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Intractable pleural effusion associated with superior vena cava and upper extremity deep vein thrombosis in a patient with advanced lung cancer

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ABSTRACT

We herein report a case with intractable pleural effusion attributed to superior vena cava (SVC) and upper extremity deep vein thrombosis in a patient with lung cancer. A 62-year-old woman presented to our hospital with shortness of breath and bilateral upper extremity edema. One year ago, she was diagnosed with stage IVB lung adenocarcinoma with bilateral malignant pleural effusions. A genetic analysis of the cells from pleural effusion revealed an epidermal growth factor receptor (EGFR) point mutation at exon 21 (L858R); since then, she was treated with gefitinib. Although her lung cancer and metastatic lesions had markedly reduced and the tumor cells in the pleural effusion had disappeared, pleural effusion remained. Contrast-enhanced whole-body computed tomography (CT) revealed intravenous thrombosis extending from the SVC to the left brachiocephalic and subclavian veins, and her pleural effusion was attributed to this thrombosis. Anticoagulant therapy with intravenous heparin and oral warfarin was started, nevertheless, the thrombus remained and pleural effusion did not decrease. After the placement of a pleuroperitoneal shunt, her pleural effusion resolved and her symptoms improved. This case highlights the importance of awareness of SVC or upper extremity deep vein thrombosis as a differential diagnosis of intractable pleural effusion in lung cancer patients.

1. Introduction

Pleural effusion in patients with lung cancer is mostly induced by cancerous dissemination to the pleura, superior vena cava (SVC) syndrome, and heart failure. We herein report a case with intractable pleural effusion attributed to SVC and upper extremity deep vein thrombosis in a patient with lung cancer, who was successfully managed with a pleuroperitoneal shunt.

2. Case presentation

A 62-year-old woman presented to our hospital with shortness of breath and bilateral upper extremity edema. She had been diagnosed with stage IVB lung adenocarcinoma with bilateral malignant pleural effusion, and metastatic lesions in both lungs, the left supraclavicular lymph node, right temporal lobe, and right ribs, one year previously. A genetic analysis of cells from pleural effusion revealed an epidermal growth factor receptor (EGFR) point mutation at exon 21 (L858R); thereafter, she was treated with gefitinib. During this treatment, her lung cancer and metastatic lesions had markedly reduced except bilateral pleural effusion (Fig. 1). With the exception of uterine myoma her past medical history was unremarkable. She had a 40 pack-year smoking history.

Her initial vital signs were as follows: heart rate, 85 beats per minute; blood pressure, 110/60 mmHg; temperature, 37.4 °C (99.3 °F); respiratory rate, 24 breaths per minute and oxygen saturation, 94% on room air. A general physical examination revealed edema of the bilateral upper extremities. Both sides of the thorax were dull to percussion with decreased breath sounds. Bilateral digital clubbing was seen. The patient's laboratory test values were as follows: white blood cell count, 8820/mm^3 with a left shift; hemoglobin, 12.4 g/dl; platelets, 182,000/mm^3; random serum glucose, 111 mg/dl; serum lactate dehydrogenase (LDH), 204 U/l; serum aspartate and alanine aminotransferase (AST and ALT), 18 U/l and 11 U/l; serum albumin, 3.1 g/dl serum blood urea nitrogen (BUN), 19 mg/dl; serum creatinine, 0.8 mg/dl; serum C-reactive protein (CRP), 0.24 mg/dl; and serum brain natriuretic peptide

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(BNP), 6.1 pg/ml. Her plasma levels of thyroid-stimulating hormone and free thyroxin were normal. Her CEA level decreased from 931.7 to 20.3 ng/ml with gefitinib treatment. Chest X-ray showed massive bilateral effusion, which was larger on the right. Electrocardiography and echocardiography revealed normal findings. Contrast-enhanced whole-body computed tomography (CT) revealed intravenous thrombosis extending from the superior vena cava (SVC) to the left brachiocephalic and subclavian vein (Fig. 2A–C). Color Doppler sonography also confirmed left subclavian vein thrombosis (Fig. 2D).

From these findings, anticoagulant therapy with intravenous heparin and oral warfarin was started, and thoracentesis of both sides was repeated. All pleural fluid analyses revealed lymphocytic predominant transudate, while cytological and microbiological studies were negative. Despite these treatments, the pleural effusion did not decrease and she required thoracentesis every 4–5 days.

On the 28th day of admission, right-sided empyema developed, which was attributable to the repeated thoracentesis, and tube drainage with intravenous antibiotics was started. Her right-sided empyema resulted in pleural adhesion and disappeared after treatment. On the other hand, her left-sided pleural effusion increased continuously, and her shortness of breath remained.

