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Lymphangitis carcinomatosa from gallbladder cancer

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ABSTRACT

A 61-year-old woman was admitted to our hospital with productive cough and fever. Computed tomography images revealed ground glass opacities in both lung fields, and a space-occupying lesion in the gallbladder. Transbronchial lung biopsy revealed a poorly differentiated adenocarcinoma with invasion of the lymph ducts; accordingly, a diagnosis of lymphangitis carcinomatosa was made. We could not administer chemotherapy due to poor performance status, and the patient died of respiratory failure 30 days after admission. Owing to pathological autopsy findings of poorly differentiated adenocarcinoma in the gallbladder, we diagnosed this as a rare case of gallbladder cancer presenting with lymphangitis carcinomatosa.

1. Introduction

In 1873, Troisier first coined the term “lymphangitis carcinomatosa,” which describes diffuse infiltration of the lymphatics of both lungs by malignant cells [1]. Dyspnea is the most frequent symptom of lymphangitis carcinomatosa, appearing in about 60% of patients with this disease state; dry cough and weight loss are the second and third most frequent symptoms, respectively [2]. The prognosis of patients presenting with lymphangitis carcinomatosa is very poor; the median survival duration from the onset of respiratory symptoms is 2 months, while that from hospital admission is 2 weeks [2].

Primary lesions for lymphangitis carcinomatosa vary and breast cancer, lung cancer and stomach cancer are the main causative primary lesions [3]. Although lung metastasis has been reported in 34.3% of gallbladder cancer autopsy cases [4], gallbladder cancer has been reported as a primary tumor for lymphangitis carcinomatosa only in one previous case [5]. In this case, diffuse alveolar haemorrhage was suspected from computed tomography (CT) findings during his life time, and it was not until pathological autopsy was performed that both lymphangitis carcinomatosa and gallbladder cancer was diagnosed [5]. Herein, we report the first case of lymphangitis carcinomatosa from gallbladder cancer which we could diagnose during her life time.

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2. Case report

A 61-year-old woman had been suffering from a productive cough from mid-August 2011. She had no smoking history, nor any medical history. The patient had been treated at another hospital using quinolone antibiotics, a bronchodilator, and expectorant drugs, assuming a diagnosis of acute bronchitis; however, her symptoms did not improve. Slight fever also appeared, and she was admitted to our hospital in early September.

At the time of admission, her body temperature, blood pressure, and heart rate were 37.0 °C, 115/66 mmHg, and 83 beats per minute with a regular rhythm, respectively. Coarse crackles were heard in both the lungs, with a respiratory rate of 16 breaths per minute. The patient's percutaneous oxygen saturation was 98% in room air. She did not have any edema in her extremities, and her performance status score was 2 [6]. Chest radiograph revealed diffuse ground glass opacities, reticular shadows in both the lung fields, and right hilar enlargement (Fig. 1). Chest CT images revealed multiple small nodular shadows, interlobular septal thickening, irregular thickening of the bronchovascular bundles, ground glass opacities, and reticular shadows in both the lung fields (Fig. 2A and B). Additionally, bilateral pleural effusion, as well as bilateral swelling in the supraclavicular, mediastinal, and hilar lymph nodes, was observed (Fig. 2A–C). Abdominal CT images revealed thickening of the gallbladder wall, a 3 cm space-occupying lesion in the body of the gallbladder, a low-density area in the anterior inferior segment (S₅) of the right hepatic lobe around the gallbladder bed, and lymph nodes swelling in the porta hepatis and para-aortic lesions (Fig. 3A and B). Only a slight dilatation of the intrahepatic bile ducts was observed (Fig. 3C).

