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【 CASE REPORT 】

Successful Treatment of Chylothorax and Chylopericardium by Radiotherapy in Lung Cancer

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Abstract:
A 58-year-old man was diagnosed with stage IVB lung adenocarcinoma in the right upper lobe and underwent systemic chemotherapy. Seven months after the diagnosis, large left pleural and pericardial effusion was detected. The patient developed both chylothorax and chylopericardium following superior vena cava (SVC) obstruction with mediastinal lymphadenopathy caused by lung carcinoma. Since conservative treatment of the chyle leakage was ineffective, we administered radiotherapy to treat the SVC obstruction and mediastinal lymphadenopathy. After radiotherapy, the chylothorax and chylopericardium gradually resolved, and no further chyle leaks were identified on follow-up computed tomography. This case indicates that radiotherapy can be used to ameliorate lung cancer-related chylothorax and chylopericardium.

Key words: chylothorax, chylopericardium, lung cancer, radiotherapy

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Introduction

Chylothorax combined with chylopericardium is a complication of cardiovascular surgery that has been reported with an incidence of 0.25% (1). Some reports have described other causes as well, such as malignant tumor, Behcet's syndrome, pulmonary lymphangiectasia and superior vena cave (SVC) stenosis (2-4). Chyle leak is managed either by a conservative or surgical approach. However, in cases with combined chylothorax and chylopericardium, conservative treatments may be ineffective, and a more invasive surgical treatment may be needed to resolve chyle leak.

Surgical treatments have high success rates, but they are associated with a high risk of complications. If surgical treatment is not suitable for a patient, radiotherapy can be considered as an alternative. However, a number of studies have suggested the possible involvement of radiotherapy in chyle leak and accumulation.

We herein report a patient with combined chylothorax and chylopericardium related to lung cancer that was successfully treated by radiotherapy.

Case Report

A 58-year-old man with a history of depression visited our hospital in October 2018. The patient was a current smoker (1 pack/day for 38 years). Chest computed tomography (CT) showed a tumor in the right upper lung lobe with mediastinal invasion, SVC constriction and enlarged mediastinal lymph nodes. Transbronchial lung biopsy specimens revealed adenocarcinoma. A mutational analysis for epidermal growth factor receptor, anaplastic lymphoma kinase, c-ros oncogene 1 and B-raf proto-oncogene serine/threonine-protein kinase were negative. The tumor proportion score of programmed cell death ligand 1 measured by 22C3 immunohistochemistry assays was 20%.

Head magnetic resonance imaging showed metastases at a few locations in the brain. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT did not detect other distant metastases. The TNM classification was cT4N2M1c, stage IVB.

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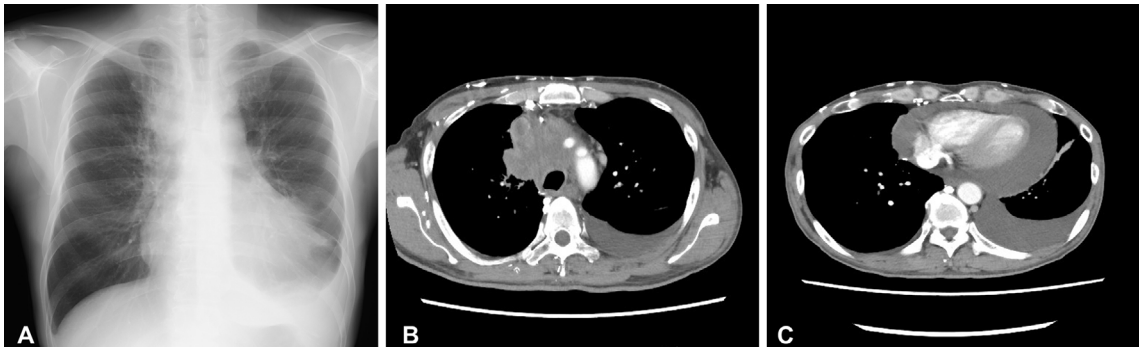

