

[CASE REPORT]

Refractory Chylothorax and Lymphedema Caused by Advanced Gastric Cancer

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Abstract:

Chylothorax is the accumulation of lipid pleural effusion. Few reports have described chylothorax caused by gastric cancer. A 45-year-old woman presented with progressive lymphedema and bilateral chylothorax. Although repetitive thoracentesis was performed to relieve her dyspnea, swelling of her axillary lymph nodes became significant. Positron emission tomography/computed tomography demonstrated the accumulation of ¹⁸F-fluorodeoxyglucose in these nodes, and a lymph node biopsy showed signet ring cell carcinoma. The primary site was a 0-IIc type lesion in the gastric body that was only detected by upper gastrointestinal endoscopy. The patient was diagnosed with advanced gastric cancer 3.5 months after presentation for chylothorax.

Key words: chylothorax, lymphedema, gastric cancer, signet ring cell carcinoma

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Introduction

Chylothorax is an accumulation of triglyceride-rich fluid in the pleural cavity. Two major causes of chylothorax are trauma and malignancy, and many cases are idiopathic. The main malignancy that causes chylothorax is lymphoma, which accounts for 45% of cases of chylothorax (1). Few case reports have described chylothorax caused by advanced gastric cancer. Confirming a diagnosis of gastric cancer sometimes requires substantial time in patients with chylothorax.

We herein report a case of advanced gastric cancer accompanied by chylothorax with a complex pathogenesis requiring a long time to determine a definitive diagnosis. We also review previous reports of similar cases.

Case Report

A 45-year-old Chinese woman with no significant medical history was referred to our hospital for the management and examination of her bilateral chylothorax. Eight months before this referral, she presented with genital and bilateral leg

edema at the previous hospital. Indocyanine green lymphography showed dermal backflow on the bilateral lower extremities, confirming that she had lymphedema. She was considered to have idiopathic lymphedema and underwent lymphatic-venous anastomosis of her left leg, and the edema slightly improved. However, three months after the surgery, she developed difficulty breathing because of bilateral pleural effusion. Thoracentesis at the previous hospital revealed chylothorax. The pleural effusion accumulated so rapidly that the patient required thoracentesis every several days to relieve her shortness of breath. She did not complain of any gastric symptoms. She had a history of appendicitis (surgically treated) and purpura. She had no history of thoracic surgical procedures or trauma. She had never smoked.

On admission, her vital signs were as follows: body temperature of 36.5°C, heart rate of 103 bpm, blood pressure of 112/68 mmHg, and oxygen saturation of 97% while breathing 2 L of oxygen. A physical examination was significant for decreased breath sounds in the bilateral lungs and diffuse edema, excluding her face and right upper limb. Swollen cervical and axillary lymph nodes were also found.

Laboratory tests showed that the C-reactive protein level was slightly high (2.9 mg/dL) and that the carcinoembryonic

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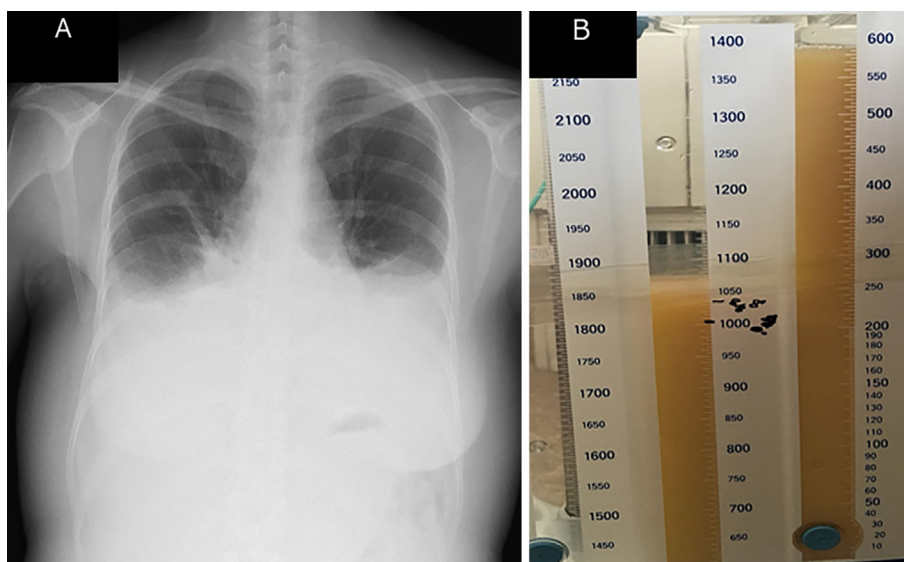


