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CASE REPORT

Spontaneous pneumothorax due to bronchopleural fistula following reirradiation for locoregionally recurrent squamous cell lung cancer

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Key Clinical Message

Spontaneous pneumothorax following radiotherapy for pulmonary malignancy is an unusual clinical condition. Here, we report a case of a 78-year-old male suffering from dyspnea during radiotherapy for squamous cell lung cancer of the right main bronchus. Imaging studies and fiberoptic bronchoscopy revealed that pneumothorax was due to a bronchopleural fistula.

Keywords

Bronchopleural fistula, reirradiation, spontaneous pneumothorax, squamous cell lung cancer.

Introduction

Pneumothorax is defined as air in the pleural cavity [1]. Primary spontaneous pneumothorax occurs in the absence of clinically apparent lung disease, whereas secondary spontaneous pneumothorax is a complication of underlying lung disease [1–3]. Chronic obstructive pulmonary disease and pneumocystis pneumonia are the most common causes of secondary spontaneous pneumothorax. Approximately 70% of secondary spontaneous pneumothorax cases are associated with chronic obstructive pulmonary disease [2], whereas less than 5% of cases are a result of malignancy [4]. One mechanism underlying spontaneous pneumothorax in the case of malignancy is the development of a bronchopleural fistula (BPF), a channel between the bronchial and pleural space created by direct tumor invasion into the pleural space, tumor necrosis as a result of treatment, or vascular occlusion within a tumor itself [5]. In the current report, we present a case of BPF during reirradiation of squamous cell lung cancer.

Case Report

In February 2012, a 78-year-old male with a 22.5-pack-a-year smoking history was diagnosed with stage IIB squamous cell lung carcinoma (T3N0M0). The tumor was present at the right hilar area, distended into the right main bronchus and had no surgical indications (Fig. 1A and B). He was initially treated with concurrent chemoradiotherapy. Irradiation was performed by three-dimensional conformal radiation using a 10-MV photon beam from a linear accelerator (Fig. 2A and B). The total radiation dose was 66 Gy, divided into 33 fractions, and the radiation field contained the primary site and the right hilum. Elective nodal irradiation was not performed. The

concurrent chemotherapy consisted of weekly carboplatin and paclitaxel and was followed by consolidation chemotherapy.

In May 2012, the tumor size was decreased (Fig. 1C). In August 2012, although the patient did not have any symptoms, a follow-up chest computed tomography (CT) showed reticular interstitial process in the right lung and a small pneumothorax (Fig. 1D), but there was no fistula (Fig. S1A and B). The patient was diagnosed with radiation pneumonitis. The tumor was enlarged compared to 3 months before (Fig. 1D), but still diagnosed as stable disease (SD) according to RECIST criteria. Since he did not show any symptoms, we followed him up without any treatment. In December 2012, a chest CT showed no differences compared to the one in August 2012 (Fig. S2).

In March 2013, when the patient's right upper lobe collapsed (Fig. 1E), we suspected tumor recurrence. A positron emission tomography (PET)-CT scan confirmed locoregional relapse (Fig. 1F). A chest CT did not show obvious fistula (Fig. S1C and D). As a first-line therapy for the recurrent, advanced squamous cell lung cancer, the patient was prescribed a dose of 80 mg/m^2 S-1 to be taken orally twice daily for 28 days over a 6-week cycle. Due to hepatotoxicity, after 1 month, the S-1 was discontinued. As a second-line therapy, vinorelbine was prescribed at a dose of 25 mg/m^2 on days 1 and 8 of a 3-week cycle. After three cycles, in August 2013, we noticed a cavity connecting the right main bronchus to a tube-like, hollow space in the right dorsal region of the tumor (Fig. S1E and F). After four cycles, the tumor stabilized, and vinorelbine was stopped; the patient was then followed up at our out-patient clinic. After 10 months, in June 2014, the size of the primary tumor was slightly bigger (Fig. 1G), and multiple intrapulmonary metastases were developed (Fig. 1H and I); as a third-line therapy, gemcitabine was prescribed at a dose of 1000 mg/m^2 on days 1 and 8 in a 3-week cycle. During the first cycle of gemcitabine, the patient experienced gradually increasing cough and sputum, and he had difficulty breathing. At the beginning of the third cycle of gemcitabine, a CT imaging revealed a right main bronchial stricture due to locoregional relapse (Fig. 3A). The tube-like hollow space was present, but fistulae were not evident (Fig. 3B and C). The fourth cycle of gemcitabine was suspended, and reirradiation to reduce the size of the tumor at the right main bronchus was chosen to control the patient's shortness of breath. The radiotherapy field overlapped with the previous one (Fig. 2C). The planned prescribed radiation dose was 50 Gy, divided into 25 fractions. At the first radiotherapy treatment, the patient had a small amount of hemoptysis.

