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【 CASE REPORT 】

Clinical Response of Primary Malignant Pericardial Mesothelioma with Peritoneal Dissemination to Nivolumab

Shun Fujiwara[1], Yoshihito Kano[1,2], Yasuhiro Maejima[3], Tomoyuki Fujioka[4], Kazuhiro Tamura[5], Susumu Kirimura[5], Satoshi Miyake[2,6] and Ryuichi Okamoto[1]

Abstract:

Malignant pericardial mesothelioma (MPM) is extremely rare, and peritoneal dissemination has not yet been reported. There is no consensus regarding appropriate pharmacological treatment for MPM, including immune checkpoint inhibitors (ICIs). We herein report a 36-year-old man with MPM diagnosed by peritoneal dissemination and treated with an ICI. Cytology of the ascites revealed malignant peritonitis, and a re-evaluation of a pericardial biopsy performed at the previous hospital led to a diagnosis of MPM. The patient was treated with nivolumab and showed a clinical response despite several complications, such as renal dysfunction and performance status deterioration. This case report provides suggestive information for the diagnosis and ICI therapy of a rare type of mesothelioma.

Key words: malignant pericardial mesothelioma, peritoneal dissemination, nivolumab, rare tumor

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Introduction

Malignant pericardial mesothelioma (MPM) is extremely rare and has a poor prognosis (1). According to the Japanese Ministry of Health, Labour, and Welfare, malignant mesothelioma arises from the surface of the mesothelium and pleura in 85.5% of cases, peritoneum in 13.2%, pericardium in 0.8%, and testicular tunica vaginalis in 0.5% (2). The disease is highly invasive and difficult to diagnose, and 75% of cases are anatomically diagnosed (3). At present, MPM is treated as a malignant pleural mesothelioma, as there is no established treatment strategy.

We herein report a case of MPM diagnosed by peritoneal dissemination that was treated with an immune checkpoint inhibitor (ICI).

Case Report

A 36-year-old man presented to our hospital with dyspnea and lower-leg edema. One year prior, the patient had been diagnosed with acute pericarditis after complaining of chest and back pain. Colchicine and ibuprofen were ineffective, and the pericarditis worsened. Prednisolone was introduced, which was effective, but the symptoms flared up as the dose was reduced.

To determine the cause of constrictive pericarditis and treat cardiac tamponade, tissue sampling and pericardial drainage were performed six months prior. Because the cause was unknown and it was difficult to reduce the dose of prednisolone, the patient was transferred to our hospital. However, his condition could not be controlled with outpatient medical treatment; therefore, he was admitted to our hospital.

We considered performing pericardiectomy to relieve the patient's symptoms; however, the patient's condition deteriorated quickly, and the steroid dosage could not be decreased from 20 mg/day. Therefore, we decided that the patient was ineligible for surgery given his poor condition.

He had a history of childhood asthma and no family his-

[1]Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University (TMDU), Japan, [2]Department of Clinical Oncology, Tokyo Medical and Dental University (TMDU), Japan, [3]Department of Cardiovascular Medicine, Tokyo Medical and Dental University (TMDU), Japan, [4]Department of Radiology, Tokyo Medical and Dental University (TMDU), Japan, [5]Department of Pathology, Tokyo Medical and Dental University (TMDU), Japan and [6]Department of Palliative Care, Tsuchiura Kyodo General Hospital, Japan
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Correspondence to Dr. Yoshihito Kano, kano.canc@tmd.ac.jp

