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CASE REPORT

Development of Pseudochylothorax in a Patient with Lung Squamous Cell Carcinoma and Rheumatoid Arthritis

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ABSTRACT

Pseudochylothorax is a rare disease entity. It is characterized by a milky white pleural fluid with a cholesterol/triglyceride ratio >1. According to published reports, most patients had associated diseases, including rheumatoid arthritis and tuberculosis, with only one patient having oropharynx carcinoma associated with lung metastases. Herein, we describe the development of pseudochylothorax in a patient with rheumatoid arthritis and lung squamous cell carcinoma. Cancer cells were confirmed in the pleural fluid, but there was no thoracic duct damage caused by cancer invasion or tuberculosis-related lesions in the lung field or intrathoracic lymph nodes. Anticancer treatment included immune checkpoint inhibitors, and the appearance of a cavity within the mass and pneumothorax were associated with lung cancer treatment. Although the mechanism of pseudochylothorax onset was unknown, we do believe that this clinical course would provide some suggestive information on treatment for patients with a similar course in the future.

Keywords: pseudochylothorax, rheumatoid arthritis, lung cancer, adenosine deaminase.

INTRODUCTION

Pseudochylothorax is a rare type of pleural fluid that is characterized by a high cholesterol content (1-5). Pleural fluids with a milky-white appearance and a high lipid content are divided into pseudochylothorax and chylothorax, which are distinguished by quantifying the percentage of lipid content in the pleural fluids. These two types of pleural fluids have different etiologies, pathogeneses and clinical implications, so it is important to distinguish between them (1-5). The most commonly reported causes of pseudochylothorax were rheumatoid arthritis, tuberculosis, paragonimiasis, echinococcosis, or trauma (1-5). In addition, there was only one case report regarding the development of pseudochylothorax in a patient with malignant disease (6).

Here, we present a case of pseudochylothorax that developed in a lung cancer patient with rheumatoid arthritis as a comorbidity. To the best

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of our knowledge, there have been no reports of a patient with such complicated conditions developed pseudochylothorax. We believe that this report will provide some suggestions for the future treatment of patients who have a similar course. ❑

CASE REPORT

A 71-year-old male was referred to our department due to a cough that persisted for several months. He had no smoking habit. He had been diagnosed as having rheumatoid arthritis three years previously. Rheumatoid factor was 440 IU/mL at the time of diagnosis of rheumatoid arthritis (normal range: less than 150 IU/mL) and 485 IU/mL at the time of referral to our department. However, he had no symptoms or findings other than in his joints. Oral methotrexate was started at the time of diagnosis of rheumatoid arthritis, but the dosage of methotrexate was not changed until the time of his referral to our department. He received neither corticosteroids nor TNFα blockers. Chest radiography and computed tomography (CT) taken at that time revealed a nodule in the lower lobe of the right lung and moderate ipsilateral pleural fluid (Figure 1-A, B). A biopsy specimen obtained by bronchoscopy was diagnosed histologically as lung squamous cell carcinoma. A clear and slightly yellowish pleural fluid was obtained by thoracentesis, and squamous cell carcinoma cells were confirmed in the fluid (Table 1). Smear, culture and polymerase chain reaction were negative for tuberculosis in the pleural fluid sample and peripheral lung lavage fluid samples. The patient was diagnosed with clinical stage IVA (T2bN1M1a), and combined chemotherapy with carboplatin, paclitaxel and pembrolizumab was initiated. With this anticancer treatment, shrinkage of the nodule and a decrease of right pleural fluid were observed (Figure 2-A, B). A chest CT scan taken three months after the initiation of anticancer treatment confirmed the re-enlargement of the nodule in the right lower lobe and the appearance of ipsilateral pneumothorax (Figure 3-A, B). There was no thoracic duct damage caused by cancer invasion or tuberculosis-related lesions in the lung field or intrathoracic lymph nodes. The pleural fluid collected by thoracentesis at that time had a milky-white color, and the lipid profile showed cholesterol 558 mg/dL, triglycerides usually 15 mg/dL and cholesterol/triglyceride ratio 37.2 (Table 1). The level of adenosine deaminase (ADA) was found to be high at 57.0 IU/L in the pleural fluid, and cytology showed 52% lymphocytes and 6% neutrophils. Squamous cell carcinoma cells were also found in the fluid. Serum values measured at the same time were cholesterol (133 mg/dL) and triglycerides (74 mg/dL). Based on these results, this pleural fluid was classified as pseudochylothorax. A chest drainage tube was inserted, and it took more than two