After receiving 6 Gy of reirradiation, the patient presented with general malaise and acute dyspnea. He showed peripheral cyanosis and tachypnea, and his

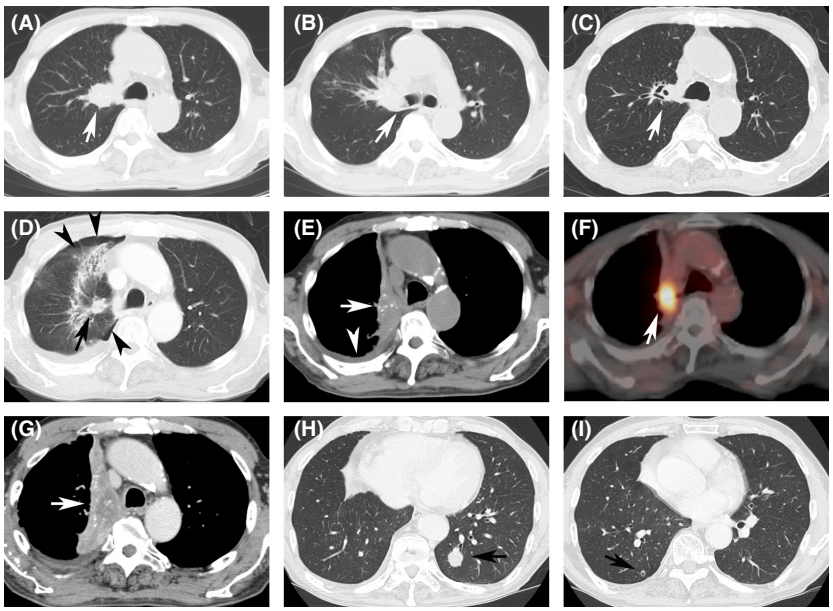

Figure 1. Chest computed tomography (CT) scan. (A) A tumor (2.4 cm in diameter, arrow) is present at the right hilar area. (B) The tumor is distended into the right main bronchus (arrow). (C) The tumor (arrow) is reduced in size after concurrent chemoradiotherapy, after 3 months of beginning of the treatment. (D) Reticular interstitial processes with small pneumothoraces (arrowheads) and the tumor (1.5 cm in diameter, arrow). (E) Atelectasis (arrow) with the right pleural effusion (arrowhead). The tumor and atelectasis are iso-density. (F) PET/CT scan shows strong ^{18}F-fluorodeoxyglucose uptake (arrow) at the right hilar area. (G) Atelectasis with the right pleural effusion. The tumor (arrow) is slightly bigger compared to (E). (H, I) Intrapulmonary metastases (arrow).

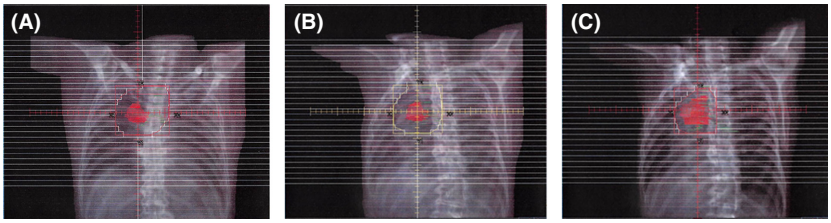

Figure 2. Radiation field. The radiation field is outlined in red. The lead shield is outlined in white. The tumor is identified by the red shaded area. (A) The first irradiation in the longitudinal direction. (B) The first irradiation in the oblique direction. (C) The second irradiation in the oblique direction.