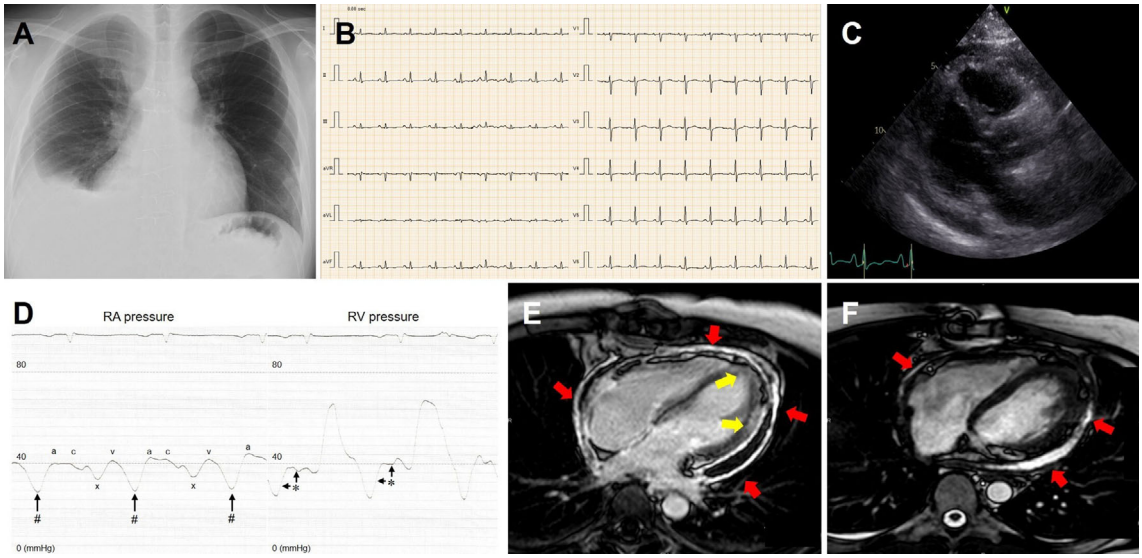

Figure 1. **A) Chest radiography shows a widened mediastinum, cardiomegaly, and right pleural effusion. B) An electrocardiogram demonstrates sinus tachycardia (125 beats/min), low potential, and a sharp P wave in the II, III, and aVF leads. C) Transthoracic echocardiography reveals pericardial thickening and decreased diastolic function owing to pericardial effusion. D) Cardiac catheterization shows a deep Y descent in the right atrial pressure waveform (#) and a dip and plateau pattern in the right ventricular pressure waveform (*). E and F) Cardiac magnetic resonance imaging. Gadolinium contrast-enhanced T1-weighted imaging (E) shows diffusely and irregularly thickened and strongly contrasted pericardium (red arrow). Some parts of the myocardium are abnormally contrasted in continuity with the inside pericardium (yellow arrow). Cine magnetic resonance imaging (F) shows pericardial effusion surrounded by thickened pericardium (red arrow).**

tory of malignant tumors or cardiac diseases. He worked as a watch salesman and had no history of asbestos exposure. Upon admission, he was 176 cm tall and weighed 86 kg. A physical examination revealed a blood pressure of 121/81 mm/Hg, regular tachycardia of 113 beats/min, and body temperature of 35.7°C. Regarding tumor markers, carcinoembryonic antigen (CEA) was 9.7 ng/mL (normal: <5.0 ng/mL), carbohydrate antigen 19-9 (CA19-9) was 73.7 U/mL (normal: <37 U/mL), and cytokeratin 19 fragment (CYFRA) was 5.0 ng/mL (normal: <3.5 ng/mL), all of which were slightly elevated. Infection, thyroid, and collagen disease markers were all within the normal ranges. The plasma brain natriuretic peptide level was 174 pg/mL. The prior physician's pericardial fluid tests revealed bloody pericardial fluid and elevated cell counts; however, tumor markers, bacterial cultures, and cytology were negative.

Chest radiography revealed enlargement of the cardiac silhouette and right pleural effusion (Fig. 1A). An electrocardiogram showed sinus tachycardia (125 beats/min), low potential, and a sharp P wave in the II, III, and aVF leads, indicating a right atrial load (Fig. 1B). Echocardiography revealed heterogeneous thickening of the pericardium, mainly at the apex, and extensive pericardial adhesions and septal bounce (Fig. 1C). A significant increase in the respiratory variability of left ventricular and right ventricular inflow velocity waveforms and hepatic venous regurgitation was also observed in the late diastolic phase. Cardiac catheterization showed a deep Y descent in the right atrial pressure waveform and a dip and plateau pattern in the right ventricular pressure waveform (Fig. 1D). These findings were consistent with constrictive pericarditis. Cardiac magnetic resonance imaging showed a diffusely and heterogeneously thickened and strongly contrasted pericardium with pericardial effusion (Fig. 1E, F). Abnormal enhancement was observed in parts of the myocardium. There was no obvious mass formation and no evidence of edema or inflammation in the pericardium. Computed tomography revealed exacerbation of pericardial effusion, new pleural effusion, and the presence of ascites compared with three months earlier (Fig. 2).