TABLE 1.
Characteristics of pleural fluid

	Pleural fluid taken at the time of diagnosis of lung cancer	**Pleural fluid taken at the time of recurrence**
Color	Clear and slightly yellowish	Milky-white
Glucose (mg/dL)	3	
Protein (g/dL)	5.0	
LDH IU/L	2945	
Number of cells (/μL)	12700	
Gravity	1.034	
pH	7.31	
Differential count of leukocytes		
leukocytes	0.91	
lymphocytes	0.03	
eosinophils	0.01	
Cytology	Class V (squamous cell carcinoma)	Class V (squamous cell carcinoma)
ADA (IU/L)	67.7	57.0
Lipid analysis		
α		39.7%
preβ+β		40.6%
other		19.7%
Total cholesterol (mg/dL)		558
Triglycerides (mg/dL)		15
Cholesterol/triglycerides		37.2

LDH: lactate dehydrogenase; ADA: adenosine deaminase

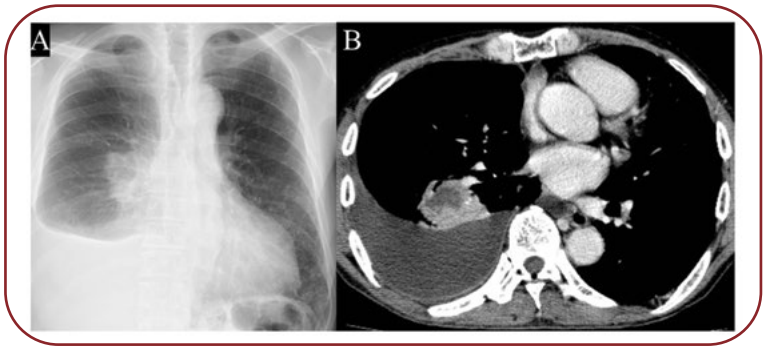

FIGURE 1. Chest radiograph (A) and computed tomography (B) taken at that time, which revealed massive right pleural fluid and a mass with low-density area in the lower lobe of the right lung

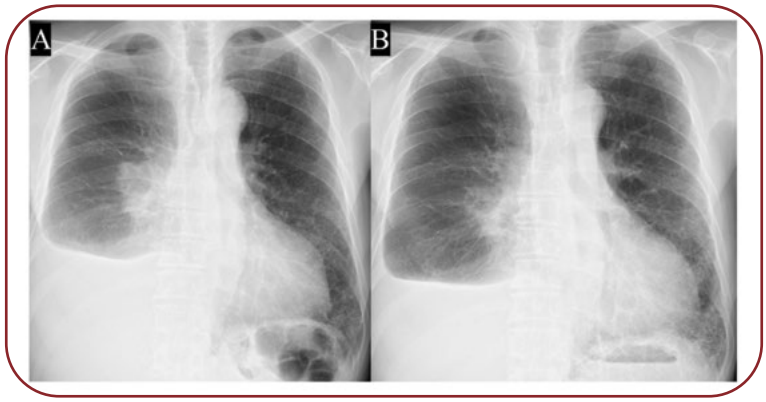

FIGURE 2. Chest radiographs taken at the initiation of chemotherapy (A) and at the time of two courses after chemotherapy (B) showing shrinkage of the nodule and decrease of the right pleural fluid and a small right sided pneumothorax

