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Case report

Is performing lobectomy after the use of bevacizumab for a lung tumor dangerous?

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HIGHLIGHTS

- A safety of major lung resection after the use of Bev remains controversial.
- Is it really dangerous to perform major lung resection after the use of Bev for a lung tumor?
- Our results provide reliable information regarding the operative safety.

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ABSTRACT

Recent new drugs, such as bevacizumab (Bev), also result in a remarkable response. However, the safety of major lung resection after the use of Bev remains controversial. Is it really dangerous to perform major lung resection after the use of Bev for a lung tumor? In this report, we describe two patients who underwent surgery safely without fragile pathological findings of the vessels.

1. Introduction

Multimodality therapies including radiation therapy have been shown to achieve an excellent local control for LA-NSCLC (locally advanced non-small cell carcinoma). Conversely, recent new drugs also result in a remarkable response. Among them, bevacizumab (Bev), which is a neutralizing antibody to vascular endothelial growth factor (VEGF), has been used for not only inoperable non-small cell carcinoma (NSCLC), but also operable patients in clinical practice without radiation [1,2]. In this regard, VEGF inhibition has the potential to affect bleeding, thromboembolism, and delayed wound healing, which might cause catastrophic consequences and secondary life-threatening complications in perioperative situations.

Few data are currently available regarding the surgical complications of pulmonary resection related to the temporal administration of VEGF-targeted therapy. Is it really dangerous to perform major lung resection after the use of Bev for a lung tumor? Our results provide reliable information about the operative safety.

2. Case report

2.1. Case 1

A 67-year-old Japanese male was referred for an evaluation of an abnormal shadow observed on a chest X-ray film. Chest computed tomography (CT) showed a 38 mm tumor, which was located in the left superior lingular segment; a 25 mm tumor, which was located in the left inferior lingular segment; and bilateral swollen lymph nodes in the hilum and mediastinal, suggesting lymph node metastasis (Fig. 1A). He was diagnosed with lung adenocarcinoma by a transbronchial lung biopsy for the tumor in the left superior lingular segment. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed a high FDG uptake in both tumors in the left upper lobe and hilum and mediastinal lymph nodes. Therefore, the lesion was clinically diagnosed to be at stage IIIB (cT3 (PM1)

Abbreviations: LA-NSCLC NSCLC, locally advanced non-small cell carcinoma; Bev, bevacizumab; VEGF, vascular endothelial growth factor; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; CDDP, cisplatin; DTX, docetaxel; PTX, paclitaxel; CBDCA, carboplatin.

