Primary malignant pericardial mesothelioma with increased serum mesothelin diagnosed by surgical pericardial resection: A case report

TAKEYUKI KUROSAWA1, KEISHI SUGINO1, KAZUTOSHI ISobe1, YOSHINOBu HATA2, YURI FUKASAWA3 and SAKAE HOMMA1

Departments of 1Respiratory Medicine, 2Chest Surgery and 3Pathology, Toho University Omori Medical Center, Tokyo 143-8541, Japan

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Abstract. A 37-year-old female smoker without a history of exposure to asbestos was referred to our hospital with persistent pericardial effusion. Chest computed tomography imaging examination revealed an irregular thickened pericardium with large amounts of pericardial effusion and a small pleural effusion. Fluorodeoxyglucose (FDG) positron emission tomography imaging demonstrated intrapericardial FDG accumulation. Blood tests revealed an increase in serum mesothelin levels. Examination of a surgically resected specimen revealed a grayish-white thickening of the pericardium, with a straw-colored mucinous pericardial effusion. Histopathological examination confirmed the diagnosis of epithelioid malignant mesothelioma. Although the patient’s condition temporarily improved, with decreased levels of serum mesothelin during chemotherapy with carboplatin and pemetrexed, she succumbed to cardiac tamponade 18 months after the initial onset of the symptoms. Primary malignant pericardial mesothelioma (PMPM) is an extremely rare and refractory disorder. Thus, an early definitive diagnosis and timely treatment are crucial for the management of PMPM.

Case report

A 37-year-old female patient complaining of progressive dyspnea and chest pain was referred to our hospital to investigate persistent pericardial effusion. The patient had no past history of exposure to asbestos. The results of the peripheral blood tests revealed a white blood cell count of 10,800/µl with 72.2% neutrophils, a hemoglobin level of 13.1 g/dl, a platelet count of 284,000/µl, a C-reactive protein level of 1.2 mg/dl and a serum brain natriuretic peptide level of 122.9 U/ml, as well as an increase in serum mesothelin levels (18.5 nmol/l; normal range, <1.5 nmol/l). The arterial blood gas analysis revealed a pH of 7.43, PaCO2 of 35.5 Torr and PaO2 of 77.0 Torr at room air. A chest radiograph revealed cardiomegaly with bilateral pleural effusion. Chest computed tomography revealed an irregular, thickened pericardium with diffuse enhancement, with loculated large amounts of pericardial and bilateral pleural effusions (Fig. 1A). Fluorodeoxyglucose (FDG) positron emission tomography (PET) images revealed intrapericardial FDG accumulation with a standardized uptake value of 6.0 (Fig. 1B). Transthoracic echocardiography showed a thickened pericardium with pericardial effusion, but no evidence of cardiac tamponade. The left ventricular function and cardiac valves were normal (Fig. 2).

The results of the pericardial fluid cytology were class V, with a suspected diagnosis of adenocarcinoma. No fungal, bacterial, or mycobacterial pathogens were isolated from the pericardial effusion. Surgical biopsy of the pericardium and drainage were performed through a subxiphoid approach under general anesthesia to make a definitive diagnosis. The thickened pericardium densely adhered to the epicardium on the left side; pericardial biopsy was performed on the right side, with drainage of 300 ml of straw-colored mucinous fluid. Scattered whitish nodules were identified on the right side of the epicardium (Fig. 3). For continuous postoperative drainage...
and sclerosing therapy, a single chest tube was inserted in the pericardial cavity through a separate stab incision. Histopathological examination revealed diffuse infiltration of the pericardium by PMPM, which consisted of epithelioid cells with abundant eosinophilic cytoplasm and large round nuclei with prominent nucleoli, arranged in a tubular-papillary pattern (Fig. 4A). Immunohistochemistry was positive for calretinin, D2-40 and Hector Battifora mesothelial cell-1, whereas it was negative for carcinoembryonic antigen (CEA) and thyroid transcription factor-1 (TTF-1) (Fig. 4B-F). Finally, the patient was diagnosed with PMPM of epithelioid type.