Figure 1. **(A) Admission chest X-ray showing a mediastinal mass, left pleural effusion and enlarged cardiac silhouette. (B, C) Contrast-enhanced computed tomography revealed superior vena cava obstruction by a large lung mass with mediastinal invasion, left pleural effusion and marked pericardial effusion.**

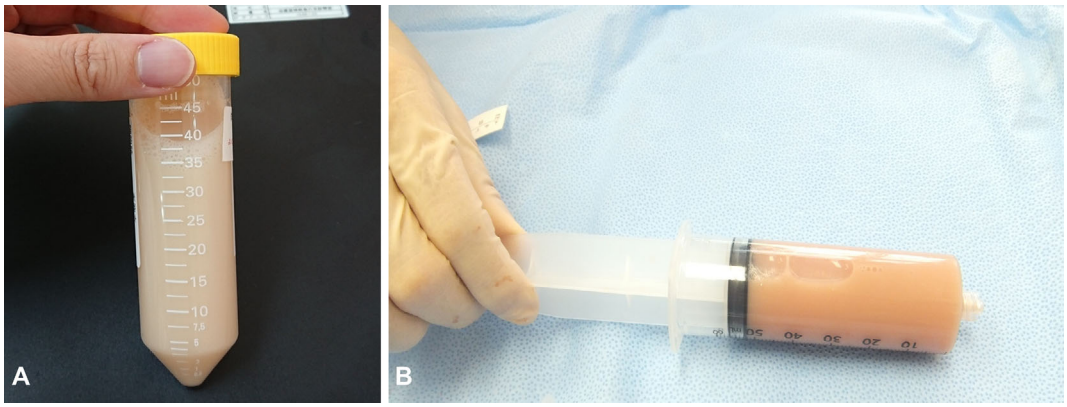

Figure 2. **(A) Chylous pleural fluid with a milky appearance. (B) Chylous pericardial fluid with a milky appearance.**

Following stereotactic radiotherapy for brain metastases, the patient underwent 4 cycles of cisplatin (75 mg/m^2) with pemetrexed (500 mg/m^2) as first-line therapy and 3 cycles of pembrolizumab (200 mg/body) as second-line therapy. However, these chemotherapies were ineffective, and the patients was considered to have progressive disease (PD) based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Chest radiography showed massive left pleural effusion and pericardial effusion. Chest CT illustrated SVC obstruction and chest wall collaterals (Fig. 1). The patient was then admitted to our hospital in May 2019.

On hospital admission, the patient's vital signs were as follows: heart rate 78 bpm, blood pressure 129/95 mmHg, and body temperature 36.2°C. The percutaneous arterial blood oxygen saturation was 97% on ambient air, and the respiratory rate was 16/min. The hearts sounds were normal, and there were reduced breathing sounds over the left lung base. Although the superficial veins of the chest were swollen, the face and upper extremities were not edematous.

The patient underwent thoracentesis of the left lung on day 1 and pericardiocentesis with replacement of a pericardial drain on day 2. Thoracentesis revealed milky fluid with a triglycerides content of 780 mg/dL and a cholesterol level of 72.0 mg/dL. The results of cytological and microbiological analyses were negative. Pericardiocentesis revealed milky and hemorrhagic fluid with a triglyceride content of 968 mg/dL and a cholesterol level of 111 mg/dL (Fig. 2). Microbiological analyses were negative, and cytological analyses showed metastasis pulmonary adenocarcinoma. After drainage of the fluid, a small amount of pericardial and pleural fluid remained, and the pericardial drainage tube was removed.

Although the patient continued a low-fat diet, chest radiography showed new cardiomegaly and left pleural effusion on day 9. Echocardiography revealed the reaccumulation of pericardial effusion and left pleural effusion. Total parenteral nutrition also failed to control the effusion. Conservative treatment was ineffective, and surgical treatment was not possible since the patient had a performance status of 3.