Figure 1. (A) Chest radiograph showing bilateral pleural effusion at presentation. (B) Pleural effusion immediately after placement of the chest drainage tubes.

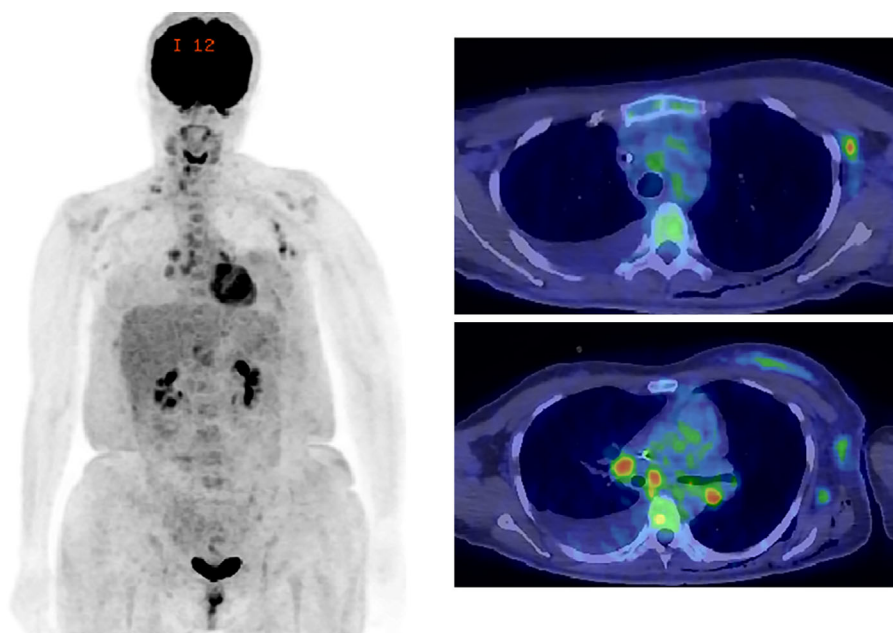


Figure 2. ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography showing swelling of multiple mediastinal and axillary lymph nodes with the accumulation of ^{18}F -fluorodeoxyglucose.

antigen level was within the reference range (0.4 ng/mL). Other laboratory findings for her complete blood count, liver, renal function, and electrolytes were normal. Filarial antibody was not detected. A urinalysis showed occult blood 2+, but the findings were otherwise normal. A chest radiograph showed bilateral pleural effusion but no signs of a tumor or infiltration (Fig. 1A). Thoracentesis showed turbid yellowish pleural effusion (Fig. 1B) with a triglyceride level of 515 mg/dL, cholesterol level of 70 mg/dL, and carcinoembryonic antigen level of 2.6 ng/mL. Cytological examinations of the pleural effusion on both sides were negative for malignancy.

^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) did not reveal a primary site of malignancy except for lymphadenopathy in the bilateral hilum, mediastinum, and left axilla (Fig. 2). Therefore, a biopsy of a left axillary lymph node was performed and revealed signet ring cell carcinoma. Although CT revealed no gastric abnormalities aside from slight ascites in the pelvic cavity, we suspected that she had gastric cancer based on the above-described findings. Upper gastrointestinal endoscopy was then performed and showed a type 0-IIc lesion at the posterior wall of the gastric body (Fig. 3). A biopsy of the gastric lesion demonstrated a pathological re-

sult similar to that of the axillary lymph node (Fig. 4). The amount of ascites increased over time, and abdominocentesis was carried out for the first time after obtaining a pathological diagnosis of gastric cancer. It confirmed malignant chylous ascites with a milky appearance. The patient was given a diagnosis of advanced gastric cancer (cT1aN0M1 stage IV) and scheduled to undergo chemotherapy. Human epidermal growth factor receptor 2 (HER2) was negative.