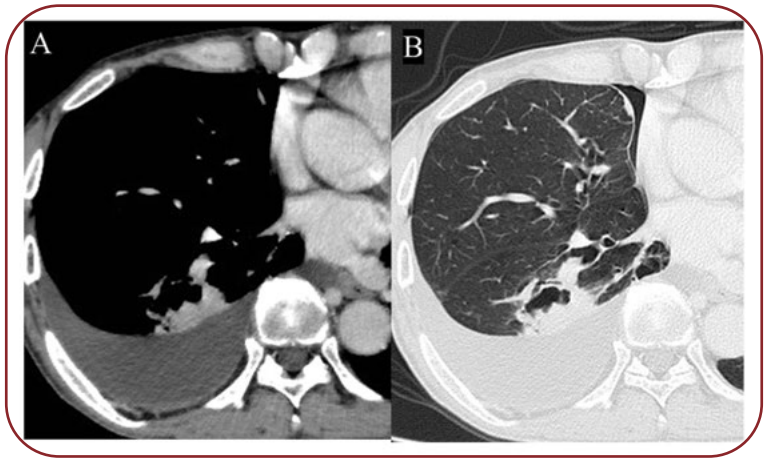

FIGURE 3. A chest computed tomography scan taken three months after the initiation of anticancer treatment confirmed the re-enlargement of the nodule in the left lower lobe and the appearance of a right pneumothorax (Figure 3-A, B). The mass had shrunk and the low-density area within the mass that had been identified before treatment had become cavity.

weeks for the pneumothorax to completely disappear, but the pneumothorax eventually resolved completely. Due to relapse of the primary tumor, treatment with pembrolizumab was changed to ramucirumab and docetaxel, and this combination therapy was continued for 12 months. Nineteen months have passed since his lung cancer diagnosis. There has been no recurrence of pneumothorax and, although a small amount of pleural effusion remains, it has neither increased nor decreased in volume. Since the patient did not have dyspnea and did not wish to have a chest tube insertion, only systemic anti-cancer treatment has been performed in an outpatient setting. ❑

DISCUSSION

Pseudochylothorax is diagnosed by the following pleural fluid findings: Milky-white pleural fluid, cholesterol >200 mg/dL, triglycerides usually <110 mg/dL and cholesterol/triglyceride ratio > 1 (1-14). Microscopic examination might reveal crystals of cholesterol. Rheumatoid arthritis was one of the most common underlying diseases in patients with pseudochylothorax (1-14). In a review by Lam et al, 44 and 33 of 104 patients with pseudochylothorax had tuberculosis and rheumatoid arthritis, respectively (4).

With regard to the mechanisms of pseudochylothorax, long-standing pleural effusions, calcification and thickening of the pleura (3, 7), inflammatory reactions associated with rheumatoid arthritis (8), and rupture of rheumatoid nodules near the pleura (16) have been reported. However, some studies reported that pseudochylothorax occurred in patients without pleural thickening (12, 15), while another one described the development of pseudochylothorax in a patient with short-term pleural fluid (3), so the mechanism of pseudochylothorax development is still unclear. In our patient, we found no pleural calcification and thickening. Since the pleural effusion at the time of lung cancer diagnosis did not show any "chyle" findings, it was assumed that pseudochylothorax developed after the lung cancer diagnosis. Therefore, the duration of the pleural fluid was determined to be less than 10 months. What remained unchanged over those almost 10 months was that the levels of rheumatoid factor continued to have elevated values, rheumatoid arthritis was controlled by continued methotrexate, and immune checkpoint inhibitors and chemotherapy for lung cancer continued. On the other hand, changes du-

ring this period included the shrinkage of the lung cancer by anticancer treatment, the occurrence of a cavity in the primary tumor, fluctuations in pleural effusion, and the appearance, disappearance and recurrence of pneumothorax.