We administered radiotherapy (40 Gy in 16 fractions) to treat the SVC obstruction and mediastinal lymph node metastasis on day 15. The clinical target volume included the tumor in the right upper lobe and mediastinal lymph node (Fig. 3). Due to the increase in left chylothorax, left chest tube replacement and nasal cannula oxygen therapy (2 L/min) were required on day 21. The percutaneous drainage tube was removed, and oxygen therapy was completed on

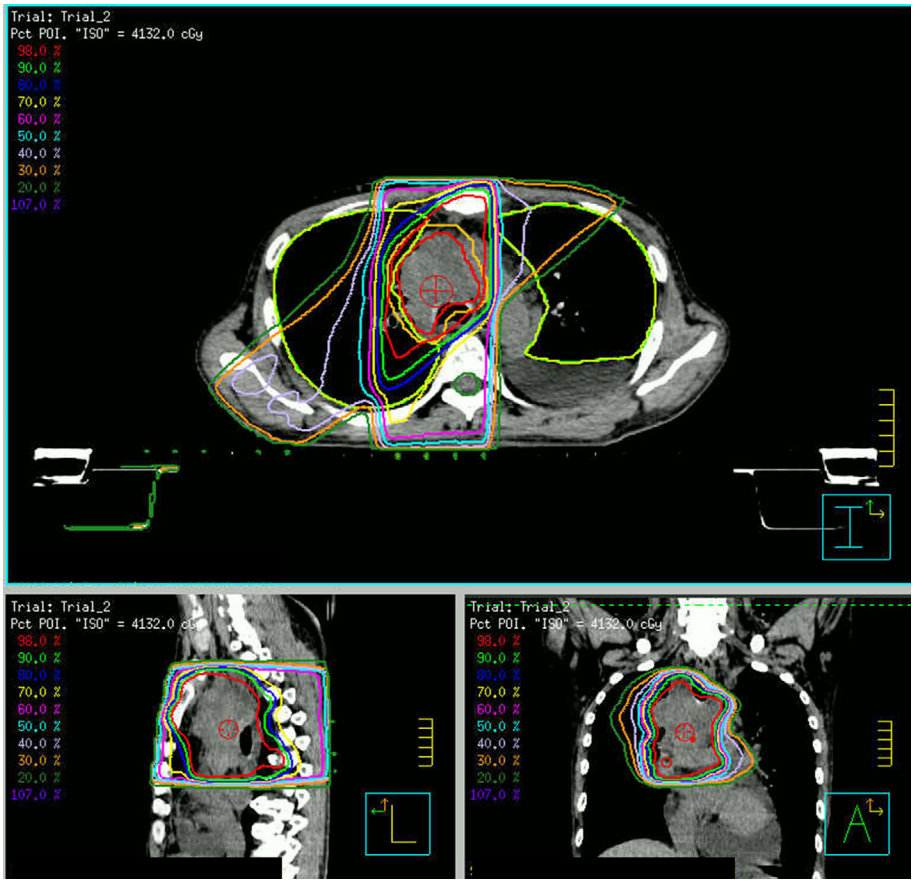

Figure 3. **Radiotherapy plan showing the isodose line on axial, sagittal, and coronal images. The clinical target volume included the tumor in the right upper lobe and mediastinal lymph node.**