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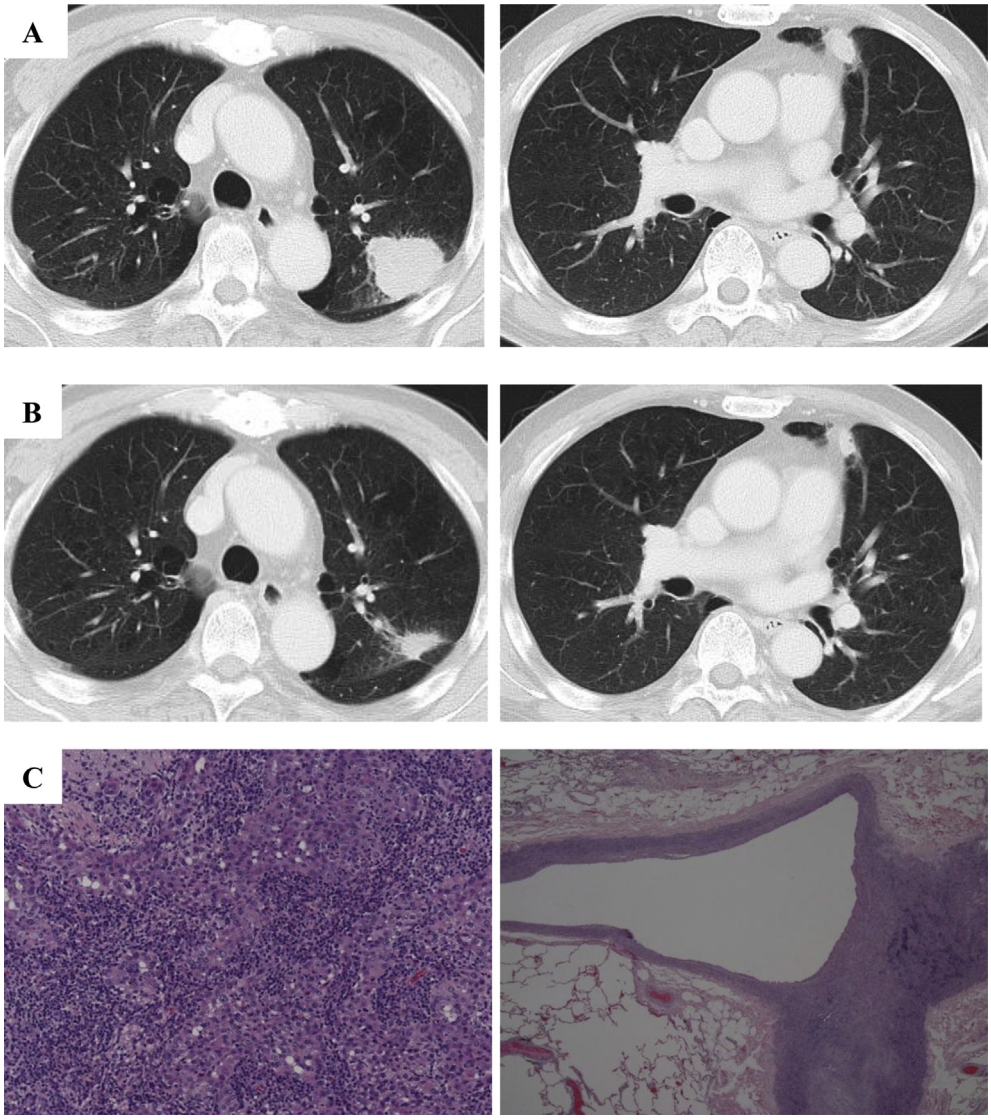

Fig. 1. Radiological evaluation by CT. A: Before treatment. A 38 mm tumor in the left superior lingular segment and a 25 mm tumor in the left inferior lingular segment were observed. B: After treatment. A radiological CT evaluation revealed remarkable shrinkage of both tumors. C: The histological findings of the resected primary tumor (hematoxylin–eosin stain) showed poorly differentiated adenocarcinoma cells admixed with a small number of nonviable swollen carcinoma cells, suggestive of a very slight therapeutic effect. No brittleness of the vessels around the main tumor or those around the pulmonary artery was seen.

N3M0). Systemic chemotherapy with 2 cycles of cisplatin (CDDP) (75 mg/m^2) and pemetrexed (500 mg/m^2) plus Bev (12 mg/kg due to hypertension) every 3 weeks was administered.

After 3 weeks of chemotherapy, a radiological CT evaluation revealed remarkable shrinkage of both tumors and no change in the hilum and mediastinal lymph nodes swelling (Fig. 1B). Thus, we believed we misdiagnosed hilum and mediastinal lymph nodes swelling (yc-T3 (PM1) N0M0 stage IIB) due to the discrepancy in the clinical response between the tumors and swollen lymph nodes. We performed left upper lobe lobectomy and systematic lymphadenectomy with far less difficulty, especially for peel-off of the great vessel on 33 days after cessation of Bev. The bronchial stump was covered with pericardial fat tissue. The total operation time was 2 h and 42 min with 35 ml of intraoperative bleeding.