As described above, rheumatoid arthritis and tuberculosis are known as the condition of pseudochylothorax. The mechanism of pseudochylothorax development in our patient was completely unknown. However, based on the accumulated evidence and clinical course, the following three possibilities were considered in our attempt to identify the mechanism of pseudochylothorax development in our patient. The first possibility is a link to lung cancer. Streit et al described the case of a patient with oropharynx carcinoma with lung metastasis; to our knowledge, it was the detailed report of a cancer patient who developed pseudochylothorax (6), in whom the presence of malignant cells in the pleural fluid were confirmed, but the mechanism of association between pseudochylothorax and cancer was not clear. In our patient, cancer cells in the pleural fluid samples were confirmed both before and after the onset of pseudochylothorax, and there was no dispute about the pleural fluid being associated with cancer. However, as pseudochylothorax is extremely rare in patients with malignancy, it was unclear whether that patient developed pseudochylothorax due to the malignancy. Additionally, although this patient underwent anticancer treatment, including an immune checkpoint inhibitor, and developed pneumothorax during the course, there was no evidence to suggest a direct relationship between these and the development of pseudochylothorax. The second possibility is an association with rheumatoid arthritis. The hypothesis is that rheumatoid nodules are associated with the development of pseudochylothorax. In our patient, a cavity became apparent after anticancer drug treatment, but this hypothesis is that the implementation of anticancer drug treatment and cavity formation are unrelated. In fact, there are reports of patients with rheumatic nodules with cavities (17, 18) and of a patient with rheumatic nodules who developed pseudochylothorax (13), so this might be possible. Although the possibility of lung squamous cell carcinoma developing around rheumatoid nodules is considered to be extremely low, there might be a hypothesis to consider. The third possibility is an association with tuberculosis. The ADA values in the pleural fluid, which were obtained during two thoracentesis, were both high. Acid-fast bacilli testing using the lavage fluid used during bronchoscopy and two pleural fluid specimens was negative. This possibility is considered low, as the patient did not develop tuberculosis during the six-year period without anti-tuberculosis drugs, despite receiving methotrexate and anti-cancer cytotoxic drugs. There was a report describing that ADA in the pleural fluid of patients with rheumatoid arthritis was different from that of those with tuberculosis (19). It was interesting that ADA in the pleural fluid was high in this patient, although the reason for this remains unknown.

At present, there is no established standard therapy for the treatment of pseudochylothorax. Therefore, this pleural lesion is usually treated with exudative pleural fluid associated with benign diseases (5). Treatment can generally be performed in consideration of respiratory symptoms, respiratory function status and extent of lesions. Some patients, like ours, might be able to be controlled with only drainage using a chest tube, while others might require pleurodesis. Pleurodesis must be performed with careful consideration of clinical indications and contraindications.

This case report should have discussed next two points but we could not do so. Firstly, we do evaluate that a proper, clear connection between the pathological status of the patient and pseudochylothorax are very important. But this patient had advanced lung cancer and the diagnosis was made on a bronchoscopic biopsy specimen, so it was not possible to obtain sufficient samples to clarify the connection. Secondly, due to insufficient evidence we were unable to describe the biological mechanisms underlying the development and diagnosis of pseudochylothorax such as the difference in the mechanism of development between chylothorax and pseudochylothorax. ❑

CONCLUSIONS

Here, we present a case of pseudochylothorax that developed in a lung cancer patient with rheumatoid arthritis as a comorbidity. He was the second cancer patient who developed pseudochylothorax and whose case was described by

a case report. Although the mechanism of pseudochylothorax development in this patient was not clear, he had rheumatoid arthritis, which has been suggested to be involved in the development of pseudochylothorax. Our patient underwent systemic chemotherapy and chest tube drainage. Fortunately, these treatments allowed long-term control of the pseudochylothorax. If control is poor, pleurodesis might be considered if the clinical conditions are suitable. Our treatment did not allow us to draw any conclusions regarding the treatment of pseudochylothorax. However, we do believe that this clinical course will provide some suggestive information on treatment for patients with a similar course in the future. ❑

Statement of ethics: This study was approved by the institutional ethics committee of our institute (NO1666). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Conflicts of interest: none declared.

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