Because management of the pleural effusion was necessary before chemotherapy, drainage tubes were placed in her bilateral pleural cavities, and a low-fat diet and 20-mg furosemide therapy were begun. Her pleural effusion was cytologically examined many times after the establishment of the definite diagnosis, and malignancy was finally confirmed. The amount of her pleural effusion decreased significantly one week after starting drainage. However, she was not able to endure the restricted diet for a long period of time, and her bilateral pleural effusion accumulated again and returned to a lipid-rich fluid. Furthermore, because she refused to undergo pleurodesis, repeated thoracentesis was performed during chemotherapy. She received four 3-week

cycles of oral capecitabine (1,800 mg/body twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m² on day 1 of each cycle). She finally agreed to undergo pleurodesis when the survey following the first two courses of chemotherapy revealed progressive disease. Pleurodesis was performed only on the right side with minocycline 400 mg and was successfully completed. However, the pleural effusion on the left side was uncontrolled. She died six months after the diagnosis of gastric carcinoma. An autopsy was not performed.

Discussion

We experienced a case of refractory chylothorax and lymphedema caused by advanced gastric cancer. Establishment of the diagnosis required 3.5 months because the pathogenesis was rare and complex. In addition, the treatment options for the gastric cancer were limited due to the difficulty in managing the chylothorax. The patient's performance status deteriorated due to the delay in confirming the diagnosis and the presence of uncontrollable pleural effusion, leading to a shorter-than-average survival period.

About half of cases of chylothorax are caused by malignancy (1), and most of these are malignant lymphomas. With the exception of lymphomas, the primary sites vary and include the lung, esophagus, and breast. A few dozen cases of chylothorax caused by gastric carcinoma have been reported to date. We herein review 14 cases for which reports were available (Table) (2-15).

Generally speaking, the causes of non-traumatic chylothorax are difficult to determine. Gastric cancer was particularly difficult to diagnose in the present case because 1) repetitive thoracentesis was negative for malignancy, 2) the patient did not complain of any gastric symptoms, and 3) the primary site was a type 0 lesion that showed no significant findings on CT. Five cases with negative cytology from pleural effusion and an absence of signs of gastric cancer on CT have been reported (2-4, 6, 7) (Table). These cases required invasive procedures, such as a lymph node biopsy, broncho-

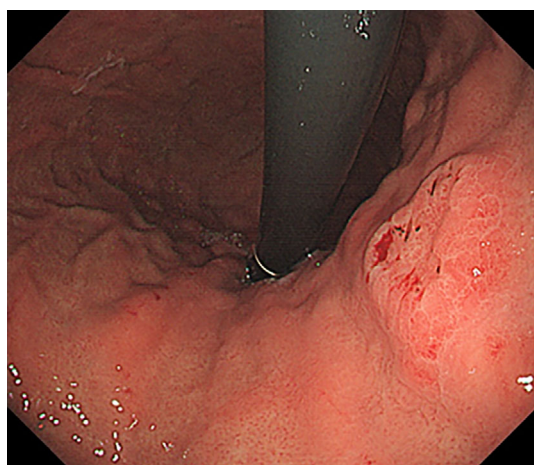


Figure 3. Upper gastrointestinal endoscopy revealed a type 0-IIc lesion at the posterior wall of the gastric body.