The pathological examination revealed poorly differentiated adenocarcinoma in the left superior lingular segment and no cancer cells were seen in the tumor in the left inferior lingular segment and in the hilum and mediastinal lymph nodes. No brittleness of the vessels around the main tumor or those around pulmonary artery was seen (Fig. 1C). The tumor size measured 21 × 20 × 17 mm in size. Therefore, the lesion was pathologically diagnosed to be at stage IA (T1aN0M0). The postoperative course was uneventful and the patient was discharged on day 7 after surgery. He currently remains alive without disease progression eight months after therapy.

2.2. Case 2

A 59-year-old Japanese male presented with bilateral lung tumors after low anterior resection for rectal cancer. FOLFOX (5-FU; 1000 mg/m^2 on days 1 and 2), leucovorin (400 mg/m^2 on day 1 and 200 mg/m^2 on day 2), and oxaliplatin (85 mg/m^2) plus Bev (5 mg/kg) every 2 weeks was administered. After three courses of chemotherapy, a CT evaluation revealed a 10 mm tumor, which was located in the right S2, a 9 mm tumor in the right S8, and a 32 mm tumor in the left S9-10 (Fig. 2A).

Four additional courses of chemotherapy were administered because intrapericardial handling was potentially necessary to

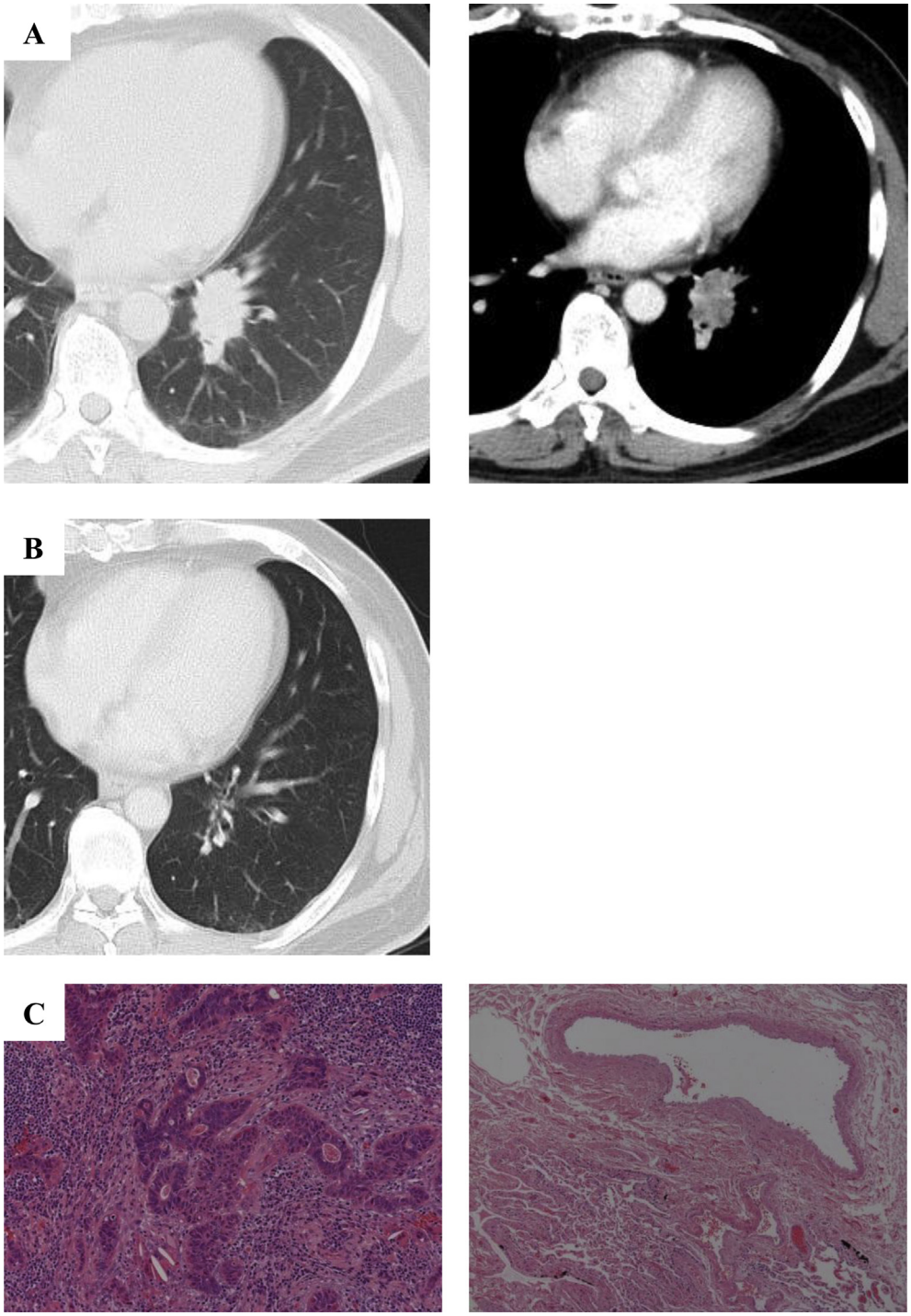

Fig. 2. A: After three course of chemotherapy. Chest CT showed a tumor adjacent to the pulmonary artery and veins in the left lower lobe were observed. B: After four additionally courses of chemotherapy. A radiological CT evaluation revealed prominent shrinkage of the tumor. C: The histological findings of the resected primary tumor showed a moderately differentiated tubular adenocarcinoma, without brittleness of the vessels around the main tumor and pulmonary artery.

perform left lower lobectomy, despite the existence of right lesions after consideration of the operative indication. After a total of seven courses of intensive chemotherapy, the right lesions disappeared and prominent shrinkage of the left tumor was observed (Fig. 2B). We performed left lower lobe lobectomy and lymphadenectomy, similar to case 1, after a 28-days interval of Bev holiday. The bronchial stump was covered with pericardial fat tissue. The total operation time was 2 h and 12 min with 61 ml of intraoperative bleeding. The pathological examination revealed moderately differentiated tubular adenocarcinoma, which was identical to the rectal cancer specimen. No brittleness of the vessels around the main tumor remained and no fragile vessels around the pulmonary artery was observed, similar to case 1 (Fig. 2C). The postoperative course was uneventful and the patient was discharged on day 7 after surgery. He currently remains alive without any complications. Two patients provided their written informed consent for