Despite the absence of a tumor on imaging, ascites cytology revealed irregularly shaped nuclei and numerous mitotic divisions, diagnosed as malignant peritonitis (Fig. 3A). Hematoxylin and Eosin (H & E) staining of pericardial tissue collected at the previous hospital failed to distinguish reactive from atypical changes (Fig. 3B, C). Thus, mesothelioma was considered a differential diagnosis, and an immunohistochemical analysis was performed on the tissue sample.

The tumor cells were positive for calretinin (Fig. 3D), antibodies against pancytokeratin, and Wilms' tumor 1 (Fig. 3E) and negative for carcinoembryonic antigen and thyroid transcription factor-1. Furthermore, fluorescence *in situ* hybridization (FISH) confirmed the homozygous deletion of p16 (Fig. 3F) and supported the diagnosis of MPM. Similar findings were noted in pleural fluid cytology, leading to the diagnosis of MPM and peritoneal and pleural dissemination. However, there were high numbers of malignant

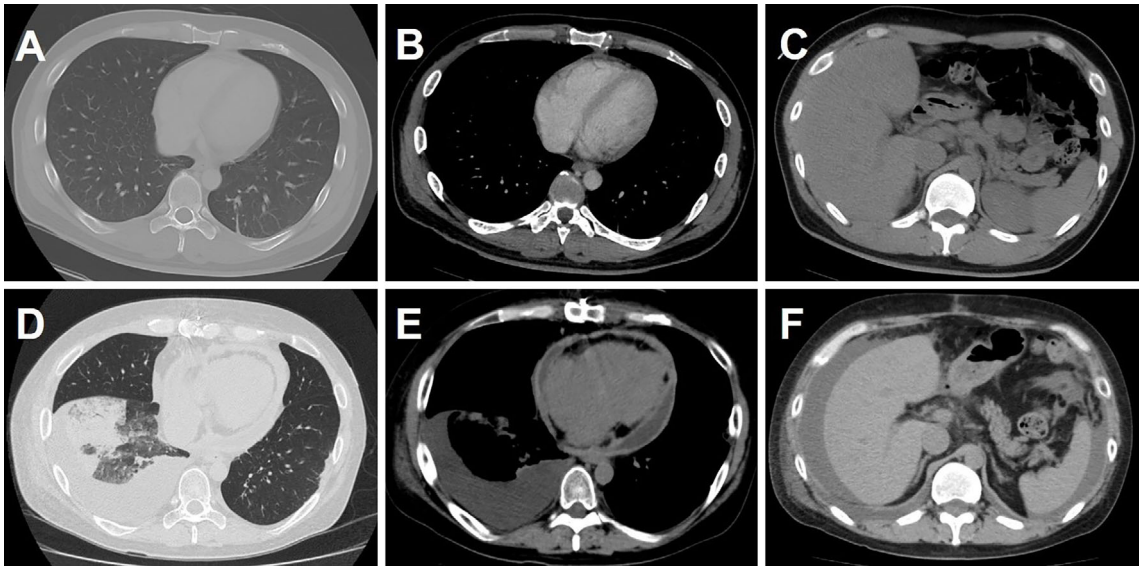

Figure 2. **Computed tomography three months prior to (A-C) and upon admission (D-F). Exacerbation of pericardial effusion and new pleural and ascites effusions are demonstrated.**