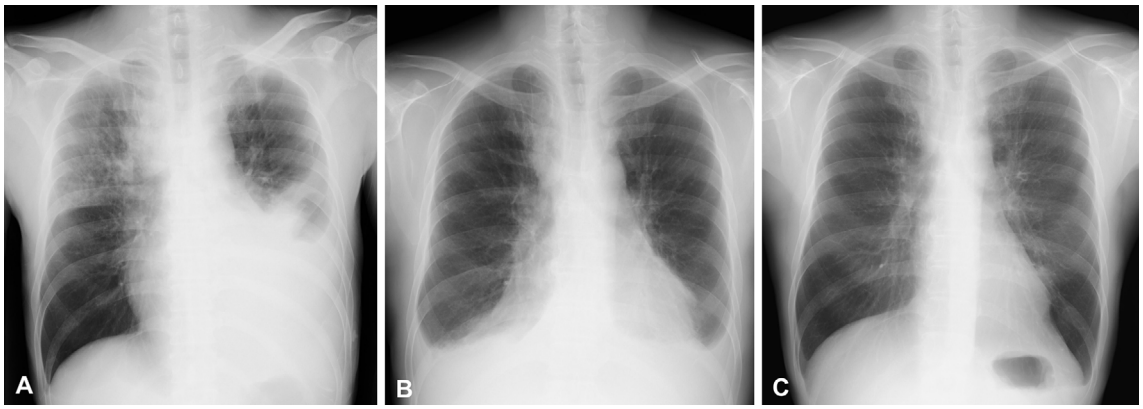

Figure 4. **(A) Chest X-ray at the start of radiotherapy, on day 15, showing the right upper and left lower field shadow, left pleural effusion and enlarged cardiac silhouette. (B) At the end of radiotherapy, on day 35, bilateral pleural effusion and enlarged cardiac silhouette are still present. (C) Chest X-ray, two months after radiotherapy, showing a marked improvement in chylothorax and chylopericardium.**

day 27. Radiotherapy was completed on day 35. Following radiotherapy, left pleural effusion and pericardial effusion gradually decreased without acute or late side effects. The patient did not develop chylopericardial tamponade and was discharged from our hospital on day 37 (Fig. 4). Two months after radiotherapy, pleural effusion and an enlarged cardiac silhouette were resolved (Fig. 5). Eight months after radiotherapy, the primary tumor and mediastinal lymph node grew again without pleural or pericardial effusion. The patient underwent 3 cycles of docetaxel (60 mg/m^2) as third-line therapy. However, the effect of chemotherapy was insufficient, and the patient was considered to have PD based on the RECIST criteria.

The patient ultimately decided to receive best supportive

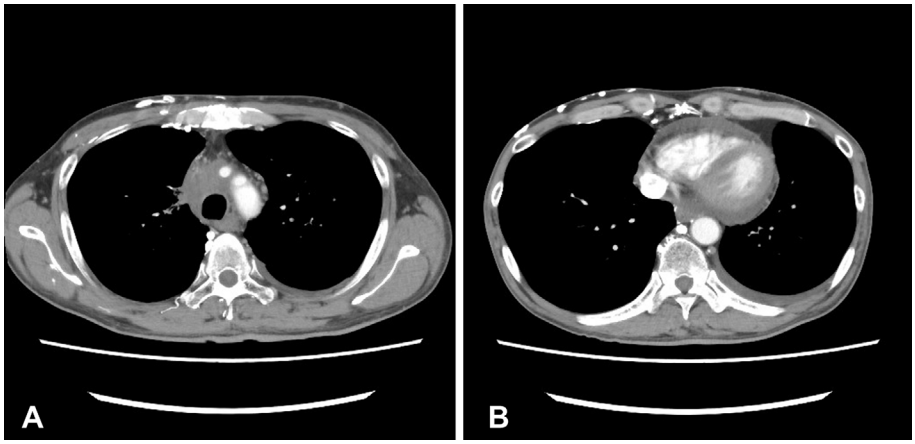

Figure 5. **(A, B) Contrast-enhanced CT performed two months after radiotherapy revealed shrinking of the tumor in the right upper lobe and mediastinal lymph node. SVC obstruction and small amounts of pericardial and pleural fluids remained.**

care and remained in remission with no recurrence of chylothorax or chylopericardium until his death after 12 months due to lung cancer.

Discussion

This case illustrates the unique presentation of a combination of chylothorax and chylopericardium secondary to lung cancer and the potential utility of radiotherapy as a treatment for such combination cases.

