing sheet (Fig. 3c). A polyglycolic acid sheet was placed on the diaphragm, which should come into contact with the tumor, for the purpose of adhering to the lung and diaphragm. After confirming that there were no other leaks, a 20-Fr chest tube was placed and the operation was completed.

No air leak from the chest tube was observed after this surgical treatment, the drain was removed on the fifth day after the operation, and the patient was discharged on the seventh day. Subsequently, no recurrence of the pneumothorax was observed.

Discussion

Considering the mechanism of action of bevacizumab, development of pneumothorax is highly conceivable. The mechanism of pneumothorax secondary to chemotherapy is assumed to be as follows. (1) Accidental rupture of the bulla or bleb; (2) bronchopleural leakage due to tumor necrosis; (3) secondary damage to the lung parenchyma due to chemotherapy or radiotherapy; (4) increased intrathoracic pressure due to obstruction or stenosis of the regional bronchi due to tumor necrosis or the tumor itself; (5) increased intrathoracic pressure is associated with vomiting due to the side effects of chemotherapy [4, 5].

Considering the pathogenesis in our case, an air leak from pulmonary metastasis was observed, most likely due to the formation of a bronchial leak from tumor necrosis. It was speculated that the delayed wound healing caused by bevacizumab led to intractable pneumothorax. Additionally, as current smokers, the presence of underlying pulmonary diseases, such as interstitial pneumonia, may also have contributed.

Since the patient is currently receiving bevacizumab, it is imperative to consider the potential impact on delayed wound healing. As elective surgery should ideally be scheduled at least 28 days after bevacizumab administration, initial management should prioritize conservative treatment in cases of secondary pneumothorax, such as in the present case [6]. However, some studies suggest that early surgical intervention may be warranted in cases of

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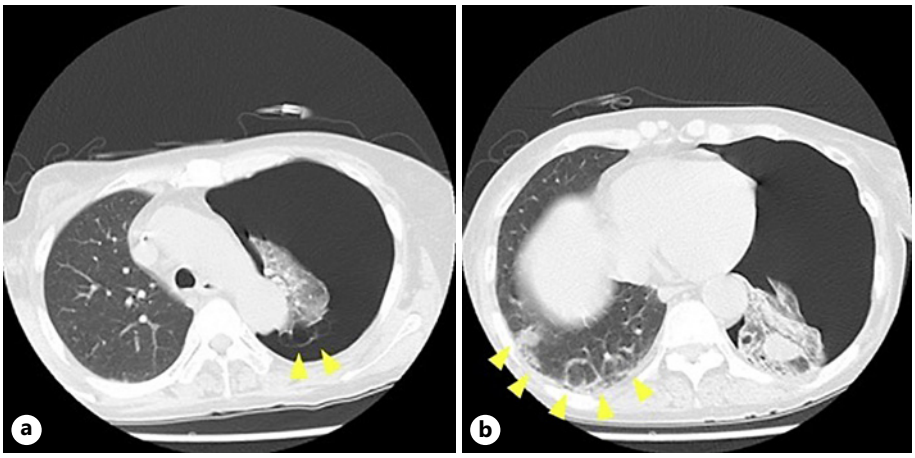

Fig. 2. Chest CT. **a** Collapse of the left lung in the left upper lung field and bulla on the left apical mediastinum side. The yellow arrows indicate the bulla. **b** Collapse of the left lung in the left lower lung field. Multiple pulmonary metastases were observed in both lungs. Interstitial pneumonia was also observed. The yellow arrows indicate multiple pulmonary metastases and interstitial pneumonia in the non-collapsed right lung. CT, computed tomography.