Laboratory measurements revealed that the white blood cell count was elevated to $14.2 \times 10^3/\mu\text{L}$. The percentage of eosinophils was elevated to 17.2%, indicating moderate peripheral blood eosinophilia with an eosinophil count of $2442.4/\mu\text{L}$ [7]. The proportion of neutrophils, lymphocytes, monocytes, and basophils was 68.8%, 8.2%, 5.7%, and 0.1%, respectively. The lactate dehydrogenase level was 517 IU/L; total bilirubin (T-Bil) level, 0.6 mg/dL; alkaline phosphatase (ALP) level, 206 IU/L; gamma-glutamyl transpeptidase (γ -GTP) level, 14 IU/L; and C-reactive protein level, 5.27 mg/dL. Among tumor markers, the carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, and CA-125 levels were elevated to 9.7 ng/mL, 395 U/mL, and 160 U/mL, respectively.

Based on abnormal CT findings in the gallbladder and liver, as well as the elevation of CRP and tumor markers, we suspected gallbladder cancer with liver metastasis, or acute cholecystitis with liver abscess. Multiple metastatic lung tumor and lymphangitis



Fig. 1. Chest radiograph obtained on the day of admission showing diffuse ground glass opacities, reticular shadows in both the lung fields, and right hilar enlargement.

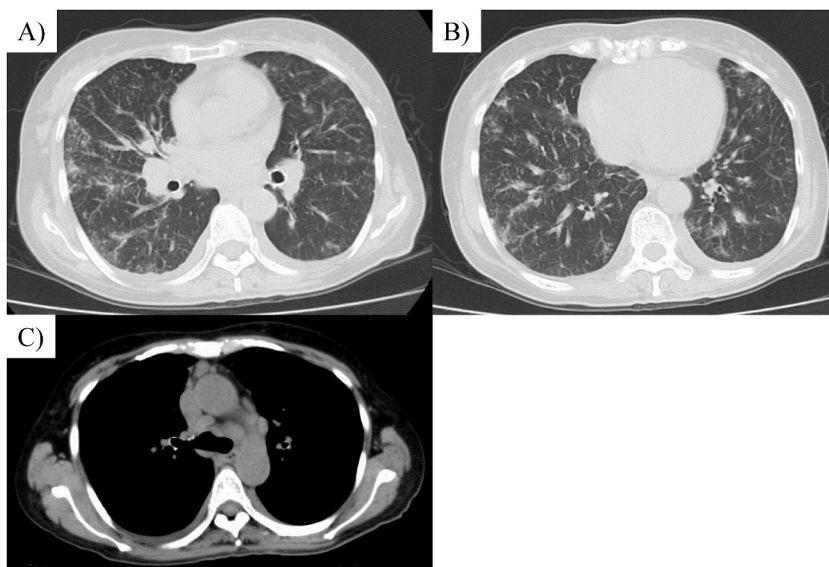


Fig. 2. (A, B) Chest computed tomography images obtained on the day of admission showing multiple small nodular shadows, interlobular septal thickening, thickening of the bronchovascular bundles, and ground glass opacities in both the lung fields, as well as bilateral pleural effusion and bilateral swelling in the hilar lymph nodes. (C) Swollen mediastinal lymph nodes.