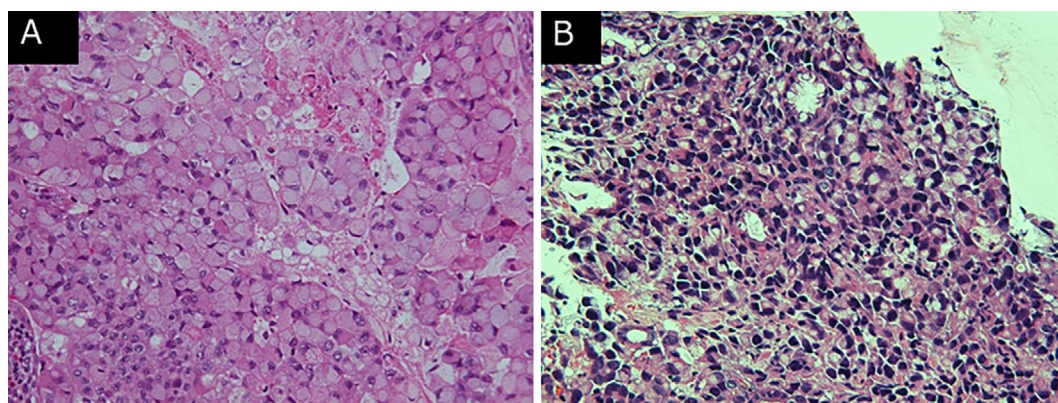


Figure 4. (A) A biopsy of left axillary lymph nodes indicating signet ring cell carcinoma [Hematoxylin and Eosin (H&E) staining; magnification $\times 40$]. (B) A biopsy of the gastric body indicating signet ring cell carcinoma (H&E staining; magnification $\times 40$).

Table. A Review of the Reported Cases of Chylothorax from Gastric Carcinoma.

Patient No.	Reference No.	Age	Sex	Pleural effusion	Lymphedema	Anatomical site of edema	Cytology of pleural effusion	Signs of gastric cancer on CT	Lymphadenopathy at presentation	The diagnosing methods	GS	Duration until diagnosis (m)	Survival time (m)
1	2	38	F	B	N	NA	negative	N	N	open lung biopsy	Y	2.5	2
2	3	23	M	B	Y	neck, upper chest, mammary area	negative	NA	Y	cervical LN biopsy, GS	Y	1.5	4
3	4	64	M	R	Y	left arm, left leg	negative → positive	N	N	GS	Y	4	6
4	5	NA	NA	L	Y	right leg	NA	N	Y	subclavicular LN biopsy, GS	Y	NA	NA
5	6	28	F	B	Y	right leg, left arm, left breast	negative → positive	N	Y	transbronchial biopsy	N	7	7
6	7	58	F	B	Y	right leg, vulva, left thigh, trunk	negative → positive	N	N	GS, skin biopsy	Y	15	4
7	8	19	F	B	Y	below the neck	positive	Y	N	cervical LN biopsy, skin biopsy	Y	2	3.5
8	9	58	F	B	Y	right arm	positive	Y	N	thoracentesis, upper GI series	N	1	4
9	10	66	F	B	N	NA	positive	N	N	thoracentesis, GS	Y	NA	NA
10	11	64	M	B	Y	right leg	positive	Y	Y	thoracentesis, GS	Y	1	3.5
11	12	77	F	B	N	NA	positive	NA	Y	autopsy	N	NA	1
12	13	61	F	B	Y	left leg	positive	Y	Y	thoracentesis, GS	Y	NA	10
13	14	32	F	R	Y	bilateral lower extremity, vulva	positive	N	N	oophorectomy	N	NA	NA
14	15	63	F	B	Y	bilateral lower extremity	NA	Y	Y	GS	Y	1	4.5
This case		45	F	B	Y	left arm, bilateral lower extremity, trunk	negative → positive	N	Y	axillary LN biopsy, GS	Y	3.5	6

NA: not available, M: male, F: female, B: bilateral, R: right, L: left, N: no, Y: yes, GS: gastroscopy, LN: lymph node, GI: gastrointestinal, m: month

scopy, and open lung biopsy. The duration before the diagnosis of gastric carcinoma ranged from 1 to 15 months, and the average survival period after the diagnosis was 3.9 months in the patients in the previous reports (Table). The duration is the average of all patients. This short survival period may have been triggered by the delay in diagnosis, which allowed the disease to become more progressive, worsened the patients' performance status, and limited the available treatment options.