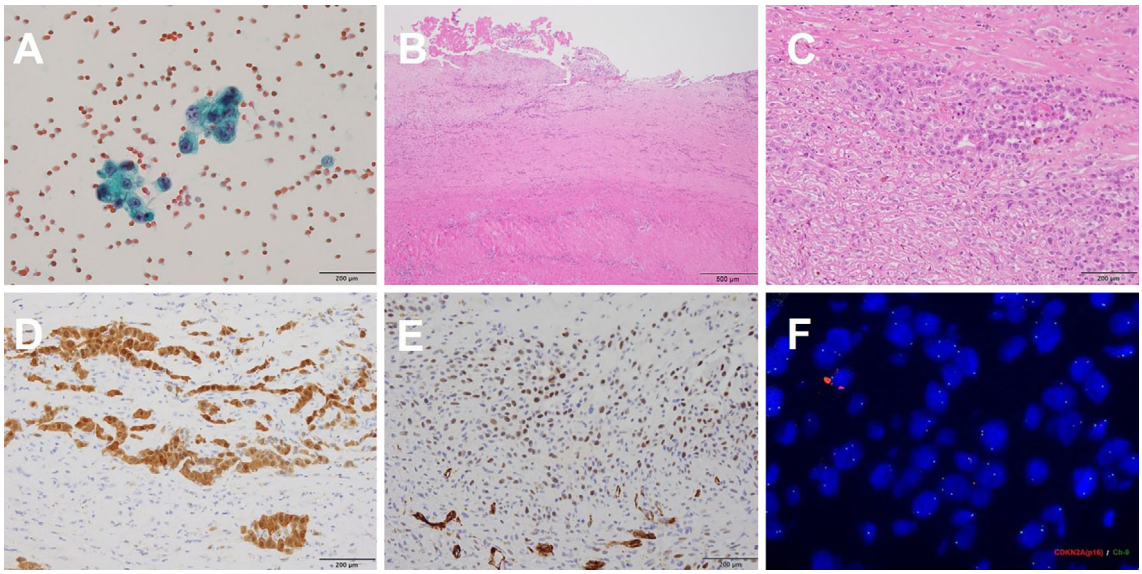

Figure 3. **Histological images of ascites obtained at our hospital (A) and pericardial tissue from the previous hospital (B-F). A) Ascites cytology reveals malignancy. B, C) Hematoxylin and Eosin staining failed to show malignancy. D) Calretinin staining is positive. E) Wilms' tumor 1 staining was positive. F) Homozygous deletion of p16 is detected.**

mesothelioma cells in the pleural effusion, and considering the extremely low frequency of MPM, we could not completely rule out the possibility of pericardial metastases from malignant pleural mesothelioma at this point.

Since the disease was rapidly worsening, introducing chemotherapy in an emergency setting was necessary. As no treatment strategy has yet been established for MPM, we obtained consensus and approval from the institutional tumor board to treat patients with malignant pleural mesothelioma with nivolumab. We obtained the patient's and family's full consent for the treatment.

Platinum and pemetrexed are used as the standard first-line chemotherapy, but nivolumab was recommended by the discussion at the tumor board because he had heart failure (New York Heart Association class IV), performance status of 3, and renal dysfunction (creatinine, 2.4 mg/dL). After the first nivolumab administration, there was a clinically partial response with improvements in the performance status, creatinine level, and cardiothoracic ratio (Fig. 4). However, his systolic blood pressure dropped to approximately 100 mmHg, and his performance status (PS) dropped to the equivalent of 4 due to leg edema and worsening respiratory status on the 45th day. In addition, his cardiothoracic ratio worsened to 52% on X-ray. Echocardiography