In this period, her lung cancer worsened in spite of gefitinib treatment. However, no malignant cells were observed in her left-sided pleural effusion, which remained transudative. The intravenous thrombosis extending from the SVC to the left brachiocephalic and subclavian vein also remained, suggesting that her intractable pleural effusion was due to SVC and upper extremity deep vein thrombosis. A transcatheter therapeutic procedure was considered but abandoned because the thrombus was too extensive. In this background, a pleuroperitoneal shunt (Denver Shunt®, Denver Biomedical Inc, Denver, CO) was placed, her left-sided pleural effusion decreased and her symptoms improved (Fig. 3). However, the patient was unable to receive second-line treatment because her Eastern Cooperative Oncology Group Performance Status (ECOG-PS) dropped from 2 to 4. No further therapeutic intervention for pleural effusion was required for the two months until her death from underlying lung cancer, and there were no problems with this shunt during the course.

3. Discussion

Malignant pleural effusion is commonly seen in patients with advanced lung cancer. There are, however, a number of lung cancer patients in whom the etiology of pleural effusion remains elusive, in spite of systematic and repeated testing. In our patient, the pleural effusion at the diagnosis of lung cancer was due to malignant pleuritis; however, the pleural effusion on both sides at this admission was lymphocytic predominant transudate with negative cytology. She had no signs of heart failure, liver or kidney dysfunction, or hypothyroidism. Only intravenous thrombosis extending from the SVC to the left brachiocephalic and subclavian vein was observed and was assumed to be the etiology of her intractable pleural effusion.

Cases of pleural effusion attributable to central vein thrombosis have been previously reported but are rarely associated with cancer and are mostly due to central venous catheterization [1–4]. In 1994, Wright et al. reported the case of a patient on hemodialysis who had left pleural effusion and ipsilateral upper extremity edema attributable to partial obstruction of the left brachiocephalic vein [5]. The patient had a left-side arteriovenous fistula for hemodialysis, and the surgical closure of it led to the complete resolution of her pleural effusion. In 2001, Muthuswamy et al. reported a similar case involving a patient on hemodialysis [6]. The patient had undergone percutaneous angioplasty of the brachiocephalic vein stenosis, and her pleural effusion disappeared completely. In 2005, Ruiz et al. reported two similar cases involving patients on hemodialysis. One patient underwent percutaneous venous angioplasty and the other patient underwent ligation of the arteriovenous fistula, and the pleural effusion of both patients resolved completely [7]. The authors of these papers proposed a mechanism by which venous pressure increases locally due to the combination of brachiocephalic stenosis and the high venous flow from an ipsilaterally located arteriovenous fistula, impeding the drainage of the left superior intercostal vein into the left subclavian and brachiocephalic veins. This pathophysiology could have caused intractable left-sided pleural effusion in our patient.

The pathophysiological mechanism of pleural effusion due to SVC syndrome is considered to be almost the same. The reported frequency of pleural effusion in patients with SVC syndrome is 6–70% [8–11]. The pathophysiological mechanism of this condition is considered to be as follows: an obstruction of the SVC below the entry of the azygos vein arch causes counter-current blood flow of the azygos system, which leads to plasma leakage into the pleural cavity [12]; then, the hydrostatic pressure of the intercostal veins increases and reveals congenital anastomosis between the intercostal and pulmonary veins (right-left shunt); finally, an increase in the production of pleural effusion and the impairment of reabsorption by the lymphatic system co-occurs, and pleural effusion increases. Regarding the location of pleural effusion associated with SVC syndrome, Rice et al. reported that 23% were unilateral left-sided, 17% were unilateral right-sided, and 39% were bilateral [11]. Our patient had bilateral pleural effusion. The characteristics of pleural effusion of this condition have been reported as transudative [13–16]. On the other hand, Rice et al. reported that in all cases, the pleural effusion of their patients with SVC syndrome was exudate, and among the 17 effusion samples obtained from patients with malignancy, malignant cells were observed in 9 samples [11]. Therefore, they assumed that the pleural effusion cytology of some of the remainder were false-negatives, and that malignancy affected the characteristics of pleural effusion. In our patient, no malignant cells were observed in repeated tests, and the pleural effusion remained transudative.

Anticoagulation and successful recanalization of thrombosis are essential in the treatment of thrombosis related pleural effusion. However, in our patient, the transcatheter therapeutic procedure was

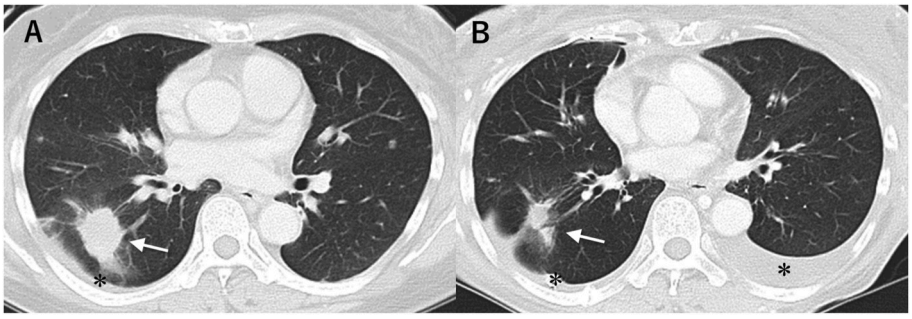

Fig. 1. Chest CT findings at the time of diagnosis (A) and on admission (B). The patient's lung cancer (white arrow) had markedly reduced but her pleural effusion (*) remained.