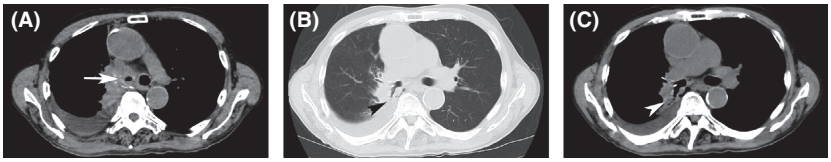

Figure 3. Chest CT scan showing (A) a right main bronchial stricture (arrow) near the tumor, which increased with right pleural effusion. (B, C) A cavity connected to the right main bronchus via a tube-like hollow space (arrowhead) in the tumor. (B) and (C) are the same images with different CT window settings. (B) CT lung window settings. (C) CT mediastinal window settings.

room-air SpO2 decreased to 85–90%. He coughed frequently, accompanied with sticky sputum that was difficult to expectorate. Oxygen was supplied via nasal cannula at a flow rate of 2 L/min. A chest X-ray revealed pneumothorax on the right side, and an 18-Fr chest tube was placed into the right hemithorax for drainage (Fig. 4A). Although the tube was placed, the lung was difficult to re-expand. The air leak persisted, and the patient's dyspnea did not improve. As his cough and sputum continued, empirical antibiotics were administered. On day 6 after the tube placement, a CT scan showed that the right main bronchus formed a connection with the pleural space, indicating that a BPF had developed (Fig. 4B and C). On day 9, a fiberoptic bronchoscopy examination revealed that the patient's right main bronchus was connected to the cavity (Fig. 5A), and the inner space was covered with white necrotic tissue (Fig. 5B). At the deeper side of the cavity, the chest tube and ribs were observed. The BPF was confirmed, which resulted in continuous pneumothorax. The size of the fistula was too large to be treated using an expandable metal stent or silicone stent. Performing a right pneumonectomy also posed a challenge because the cavity was necrotic and there was not enough margin for suture. We suggested that the patient and his family members seek out other opinions from thoracic surgical specialists; however, they hoped to avoid surgical procedures. The patient suffered from severe infections due to empyema. He died after 7 weeks of hospitalization.

Discussion

Spontaneous pneumothorax with malignancies is rare and most commonly occurs in lung cancer and metastatic sarcoma [4, 5]. Prior treatment with radiation and/or chemotherapy is often associated with its development. Most reported cases of spontaneous pneumothorax following radiotherapy are Hodgkin's disease caused by

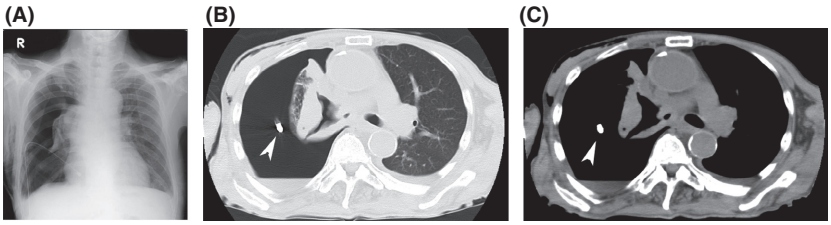

Figure 4. (A) Chest X-ray showing pneumothorax on the right side, which occurred after inserting a chest tube. (B, C) Chest CT scan showing a BPF and the connection between the right main bronchus and the pleural space. Arrowhead shows the chest tube. (B) and (C) are the same images with different CT window settings. (B) CT lung window settings. (C) CT mediastinal window settings.

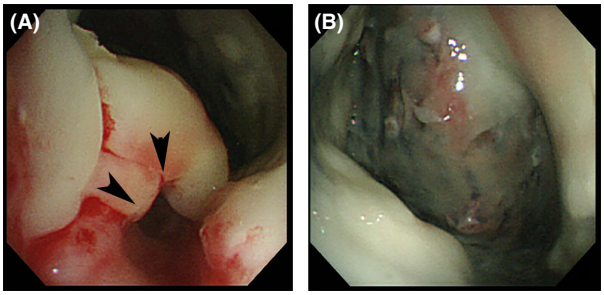

Figure 5. (A) A fiberoptic bronchoscopic view of the BPF opening (black arrowheads). (B) Right thoracic cavity with necrotic tissues.

mantle irradiation [6]. Spontaneous pneumothorax following radiotherapy in lung cancer has rarely been reported [6–11].