Chyle is a milky white fluid with a high concentration of chylomicrons and triglycerides. Chylothorax is rare condition in which chyle leaks into the pleural space. Chylopericardium, the accumulation of chyle in the pericardial space, is less common than chylothorax. The etiology of chyle leaks and accumulation includes primary idiopathic, trauma, iatrogenic after thoracic and cardiac surgery, malignant tumors, tuberculosis, sarcoidosis, Beçhet's syndrome, thrombosis of the subclavian vein and Gorham syndrome. Many cases are either chylothorax or chylopericardium alone, and the combination of these is extremely rare. To our knowledge, there has only been one such case in a patient with lung cancer that was successfully treated by pleuroperitoneal shunt. In that case, ligating the thoracic duct via thoracotomy was ineffective, and chyle leak continued for two months (5). In cases of the combination of chylothorax and chylopericardium associated with lung cancer, two factors are considered. First, the enlargement of the tumor and the swelling of mediastinal lymph nodes can damage or occlude the thoracic duct, preventing outflow to the thoracic lymphatic system. Second, SVC occlusion elevates the venous and intrathoracic pressure, resulting in increased chylothorax outflow into the thoracic and pericardial cavities. The present case showed positive results for the cytological examination of the pericardial fluid. We hypothesized that chylopericardium had been caused by abnormal traffic between the thoracic duct and pericardial cavity due to tumor invasion. Thus, radiotherapy may have closed the fistula in the thoracic duct, with its branches stopping the chyle leak. Since lymphatic duct evaluation tests, such as lymphangiography were not possible in our hospital, the site of chyle leaks could not be confirmed.

The modes of treatment to resolve chylothorax or chylopericardium are conservative management, surgical management and treatment of underlying conditions. Conservative management includes a medical chain triglyceride diet, total parenteral nutrition, thoracentesis and pericardiocentesis, chyle drainage, somatostatin and octreotide, which is a synthetic somatostatin analog. Tanizawa et al. treated chylopericardium caused by non-small-cell lung cancer with corticosteroid alone in a patient with a poor condition (6). If conservative therapy fails to control the accumulation of chyle or if the patient has a concomitant life-threatening condition, surgical treatment should be considered. Surgical treatment involves thoracic duct ligation, thoracic duct embolization or disruption, creation of a pericardial window or a pleuroperitoneal shunt. The combination of thoracic duct ligation and creating a pericardial window is the most common and effective procedure (7). Treatment of the underlying condition may have important benefits. In particular, anticancer therapy is effective for resolving chyle leak caused by malignant lymphoma and leukemia (8).

In our case, conservative treatment was ineffective, and given his poor condition, the patient was not eligible for surgical treatment or third-line chemotherapy for lung cancer. Therefore, we administered radiotherapy to resolve mediastinal lymph node metastasis and eliminate SVC obstruction. Although radiotherapy is not widely used to treat chyle leak, several authors have reported the effectiveness of radiotherapy for chyle leak. Heaton et al. performed 40-Gy radiotherapy to treat chylothorax associated with SVC obstruction secondary to metastatic colorectal cancer (9). Himmet et al. described a case of chylothorax and chylopericardium treated by 20-Gy radiotherapy in lymphangiomatosis of the mediastinum (10). The observed effects of radiotherapy on postoperative chylothorax demonstrated the feasibil-

ity of radiotherapy with a high success rates and few treatment-related side effects. In this report, the mean radiation dose was 8.5±3.5 Gy (11). The optimal radiation dose and fractionation in the management of chylothorax and chylopericardium remain unknown. In general, radiotherapy may take time to show results compared with surgical treatment. The failure of chyle resorption or chyle loss may result in serious malnutrition, immune system dysfunction, dehydration and hypovitaminosis. A small number of patients who develop massive chyle leak do not respond to conservative management, and massive effusion causes respiratory distress and chylopericardial tamponade (12). The early use of radiotherapy may control the progression of chylothorax and chylopericardium and allow the patient to avoid invasive surgical treatment.

In conclusion, radiotherapy may be an effective treatment for combined chylothorax and chylopericardium related to lung cancer. The greatest advantage of radiotherapy is that it is less invasive than surgical management and can be performed even in cases where surgical treatment cannot be performed. Thus, radiotherapy should be the preferred treatment option for combined chylothorax and chylopericardium, as these conditions are refractory to conservative management.

The authors state that they have no Conflict of Interest (COI).

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