In the present case, FDG-PET/CT illustrated multiple

lymphadenopathy, including left axilla, mediastinum, and bilateral hilar lymph nodes, suggesting the possibility of malignancy. There was no evidence of the accumulation of FDG in the lesion of primary gastric cancer. FDG-PET/CT has been proven useful for the identification of the primary tumor site in patients with carcinoma of unknown primary site (16). Only one case report of chylothorax from gastric cancer included an explanation of the PET/CT findings (12). In that case, the patient underwent aspiration cytology of the thyroid gland upon receiving the result of FDG-PET/CT.

However, she died before the biopsy results were obtained. FDG-PET/CT may be recommended for patients with non-traumatic chylothorax when carcinoma is highly suspected but the usual clinical investigations do not reveal the primary site.

Treating patients with malignant chylothorax is difficult for several reasons. The first point of difficulty is the management of pleural effusion. The representative treatment options for non-traumatic chylothorax are low-fat diet therapy, pleurodesis, and surgery (17). The patient in the present case was not able to continue the diet therapy and initially refused pleurodesis. The second point of difficulty is due to the fact that surgical ligation of the thoracic duct is not recommended in patients with bilateral effusion because multiple leakage points likely exist. In the present case, lymphatic scintigraphy suggested that the leakage was not caused by a single site; therefore, we did not attempt surgical ligation of the thoracic duct. This difficulty in managing pleural effusion may affect the treatment of gastric carcinoma. Third, suitable chemotherapy regimens containing a large volume of fluid may need to be avoided because of respiratory failure caused by the pleural effusion. Finally, the long duration before the diagnosis and the respiratory failure may worsen the performance status and contribute to a short overall survival. Indeed, the average survival time in previous reports was 4.5 months, which is shorter than that recently reported in phase III studies of chemotherapy-naïve patients with advanced gastric cancer (18, 19).

The mechanism underlying the accumulation of fatty pleural effusion and chyloedema in patients with advanced gastric cancer is still unknown. In general, leakage of chylous fluid accompanies lymph node metastasis that obstructs the afferent lymphatic flow (20). Eight of 15 cases, including the present case, showed enlarged lymph nodes on imaging studies at presentation (3, 5, 6, 11-13, 15) (Table). However, other mechanisms of chylothorax and chyloedema may exist, as some of those patients had no signs of lymph node swelling at the time of the diagnosis (2, 4, 7-10, 14) (Table). The first such potential mechanism is the direct infiltration of malignant cells into the thoracic duct (1). The increased back pressure in the thoracic duct by tumor invasion induces regurgitation of the lymphatic flow, resulting in peripheral lymph vessel ectasia and the accumulation of chylous effusion in the pleural cavity. A second potential mechanism is diffuse metastasis into the peripheral lymphatic capillaries. Wu et al. proposed that the infiltration of tumor cells into the lymphatic circulation induces chylous fluid leakage (16). Indeed, Shibata et al. reported a case of dermal lymphatic metastasis in the lower extremities preceded by the development of chylothorax (7). Hegeman et al. also reported a case of advanced gastric cancer with pathologically proven tumor infiltration into the small lymphatic vessels of the lymphedema lesion (21). This proposal may explain the subsequent development of chylothorax and ascites after the onset of peripheral lymphedema. In the present case, the patient developed lymphedema of the lower

extremities eight months before the development of chylothorax. Subsequently, malignant chylous ascites and abdominal lymph node enlargement became apparent. Therefore, despite a lack of direct evidence, we suspect that tumor invasion into the lymphatic circulatory system caused chylous effusion in both the pleural and abdominal cavities as well as lymphedema in this patient.

In conclusion, malignancy should be vigorously investigated when encountering patients with chylothorax of unknown cause, and clinicians should be aware of the possibility of advanced gastric cancer, although it is quite rare. FDG-PET/CT is a potent imaging tool with which to identify the primary site and the lesions suitable for a biopsy. In cases of malignancy of luminal organs, it is sometimes difficult to detect the primary site by FDG-PET/CT alone; therefore, invasive diagnostic procedures, such as upper gastrointestinal endoscopy, should be considered from an earlier time point. A delay in the diagnosis allows the disease to progress and reduces the survival duration, as previous reports have shown.

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

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