Although a number of different mechanisms have been proposed to underlie pneumothorax with malignancies [5], the pathogenesis leading to spontaneous pneumothorax following radiotherapy has not been defined [6, 7]. There are three putative mechanisms [5]: first, radiation-induced pulmonary changes, as well as apical pleural and parenchymal injury, might induce focal emphysema and fibrosis, which might rupture subpleural blebs [5, 12]. Spontaneous pneumothorax following radiotherapy in association with fibrosis, which gradually develops from radiation pneumonitis, occurs several months or more after the completion of irradiation. Second, radiation-induced tumor necrosis and subsequent rupture of necrotic tissues into a bronchus or pleural space may cause BPF, leading to pneumothorax [5, 12]. Third, radiation-induced regression of an obstructing tumor may generate a one-way check valve, leading to overinflation of the affected lung and rupture of alveoli or emphysematous bullae [5, 12]. Small pneumothoraces which were identified following the concurrent chemoradiotherapy might be explained by the first mechanism. In the latter two mechanisms, spontaneous pneumothorax appears either during or shortly after radiation treatment. In the present case, spontaneous pneumothorax developed during reirradiation. The cause of the spontaneous pneumothorax was identified as a BPF. Although peripheral tumors are typically considered to be involved in BPF [5], the tumor was at the central site in this case. The tumor at the main bronchus, which may have originally extended into the pleura, became a BPF when the tumor was lysed by irradiation.

Thoracic reirradiation is one treatment choice for non–small cell lung cancer patients experiencing locoregional relapse or the development of a primary tumor in a previously irradiated area [13, 14]. Reirradiation that overlaps previously irradiated areas has been used as a palliative measure, considering its risks and the potential for radioresistance. Recently, technological improvements in radiotherapy have enabled more precise irradiation of tumors, sparing normal tissues and offering high-dose thoracic reirradiation with the aim of long-term, disease-free survival by controlling recurrent locoregional tumors. Regardless of the dose used, reirradiating the same site causes toxic effects [13, 14]. Frequently, these effects include radiation pneumonitis and esophagitis. Fatal toxic effects include hemoptysis, hematemesis, and BPF.

No reports have established a correlation between total radiation dose and frequency of spontaneous pneumothorax. Some reports have shown that spontaneous pneumothorax occurred in patients with Hodgkin's disease treated with mantle radiation when the total dose of irradiation reached more than 30 Gy [15]. In the present case, the patient received a total dose of 72 Gy; although this was beyond 30 Gy, the radiation field was considerably limited compared to that used for mantle irradiation. Therefore, it is difficult to determine the association between the total dose of irradiation and the present spontaneous pneumothorax.

Several factors may have led to BPF, including (1) the hollow-like structure of the space within the tumor, (2) the use of previous chemotherapy, and (3) reirradiation of the same site on the tumor. Reirradiation might be a trigger for BPF development.

The ultimate goal of BPF management is to achieve lung expansion after adequate pleural drainage [16]. BPF treatment options include surgical procedures and medical techniques, such as chest drainage and endoscopic fistula closure using biological glue, coils, stents, or sealants. When an infection is present, drainage of the pleural space in combination with proper antibiotics is required. Surgical treatment is chosen when a fistula is less than 5 mm in diameter [17]. The present patient's fistula was larger than 5 mm in diameter, and his pleural cavity was necrotic. Right pneumonectomy was an alternative treatment option; however, surgical reconstruction was expected to be problematic because the fistula edge was insufficient for suturing and likely fragile due to tumor involvement and the effects caused by various therapies.

Although peripheral tumors have been associated with BPF, the present case demonstrates that a BPF can cause spontaneous pneumothorax to occur even when a tumor is located at a central site. It is challenging to manage a large BPF because it cannot be easily treated endoscopically or surgically.

Consent

Because the patient himself was unable to provide consent, his daughter provided written informed consent for

publication of this case report and any accompanying images. A copy of the consent form has been made available for review by the Editor-in-Chief of this journal.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Chest CT scan shows no fistula. (A, B) No fistula in August 2012. (C, D) Hollow space (arrow), but no fistula in March 2013. (E, F) Hollow space (arrow), but no fistula in August 2013. (A) and (B), (C) and (D), and (E) and (F) are the same images with different CT window settings. (A, C, E) CT lung window settings. (B, D, F) CT mediastinal window settings.

Figure S2. Chest CT scan shows reticular interstitial processes with small pneumothoraces (arrowheads) and the tumor (arrow). The size of the primary tumor is almost the same as the one in June 2014.