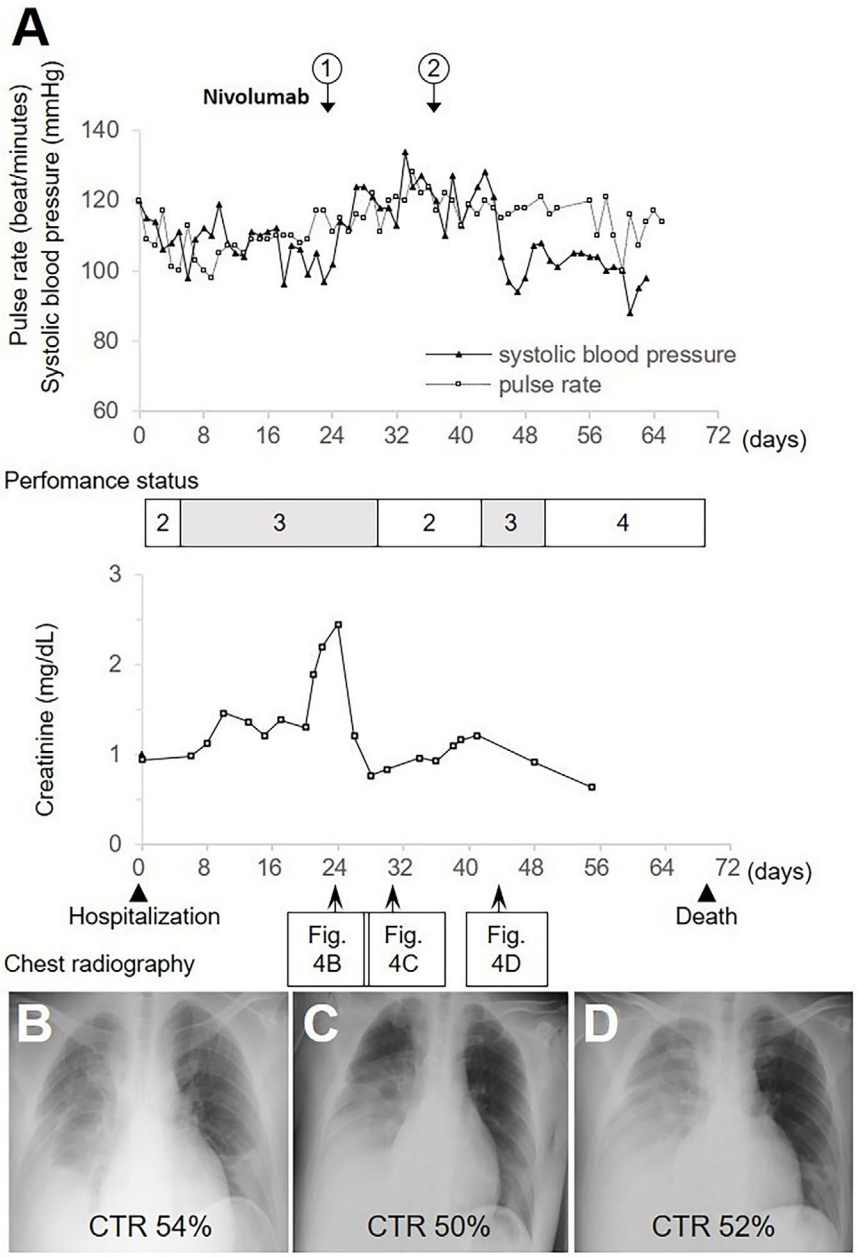

Figure 4. The clinical course of the patient is presented, indicating nivolumab administration, systolic blood pressure, pulse rate, performance status, creatinine level, and chest radiography after admission (A). Nivolumab was administered 24 days later. Chest radiographs were taken at induction (B) and on days 31 (C) and 45 (D).

showed that respiratory variability in the right ventricular inflow had increased from 24 to 55%, and constrictive pericarditis had worsened. Furthermore, the extent of pericardial adhesion increased, and left ventricular contractility decreased from 68 to 57%.

Drugs such as prednisolone, ibuprofen, and colchicine for constrictive pericarditis and diuretics (spironolactone, azosemide, furosemide, and tolvaptan) were administered for heart failure, but achieving control was difficult. After referring the patient to the best supportive care on the 46th day, his leg edema and dyspnea worsened, and oxygen therapy was needed, suggesting that heart failure had worsened further. Unfortunately, the patient subsequently died on the 71st day.

Autopsy revealed irregular thickening of the epicardium and cardiac sac with strong adhesions to the anterior and posterior surfaces and some infiltration into the myocardium (Fig. 5). These findings suggested diastolic heart failure that subsequently led to congestion of the liver, kidneys, and spleen (data not shown). Thus, heart failure was considered to have been the immediate cause of death. The histological features were consistent with those of the biopsy specimen, and the myocardium showed tumor infiltration, indicating primary pericardial mesothelioma. A mixture of epithelioid and sarcomatoid subtypes was observed, and the tumor was classified as the biphasic type (Fig. 6A). The tumor cells in

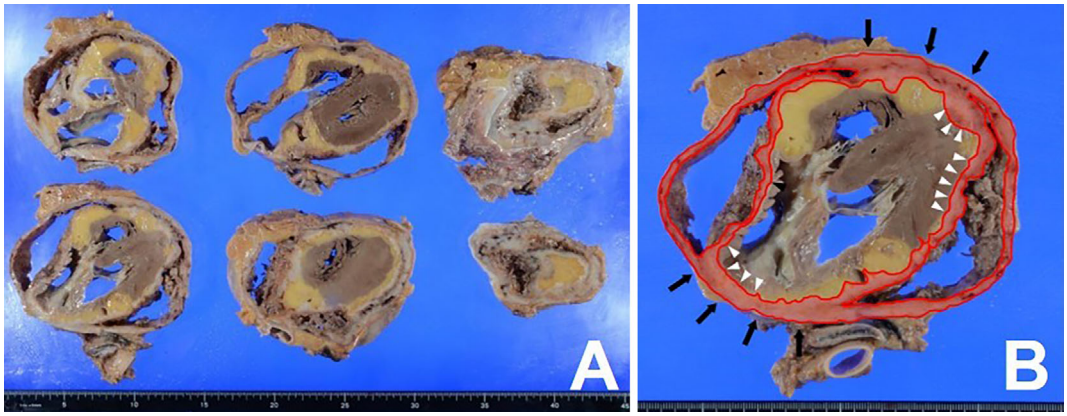

Figure 5. **A) Autopsy shows an irregularly thickened and tightly adherent epicardium and cardiac sac. B) The pericardium has extensive and uneven thickening with strong adhesions to the anterior and posterior walls (tumor extent: red line; adhesion area: black arrow). The myocardium also shows partial infiltration by the tumor (white arrow).**