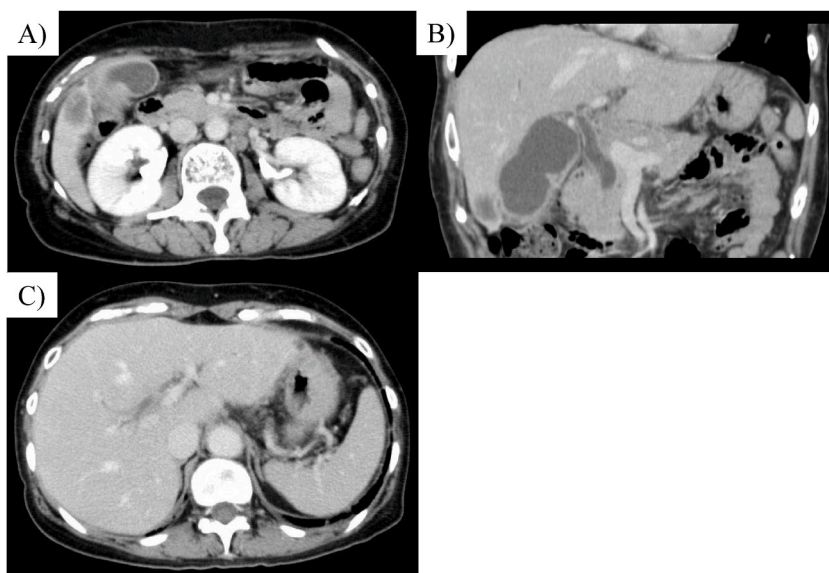


Fig. 3. Abdominal computed tomography images obtained on the day of admission showing (A) thickening of the gallbladder wall and a 3 cm space-occupying lesion in the body of the gallbladder, (B) a low-density area in the anterior inferior segment (S₅) of the right hepatic lobe around the gallbladder bed, and lymph nodes swelling in the porta hepatis lesion and para-aortic lesion, and (C) slight dilatation of the intrahepatic bile ducts.

carcinomatos were mainly suspected from chest CT findings. Since she had neither a history of allergic disease nor a dietary history suggestive of parasite infection, the medications described above and latent malignancy were suspected as the possible cause of moderate peripheral blood eosinophilia [8]. Although we suspected pulmonary sarcoidosis as another differential diagnosis from chest CT findings and eosinophilia, neither angiotensin-converting enzyme level (6.6 U/L) nor Krebs von den Lungen-6 level (296 U/mL) was elevated [9,10].

Fiberoptic bronchoscopy did not reveal abnormal mucosal findings. Bronchoalveolar lavage (BAL) was conducted from the right middle lobar bronchus (B⁴a), and the proportion of white blood cells in the BAL fluid was as follows: neutrophils, 17.5%; lymphocytes, 26.0%; eosinophils, 20.0%; basophils, 0%; macrophages, 35.5%; and unclassified, 1.0%. Adenocarcinoma cells were observed through cytology of the BAL fluid. Transbronchial lung biopsy (TBLB) from the anterior segment (S⁸) of the right lower lobe revealed poorly differentiated adenocarcinoma with invasion into the lymph ducts in the TBLB specimens (Fig. 4A). Based on the fact that neither

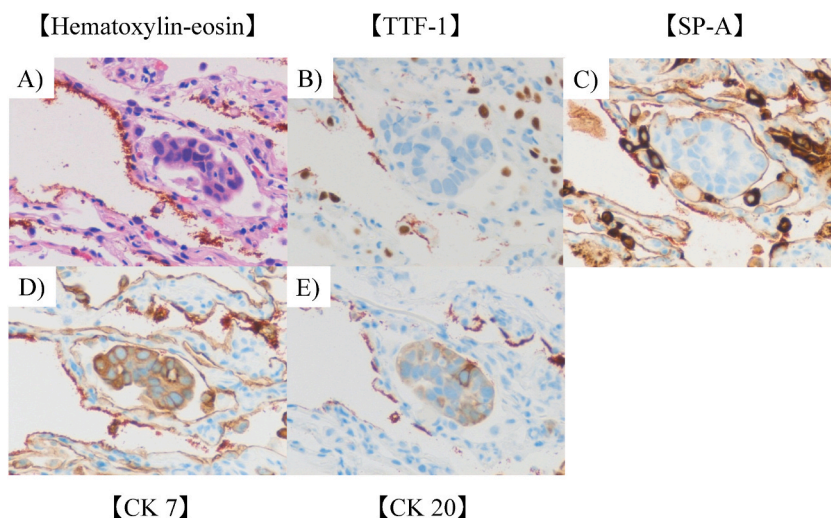


Fig. 4. Microscopic pathological findings on transbronchial lung biopsy specimen from the anterior segment (S_5) of the right lower lobe. (A) Hematoxylin-eosin staining revealed poorly differentiated adenocarcinoma cells with invasion of the lymph ducts. Immunohistochemistry was negative for (B) thyroid transcription factor-1 (TTF-1) and (C) surfactant protein-A (SP-A). Immunohistochemistry results were positive for (D) cytokeratin (CK) 7 and (E) CK 20. Original magnification, $\times 400$

granulomatous lesion nor interstitial pneumonia was observed in the TBLB specimen, we rejected the possibility of sarcoidosis. Considering these findings along with those of intrathoracic CT, lymphangitis carcinomatosa was diagnosed.

