



CASE REPORT

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Comprehensive Treatment of a Rare Primary Malignant Pericardial Mesothelioma: A Case Report and Literature Review

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ABSTRACT

Background: Primary Malignant Pericardial Mesothelioma (PMPM) is an extremely rare aggressive malignancy with nonspecific symptoms; thus, cases of PMPM are usually found incidentally. Despite treatment, it is considered as extremely fatal.

Case presentation: We encountered an asymptomatic 64-year-old woman diagnosed with PMPM by Positron Emission Tomography/Computed Tomography (PET/CT). After 22 months of supportive treatment and chemotherapy, she presented to our facility with progressive dyspnoea. Surgery was performed. Excision biopsy showed thickening pericardium and many poorly circumscribed masses, and cut sections showed friable grey–white tissue with areas of necrosis. Pathological examination confirmed epithelium-like malignant mesothelioma. The patient was continuously treated with a previously prescribed chemotherapy regimen. The patient did not exhibit dyspnoea recurrence, and PET/CT showed no progression 7 months postoperatively.

Conclusion: Comprehensive treatment, including chemotherapy, supportive treatment, and timely surgery, is effective for unresectable PMPM. When patients present with symptoms caused by PMPM that are not relieved by medication, we recommend prioritising urgent surgery.

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KEYWORDS

Primary malignant pericardial mesothelioma; Comprehensive treatment; Diagnosis; Case report

ABBREVIATIONS

MSCT: Multislice Computed Tomography; CMR: Cardiac Magnetic Resonance; PET/CT: Positron Emission Tomography/Computed Tomography; TTE: Trans Thoracic Echocardiography; PMPM: Primary Malignant Pericardial Mesothelioma

Introduction

Cardiac tumours are rare [1]. Pericardial malignancies account for only 0.0025% of all malignant tumours and less than 2% of all cardiac tumours [2,3]. PMPM, originating from pericardial mesothelial cells, can be divided into diffuse and localised types. The diffuse type is characterised by obvious bleeding, exudation, and infiltrative growth, especially along the pericardium. In the early stage, PMPM can only show nodule-like, plaque-like or warty protrusions on the pericardial surface, and then the pericardium gradually thickens. In the late stage, part or even all of the heart is surrounded by the tumour, resulting in symptoms of cardiac compression. PMPM invades the heart or other organs owing to its insidious nature and atypical symptoms. PMPM has a poor prognosis because it is difficult to treat with radical surgical resection, and there is insufficient evidence regarding the effects of radiotherapy and chemotherapy on this disease entity. Thomason et al. presented a case report and review of PMPM, and Basso provided rec-

ommendations for its treatment, but standardized guidelines for the treatment of PMPM are lacking.

Case Presentation and Therapy

A 64-year-old female patient with an unremarkable medical history, except for cholecystectomy for cholecystitis with gallstones 7 years prior, presented to our facility with asymptomatic massive pericardial effusion accidentally found through Trans Thoracic Echocardiography (TTE). Multi Slice Computed Tomography (MSCT) and CMR showed moderate pleural effusion on both sides (further laboratory tests revealed that the Rivalta reaction was weakly positive, and tumour markers were negative) and multiple thickened pericardium (Figures 1a and 1b). 18F-FDG imaging-Position Emission Tomography/Computed Tomography (PET/CT) showed scattered a partial increase in pericardial metabolism (SUV-max=5.75-6.82) but no distant metastasis (Figures 2a-2d). A malignant pericardial tumour was suspected and appeared to be completely unresectable. For further diagnosis, ultrasound-guided pericardiocent-

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testis was performed, and laboratory analysis revealed that adenosine deaminase tests were negative, and no tumour markers were found, which may be related to too few punctured tissues or the poor diagnostic effect of pericardial effusion on malignant pericardial tumours. Pericardial effusion did not recur after pericardiocentesis. After multidisciplinary discussions, she received supportive treatment and chemotherapy with pemetrexed plus cisplatin for 21 days for four cycles. During the first cycle of chemotherapy, the patient presented with nausea and platelet levels of <50000 cell/mm³ after the administration of pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²). For the second cycle, we reduced the dose of pemetrexed to 250 mg/m² and the dose of cisplatin to 37.5 mg/m². She tolerated this reduced dose and completed all four cycles of chemotherapy. However, her platelet count was still low,

even though she received best supportive treatment. She continued to receive best supportive treatment, and we re-evaluated her *via* MSCT and TTE every six months. No tumour progression was noted on MSCT at the 6-month follow-up. However, it did reveal that the tumour had grown during the 12th month. A second four-cycle round of chemotherapy was recommended. However, her performance status deteriorated gradually at the end of the first cycle of the second round, and she was unable to receive additional palliative chemotherapy. Oncologists and nutritionists recommend the suspension of chemotherapy while maintaining comprehensive best supportive care. The nutritional status of the patient improved significantly, but her pericardial disease was found to have progressed at the 22nd month of follow-up.