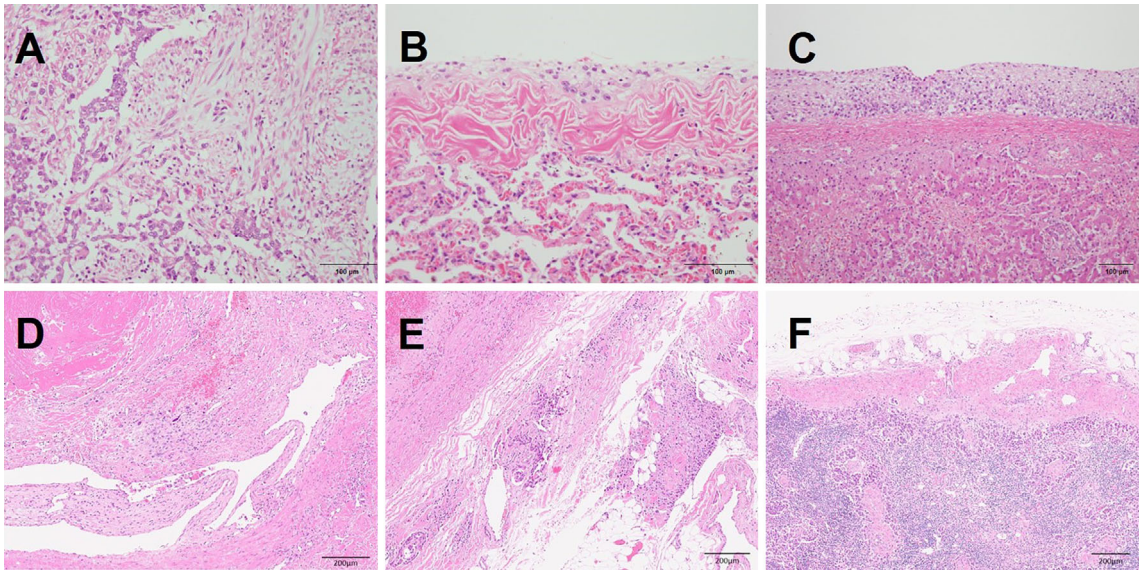

Figure 6. **Histological images were obtained at autopsy. A) Hematoxylin and Eosin staining shows that the tumor is classified as a biphasic type. B) and C) The tumor cells are localized on the surface of the pleura (B) and peritoneum (C). D-F) Hematogenous and lymphatic metastasis were detected. D) Left subclavian vein, E) right internal jugular vein, and F) right supraclavicular lymph node.**

the pleura and peritoneum were considered disseminated, since they were localized on the surface (Fig. 6B, C). Hematogenous and lymphatic metastases were observed (Fig. 6D-F). There was no evidence of asbestos exposure or autoimmune diseases.

Discussion

MPM is an extremely rare tumor with a prevalence rate of 0.0022% (4). Owing to its late diagnosis and poor treatment response, MPM is recognized as a highly fatal disease. A pathological examination confirmed the diagnosis in the present case because there were no specific biomarkers or imaging findings. To make the diagnosis in other cases, 70% involved a biopsy of the pericardium, whereas only 10% involved pericardial fluid sampling (5). Mesothelioma can be distinguished from reactive mesothelioma by the detection of homozygous p16 deletion on FISH, since mesotheliomas usually show homozygous deletion of p16 (6). In the present case, however, the diagnosis was difficult to make, and the patient was diagnosed a year after the onset of symptoms, preventing early therapeutic intervention. In cases of suspected mesothelioma, a biopsy of the pericardium may be preferable to cytology, and immunohistochemical staining should be conducted aggressively.