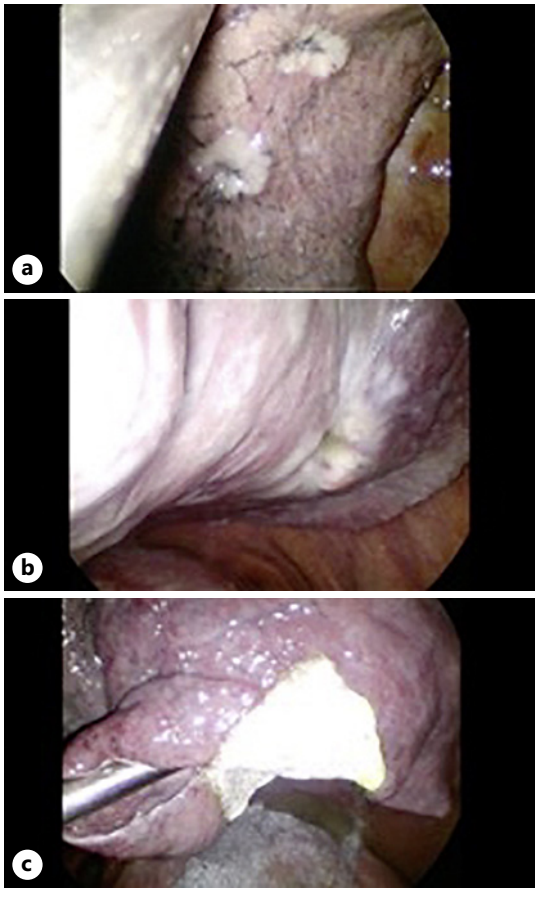

Fig. 3. Operative findings. **a** Multiple lung tumors. **b** Tumor with suspected air leakage. **c** The tumor was covered with a TachoSil® tissue-sealing sheet.

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refractory pneumothorax with fistula formation or empyema in patients with multiple lung metastases from colorectal cancer as well as secondary pneumothorax resulting from bevacizumab treatment in patients with lung cancer, and the timing of surgical intervention must be carefully evaluated [7].

In this case, pleurodesis was initially chosen as a therapeutic strategy but proved ineffective even after two attempts. More than 2 weeks had elapsed since drain insertion, and the risk of infection was considered significant for further retention; therefore, surgical intervention was performed 23 days after the last administration of bevacizumab. The postoperative progression was uneventful, and no recurrence of pneumothorax was observed. If pneumothorax progresses to empyema, it becomes even more intractable, delaying resumption of breast cancer treatment. Therefore, surgical treatment should be considered even within 28 days of the last dose of bevacizumab if medical treatment does not improve the patient's condition.

In this case, the treatment for pneumothorax took approximately 1 month. However, there are also reports of other malignancies, including breast cancer, that require treatment for 2 months or more [8]. In advanced cases, bevacizumab in combination with chemotherapy is often introduced in the treatment of breast cancer, as it has been shown to have a high rate of tumor shrinkage and prolongation of progression-free survival [9]. However, long-term cessation of breast cancer treatment due to severe adverse events, as in the present case, can lead to progression of the underlying disease. Thus, caution should be exercised when considering its indications, particularly when administering bevacizumab to patients with pulmonary disorders, such as emphysema and interstitial pneumonia, which are common risk factors for secondary pneumothorax, and in smokers, as there is a risk of developing pneumothorax. If conservative treatment after the onset of pneumothorax does not improve over a long period of time, it is necessary to recognize that hesitation to undergo surgical intervention has a negative impact on the progression of the disease.

Conclusion

We report a case of secondary pneumothorax during paclitaxel plus bevacizumab therapy in a patient with breast cancer and lung metastasis. Conservative treatment should be attempted first for secondary pneumothorax caused by bevacizumab. However, if there is minimal improvement, surgical intervention should be considered as soon as possible. Although secondary pneumothorax is a rare complication, delayed diagnosis can lead to fatal outcomes. Awareness of this potential complication is crucial when using bevacizumab. It is also important to consider the patient's history of lung disease and smoking status.

Statement of Ethics

Written informed consent was obtained from the patient for publication of details of their medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local and national guidelines.

Conflict of Interest Statement

M.T. received lecture fees from AstraZeneca, Eli Lilly, and Daiichi Sankyo. The other authors have no conflicts of interest to declare.

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Author Contributions

Y.M., T.O., M.H., K.S., S.M., and M.T. provided clinical care, and J.M. and T.K. performed the surgery. Y.M. drafted the manuscript. M.T. and T.K. provided the expertise and feedback to Y.M. The final manuscript has been read and approved by all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

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