Since we considered it difficult to obtain an appropriate biopsy specimen from the space-occupying lesion in the body of the gallbladder, biopsy specimens were obtained from the low-density areas in the anterior inferior segment (S_5) of the right hepatic lobe. Poorly differentiated adenocarcinoma with strong necrosis was detected. Immunohistochemical analysis was conducted using the TBLB specimens to identify the primary site of the tumor. Since they were negative for thyroid transcription factor-1 (TTF-1; Fig. 4B) and surfactant protein-A (SP-A; Fig. 4C), we judged that lung cancer was not the primary site. Based on the positive results for cytokeratin 7 (CK 7; Fig. 4D) and CK 20 (Fig. 4E), we diagnosed gallbladder cancer as the primary site and lung tumor as metastasis.

The patient's productive cough did not improve with a cough suppressant, and she began to experience dyspnea and hypoxemia several days after admission. We initiated the oral administration of oxycodone hydrochloride hydrate and oxygen therapy against dyspnea and acute respiratory failure, respectively. According to the guidelines of the Japanese Society for Palliative Medicine, we also started intravenous corticosteroids administration with the intention of relieving dyspnea [11]. In the present case, we chose 1000 mg/day of methylprednisolone for the first 3 days; the dose of corticosteroids was decreased to 40 mg/day of prednisolone on the 4th day and subsequently tapered afterward.

Jaundice and right hypochondralgia occurred—both of which gradually worsened—with an increase in the levels of T-Bil (9.2 mg/

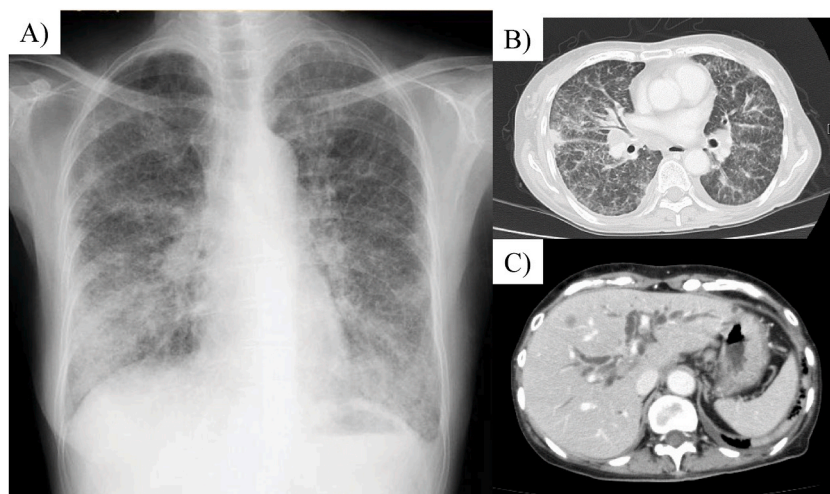


Fig. 5. (A, B) Follow-up chest radiograph and computed tomography images obtained approximately 3 weeks after admission showing an increase in bilateral ground glass opacities and reticular shadows. (C) Intrahepatic bile ducts were dilated owing to the lymph nodes swelling around both hepatic ducts.

dL), ALP (2355 IU/L), and γ -GTP (684 IU/L), as measured in late September (22 days after admission). Although the percentage of eosinophils in peripheral blood decreased to $<0.5\%$ after corticosteroid administration, chest radiograph and CT images revealed an increase in bilateral ground glass opacities and reticular shadows (Fig. 5A and B). Additionally, as the intrahepatic bile ducts were dilated due to lymph nodes swelling around both hepatic ducts (Fig. 5C), endoscopic nasal biliary drainage was performed. Her general condition rapidly deteriorated and performance status score worsened to 3 [6], from which we judged that administration of systemic chemotherapy was impossible; we therefore chose the best supportive care. Moreover, since her dyspnea and respiratory failure deteriorated despite oxygen therapy and the administration of oxycodone hydrochloride hydrate and corticosteroids, continuous intravenous infusion of midazolam was used for relief of dyspnea.