Metastasis occurs in 25-45% of cases, mostly in the regional lymph nodes, lungs, and kidneys (1). According to a recent report, 83% of patients had metastases, with the majority having metastases to the mediastinum and others to the lungs and liver (5). However, peritoneal dissemination

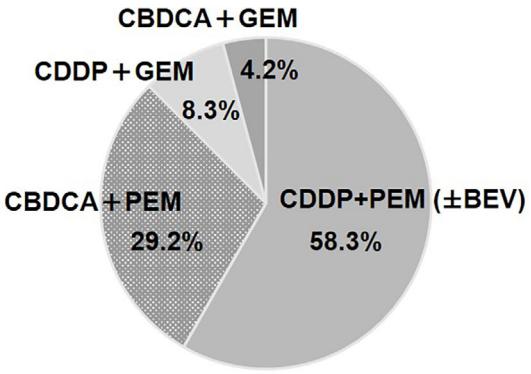

Figure 7. A total of 24 cases were identified by searching PubMed (published from 1981 to 2021) and the Japan Medical Abstracts Society (published from 1977 to 2021) with the terms "malignant pericardial mesothelioma" and "chemotherapy" or "malignant pericardial mesothelioma" and "immune checkpoint inhibitor." CDDP: cisplatin, PEM: pemetrexed, BEV: bevacizumab, CBDCA: carboplatin, GEM: gemcitabine

has not been reported. There are two mechanisms underlying peritoneal dissemination: lymphatic and direct. In the present case, an autopsy confirmed the presence of lymph node metastasis, which led to peritoneal dissemination. Cases of recurrent pericardial effusion of unknown etiology should rule out MPM. Furthermore, it should be remembered that pleural effusions and ascites can be complicated.

MPM can be treated with surgery, radiation, and chemotherapy. However, there is no consensus on beneficial treatments. Pericardial mesothelioma usually shows a poor response to treatment, with a median time from the diagnosis to death of six months (7). Recent studies have shown that chemotherapy can improve the survival time (5). According to several reports, combining different chemotherapeutic agents may be effective. Patients who received a platinum agent with or without pemetrexed showed a statistically significant survival benefit (5). However, the efficacy of ICIs is limited.

The literature was searched using PubMed (published from 1981 to 2021) and the Japan Medical Abstracts Society (published from 1977 to 2021) using the terms "malignant pericardial mesothelioma" and "chemotherapy" or "malignant pericardial mesothelioma" and "immune checkpoint inhibitor." A total of 24 cases were accumulated, and the drugs selected in the first line were mostly pemetrexed plus platinum without ICIs (Fig. 7). There was only one case in which ICIs were used after the first line, and the patient was on pembrolizumab in the second line and did well, surviving 4.5 years after the diagnosis (8). Good outcomes have been observed for malignant pleural mesothelioma. As a first-line therapy, CheckMate-743 showed that nivolumab plus ipilimumab significantly improved the prognosis compared with platinum-based therapy (9). Both the MERIT study and NivoMes trial demonstrated efficacy in second-line therapy (10, 11). Therefore, ICIs are expected to be effective against MPM.

In Japan, nivolumab and a combination of nivolumab and ipilimumab were approved for malignant pleural mesothelioma treatment in August 2018 and May 2021, respectively. Nivolumab monotherapy was selected in the present case, as the treatment was initiated before the approval of combination therapy. Our patient showed improvement after treatment initiation. Nivolumab might have improved the pericardial flexibility in our case, which increased the systolic blood pressure and decreased the cardiothoracic ratio on chest radiography, indicating a reduction in heart failure symptoms (Fig. 4). A reduction in renal congestion and an increase in effective circulating plasma volume improved our patient's renal dysfunction. However, after three weeks of treatment, the heart failure worsened, and it became impossible to assess whether or not the therapy was effective. Considering the poor performance status at the time of treatment initiation, the therapeutic effect might be underestimated in this case, therefore, patients under better conditions are required for authentic evaluation. Further case studies are needed to evaluate the effect of ICIs.

To our knowledge, this is the first case report of MPM with peritoneal dissemination. MPM is extremely rare, but in cases with recurrent pericardial effusions and complicated thoracic ascites, mesothelioma should also be included in the differential diagnosis, and a tissue biopsy and immunohistochemical analysis should be conducted. There is no consensus regarding the treatment at present, and the prognosis is poor. However, ICIs are expected to be effective. An appropriate treatment method should be established with the accumulation of more cases in the future.

Written informed consent was obtained from the patient to publish this paper.

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

Shun Fujiwara and Yoshihito Kano contributed equally to this work.

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