treatment, and privacy policy fully explained.

3. Discussion

The application of Bev for a lung tumor in an induction setting remains controversial. Finley et al. reported the operative outcomes using CDDP + docetaxel (DTX) + Bev as induction therapy in patients with operable lung cancer [3]. They conducted a phase II trial enrolling 30 cases that underwent resection with curative intent. Among the CDDP+ DTX+ Bev group, seven grade 3 and 4 complications (including two empyemas, one anastomotic dehiscence, and one gastrointestinal hemorrhage) were reported in the study group compared with two in the control group ($p = 0.004$). Therefore, they described that patients receiving CDDP+ DTX+ Bev induction had a higher incidence of grade 3/4 complications. On the other hand, Bertino et al. reported preoperative Bev in combination with paclitaxel (PTX) and carboplatin (CBDCA) for resectable NSCLC [4]. No postoperative complications were observed in 4 of the enrolled patients. Their limited data provided early evidence that Bev can safely be added to preoperative chemotherapy. In fact, two phase II studies, induction setting including Bev, have been launched in USA and Japan [1,2].

At present, no reports regarding the clinical images and pathological findings focused on vessel fragility for a lung tumor have been published. In this report, we described two patients who underwent surgery safely without fragile pathological findings of the vessels. This finding suggests reliable information about the operative safety.

Ethical approval

Not available. Two patients provided their written informed consent for treatment, and privacy policy fully explained.

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The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

Author contribution

HU contributed to the conception and design. YN, HK, and HU did the data collection. HU did the writing of the article and the critical revisions. YN and HK did the analysis and interpretation.

Conflict of interests

None declared.

Guarantor

Not available.

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