The patient died of respiratory failure in early October (30 days after admission), and a pathological autopsy was performed after obtaining consent from her family. At autopsy, we found a tumor measuring 2.5 cm \times 1.3 cm in the body of the gallbladder, along with invasion and multiple metastases to the liver (Fig. 6A and B). Based on the microscopic findings, a pathological diagnosis of poorly differentiated adenocarcinoma of the gallbladder was made (Fig. 6C). The weights of both lungs had increased (right, 990 g and left, 925 g; Fig. 7A). The microscopic findings revealed that poorly differentiated adenocarcinoma had invaded into the lymph ducts (hematoxylin-eosin staining; Fig. 7B); immunohistochemical results for D2-40 were positive (Fig. 7C), from which we confirmed the pathological diagnosis of lymphangitis carcinomatosa.

The patient also exhibited cancer invasion to the duodenum, bile duct, and pancreas; dissemination to the peritoneum and diaphragms (Fig. 8A); distant metastasis to both the adrenal glands; and lymph node metastases around the trachea, both the visceral pleurae, stomach, and abdominal aorta. Although no abnormal findings were detected in the heart through macroscopic findings (Fig. 8B), gallbladder cancer cells were observed in the lumen of the right ventricle in microscopic findings (Fig. 8C).

3. Discussion

Gallbladder cancer is the sixth most common gastrointestinal cancer and the most common malignancy of the biliary tract [12]. Adenocarcinoma is the most frequent histological type, accounting for 98% of all gallbladder tumors [13]. Two-thirds of all cases of adenocarcinoma are moderately or poorly differentiated and tend to invade the deeper layers of the gallbladder in the early phase [14]. The anatomical characteristics of the gallbladder wall are the lack of the muscularis mucosae and submucosa, a thin muscularis propria, and rich vascular and lymphatic vessels in the subserosa [14]. Therefore, when gallbladder cancer perforates the tunica muscularis and invades the subserous layer, the tumor can easily invade the neighboring organs, as well as cause distant metastasis.

Three possible mechanisms have been suggested for the spread of lymphangitis carcinomatosa. The first theory is that obliterating endarteritis occurs due to hematogenous tumor metastasis and tumor cells penetrate through vascular walls into the perivascular lymphatics [15]. The second theory is that diffuse retrograde permeation and embolization of the lymphatics can occur from mediastinal and hilar lymph node metastasis [15,16]. The third theory involves antegrade permeation and embolization of lymphatics from metastases to the pleurae or subpleural connective tissue [17]. In the present case, metastasis to the lungs and intrathoracic lymph nodes in CT images, and existence of metastasis to visceral pleurae in pathological autopsy findings were indicative of all these three theories.

From an anatomical point of view, hematogenous lung metastasis can occur when tumor cells directly invade the liver or metastasize to the liver via the gallbladder and portal veins, as well as when tumor cells grow and increase in the liver and are carried to the lungs via the hepatic vein, inferior vena cava, right atrium, right ventricle, and pulmonary vein [18]. In fact, microscopic findings in the present case demonstrated the existence of gallbladder cancer cells in the lumen of the right ventricle. On the other hand, metastasis to the mediastinal and hilar lymph nodes occurs via the abdominal lymph nodes. As the first likely reason for the rarity of lymphangitis carcinoma in gallbladder cancer cases, we considered a greater anatomical distance from the gallbladder to the lungs than from the breast and stomach to the lungs. The second possible reason is that gallbladder cancer is often diagnosed based on frequent initial symptoms: abdominal pain and jaundice by local tumor growth, liver invasion and metastasis, and abdominal lymph node swelling before the appearance of intrathoracic metastasis [19].