The patient’s condition temporarily improved and the serum mesothelin levels decreased during chemotherapy with carboplatin (area under the curve of 5.0) and pemetrexed
(500 mg/m²) with usual vitamin supplementation every 28 days for a 4-week cycle. However, her condition worsened, with elevated serum mesothelin levels, immediately after chemotherapy. As a result, the patient received no further chemotherapy apart from pleurodesis, due to the massive pleural effusion. Eventually the patient succumbed to cardiac tamponade 18 months after the initial onset of the symptoms (Fig. 5).

Discussion

PMPM is an extremely rare malignancy, with an incidence of ~0.0022% according to one of the largest necropsy series (1). PMPM is associated with a wide patient age range (1-79 years) and the male-to-female ratio is 2:1 (2). PMPM is less significantly associated with exposure to asbestos compared with pleural malignant mesothelioma (2). In the present case, the patient had no history of asbestos exposure. Furthermore, there was no evidence of the presence of asbestos bodies on histological examination at autopsy.

PMPM is often discovered at a late stage during the clinical course, or at autopsy (3). The diagnostic yield of pericardial fluid cytology is only 24% of the PMPM cases (4). Therefore, the majority of the patients with PMPM are diagnosed using either surgical or autopsied specimens. The differential diagnosis of tumors affecting the pericardium includes metastases to the pericardium from cancer in other organs, hematological malignancies, melanoma and, rarely, primary cardiac tumors. The histological and immunohistochemical studies of pericardial mesothelioma resemble those of pleural mesothelioma. Immunohistochemically, negativity for adenocarcinoma markers, such as CEA and TTF-1, and
positivity for mesothelial markers, such as calretinin and cytokeratins 5/6, are useful in differentiating mesotheliomas from adenocarcinomas (5). In the present case, adenocarcinoma was initially suspected on the basis of cytology results. However, the histological and immunohistochemical findings led to a definitive diagnosis of epithelioid type PMPM.

It was recently suggested that FDG-PET for PMPM may be useful for disease staging and preoperative evaluation (6). In the present case, an accumulation of FDG was detected, corresponding with the pericardial tumor. Furthermore, mesothelin is currently considered to be the best novel serum biomarker of malignant pleural mesothelioma. According to a meta-analysis on the efficacy of serum mesothelin in patients with pleural malignant mesothelioma, the sensitivity and specificity of mesothelin ranged widely from 19 to 68% and from 88 to 100%, respectively (7). Our patient presented with an increase in serum mesothelin levels at initial diagnosis of PMPM. Subsequently, the serum mesothelin level exhibited a trend towards a decrease after chemotherapy, whereas it increased along with a deterioration of the patient's general condition. We hypothesized that the serial changes of the serum mesothelin level may be correlated with the onset of PMPM and the disease status.

Treatment guidelines for PMPM have not yet been established. In fact, PMPMs are treated with a palliative approach based on surgery, chemotherapy and radiotherapy. Therefore, the median survival for PMPM patients diagnosed antemortem is <4 months. Surgical resection is one of the treatment options for localized disease. However, it is difficult to remove the tumor completely, as the majority of the patients with PMPM are already at an advanced stage at the time of diagnosis (8). Radiation therapy has little effect on PMPM, but has been used as adjuvant therapy in patients with PMPM undergoing incomplete resection (9). Finally, combination chemotherapy with cisplatin and pemetrexed has demonstrated prolonged survival in pleural malignant mesothelioma and is also considered as first-line treatment in PMPM (1,10). Our patient was administered a combination of carboplatin and pemetrexed, rather than cisplatin, to reduce cardiac burden. Consequently, our patient survived for 18 months, which was longer compared with cases reported in previous studies.

In conclusion, we herein present an extremely rare PMPM case with increased levels of serum mesothelin diagnosed by surgical pericardial resection. It is crucial to make a timely definitive diagnosis and administer treatment during the early stages of PMPM.

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