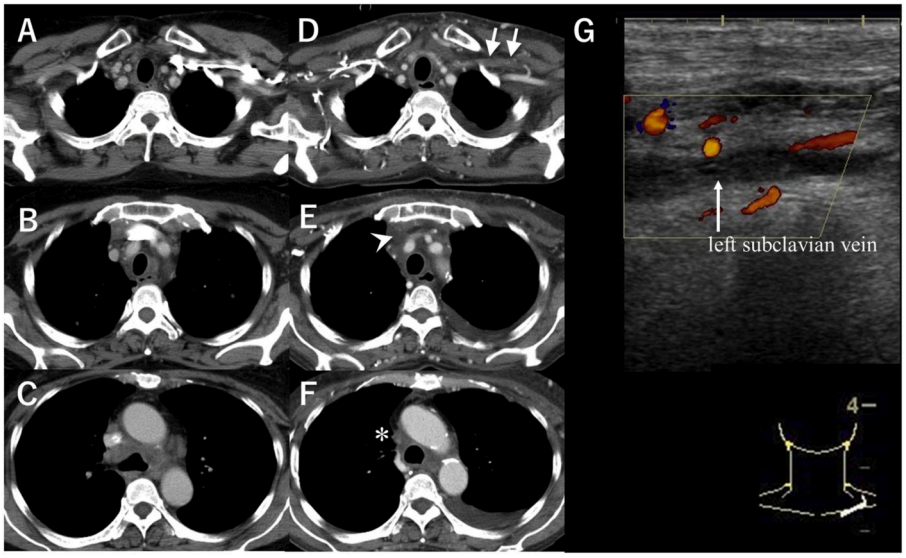

Fig. 2. Contrast-enhanced chest CT findings at the time of diagnosis of lung cancer (A, B, C). CT images on admission reveled intravenous thrombosis extending from the SVC (* on F) to the left brachiocephalic (arrowheads on E) and subclavian vein (white arrows on D). Color Doppler sonographic findings of left subclavian vein thrombosis (G). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

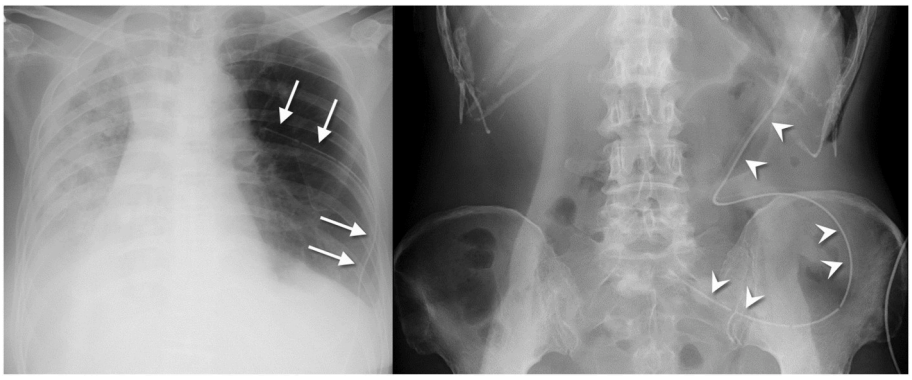

Fig. 3. A pleuroperitoneal shunt (Denver Shunt®, Denver Biomedical Inc, Denver, CO) positioned in the thoracic (white arrow) and abdominal cavity (arrowheads).

abandoned because her thrombus was too extensive. A pleuroperitoneal shunt was placed instead of a pleurodesis to control her symptoms due to pleural effusion. We avoided pleurodesis because her right pleura was already adherent due to pleurisy and pleurodesis was thought to be associated with a high risk of developing a high degree of restricted ventilation. Pleuroperitoneal shunt insertion has been reported to be effective and safe for relieving symptoms of patients with intractable pleural effusion [17]. The previously reported frequency of complications associated with this procedure was 14.8%, including infection, tumor seeding into the peritoneal cavity, and shunt occlusion. Our patient was unable to receive second-line treatment because her ECOG-PS dropped from 2 to 4. Therefore, we determined that the benefits of this treatment outweighed the disadvantages.

In conclusion, this case highlights the importance of awareness of SVC or upper extremity deep vein thrombosis in the differential diagnosis of intractable pleural effusion in lung cancer patients.

Role of the study

Kosuke Tsuruno: Data collection, Interpretation of data, Writing of the manuscript.
Kazunori Tobino: Writing of the manuscript.
Mitsukuni Sakabe: Data collection.
Masanobu Okahisa: Data collection.
Saori Nishizawa: Interpretation of data.
Kohei Yoshimine: Interpretation of data.
Yuki Ko: Data collection.
Hiromi Ide: Data collection.

Declaration of competing interest

All the authors have no conflict of interest about this case report.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2020.101094.

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