Surgery can delay the occurrence of pulmonary lymphangitis carcinomatosa by decreasing the number of tumor cells. Even in cases wherein intrathoracic metastasis was observed at the time of diagnosing gallbladder cancer, systemic chemotherapy, such as cisplatin and gemcitabine, might play a role in the decrease of tumor cells, thereby preventing lymphangitis carcinomatosa [20]. In the present case, we speculated that the exceptionally rapid metastasis to the lungs and intrathoracic lymph nodes caused lymphangitis carcinomatosa, and productive cough appeared as the initial symptom before abdominal pain and jaundice.

Although the efficacy of corticosteroids for the relief of dyspnea in patients with lymphangitis carcinomatosa is not established, we often administer them conventionally in daily clinical practice since its use is recommended weakly, with very weak evidence according to clinical guidelines from the Japanese Society for Palliative Medicine [2,11]. While 4–12 mg/day of dexamethasone is an option for the initial dose, there are no apparent recommendations regarding the dose of corticosteroids [11]. In the present case, we used 1000 mg/day of methylprednisolone as the initial dose, expecting that her dyspnea would rapidly improve; ultimately, this resulted in failure. Considering that 4–12 mg/day of dexamethasone is equivalent to 20–60 mg/day of methylprednisolone in terms of glucocorticoid activity, the initial dose of corticosteroids was large in the present case.

Another characteristic of the present case was the presence of eosinophilia in the peripheral blood and BAL fluid. Malignant tumors that metastasize to the lungs are associated with peripheral blood eosinophilia [21], and increased eosinophil counts in both the peripheral blood and BAL fluid have been observed in patients with Hodgkin disease [21,22]. In fact, tumor-derived eosinophilopoietic factors—such as granulocyte-macrophage colony-stimulating factor—is considered to be involved in the process of eosinophilia in patients with malignancies [23].

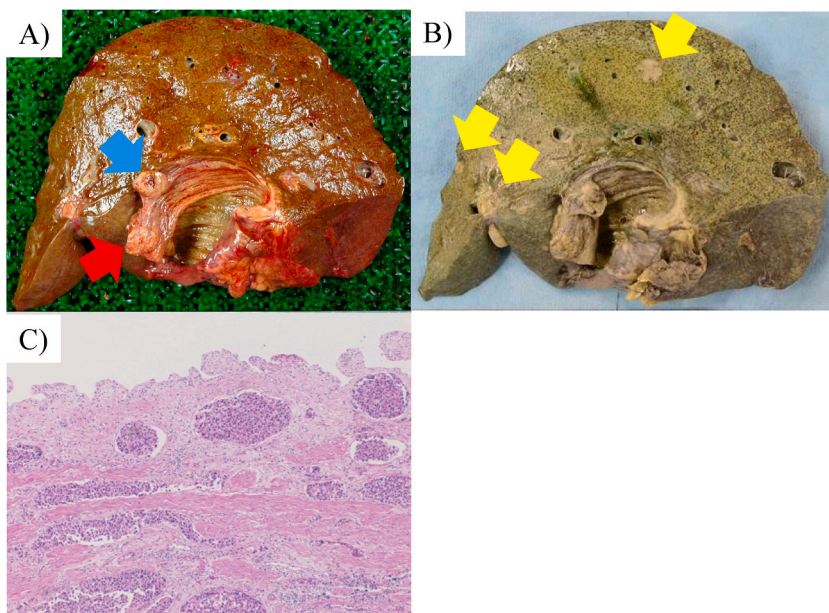


Fig. 6. Main macroscopic and microscopic findings considering the pathological autopsy of the gallbladder. (A) A 2.5 cm × 1.3 cm space-occupying lesion observed in the body of the gallbladder (red arrow) along with liver invasion (blue arrow). (B) Cut surface of the liver and gallbladder after formalin fixation. Multiple liver metastases were detected (yellow arrow). (C) Hematoxylin-eosin staining of the gallbladder tumor reveals poorly differentiated adenocarcinoma cells with invasion of the lymph ducts (original magnification, ×200).

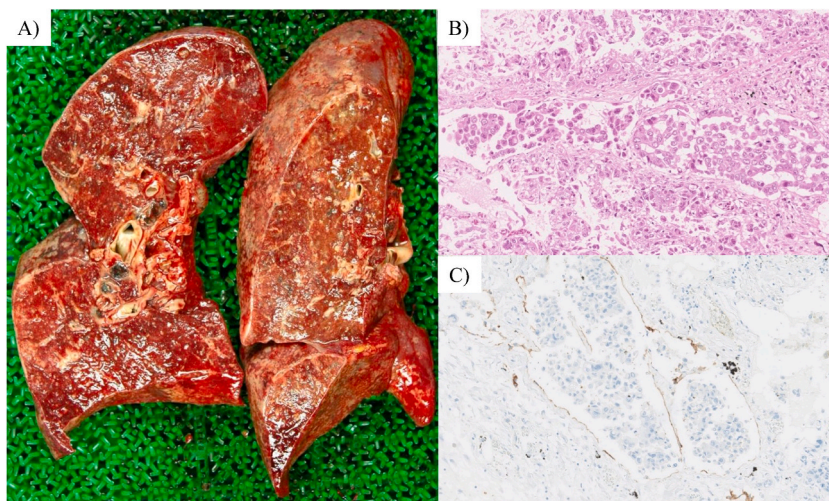


Fig. 7. (A) Macroscopic findings of the pathological autopsy of both lungs. The weights of the right lung and left lung had increased to 990 g and 925 g, respectively. (B) Microscopic findings of the lung. Hematoxylin-eosin staining revealed poorly differentiated adenocarcinoma cells with lymphatic invasion. (C) Lymphatic invasion confirmed by D2-40 immunostaining. B, C: Original magnification, ×400

In conclusion, clinicians should be aware of the possibility that gallbladder cancer can cause lymphangitis carcinomatosa. The quality of life and prognosis of patients with lymphangitis carcinomatosa can severely deteriorate due to acute progressive respiratory symptoms and respiratory failure [2]. Accordingly, the development of anticancer medication therapy, such as molecular targeted drugs and immune checkpoint inhibitors, is warranted to improve the prognosis of patients with this difficult-to-treat condition.

Patient consent for publication

Informed consent was obtained for publication from her families.

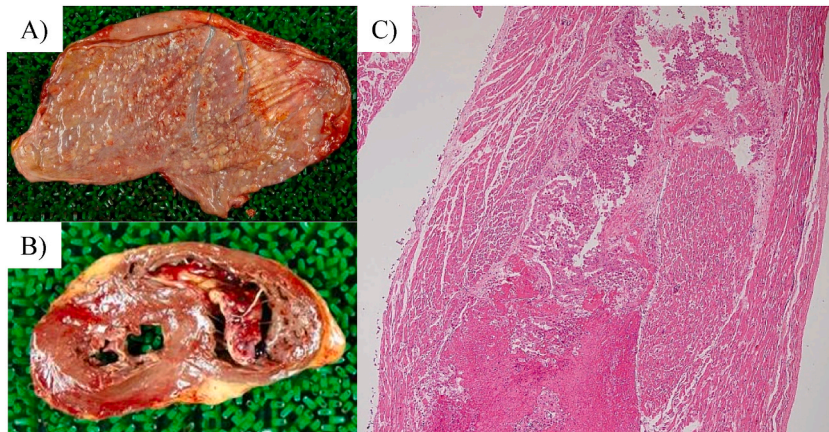


Fig. 8. (A) Gross finding of the diaphragm. Cancer cells disseminated to the diaphragm. (B) Cut surface of heart. (C) Microscopic findings of right ventricle (hematoxylin-eosin staining; original magnification, $\times 200$). Although no abnormal findings have been detected in the heart via macroscopic findings, gallbladder cancer cells were observed in the lumen of the right ventricle in microscopic findings.

Declarations of competing interest

The authors have no conflict of interest to declare.

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