Figure 1. a) MSCT at the initial visit: Multiple areas of thickened pericardium; b) MSCT at 22 months: Partial thickening of the pericardium compared to prior imaging

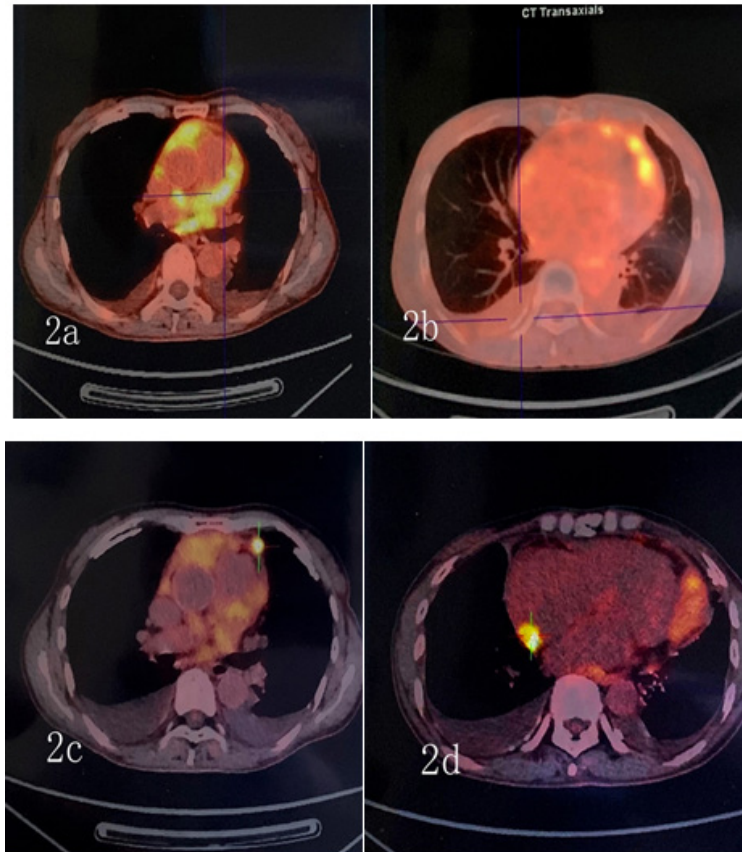


Figure 2. (a,b) PET/CT at the initial visit; (c,d) PET/CT at 22 months

The patient presented to our facility with progressive dyspnoea but no orthopnoea, chest pain, or other forms of discomfort in the 22nd month. On clinical examination, her heart rate was 130 bpm, and her respiratory rate was 30 breaths/min with an oxygen saturation of 95% on room air. Her blood pressure was 100/60 mmHg with evidence of pulsus paradoxus, and her central venous pressure was 14 cm H₂O. In addition, she had bilateral congested neck veins and distant heart sounds. Most serologic tests were within the normal range. ECG showed low voltage and sinus tachycardia. TTE revealed a thickened pericardium and a noticeable oval capsule mass compressing the left ventricle throughout the entire cardiac cycle (Figure 3). MSCT and CMR revealed partial thickening of the pericardium comprised of diffuse masses of varying sizes (Figure 1b, Figure 4). Re-examination by PET/CT showed that metabolism of some of the masses had significantly increased, while others had not, but the range was significantly increased compared with that from 22 months prior; no distant metastasis was observed (Figures 2c and 2d).

Her pleural effusion increased significantly, and her dyspnoea symptoms were not relieved, even after closed thoracic drainage. Thus, pericardiectomy and pericardial mass resection and biopsy were subse-

quently performed (Figure 5). Some masses were observed to surround the aorta and pulmonary artery and involved the left ventricle [4]. These masses could be resected to a certain point, even if they could not be completely resected. Therefore, partial resection of the anterior pericardium was performed. The pericardium at the junction of the superior vena cava and the right atrium was partially removed to loosen the constriction of the mesothelium. Gross pathology of some of the masses revealed a well-defined encapsulated tumour, and the cut section showed friable grey-white tissue with areas of chocolate-like necrosis (Figure 5). The histopathology showed epithelium-like malignant mesothelioma, AE1/AE3(+), Calretinin(+), D240(+), CK56(partial+), CK7(+), mesothelial(+), Vimentin(partial cells+), WT-1(-), MOC-31(-), Ber-EP4(-), TTF-1(-), Napsin A(-), P53(partial+), PAX-8(-), CK19(+), CK20(-), ER(-), PR(-), and Ki67(approximately 60%+) (Figure 6). Histologic sectioning confirmed that the tumour was PMPM. After surgery, the patient's central venous pressure decreased to 3 cm H₂O, and her blood pressure increased and remained stable at 110/80 mmHg. We present preliminary data from a case report to provide specific medical evidence for the development of relevant guidelines (Figure 7).

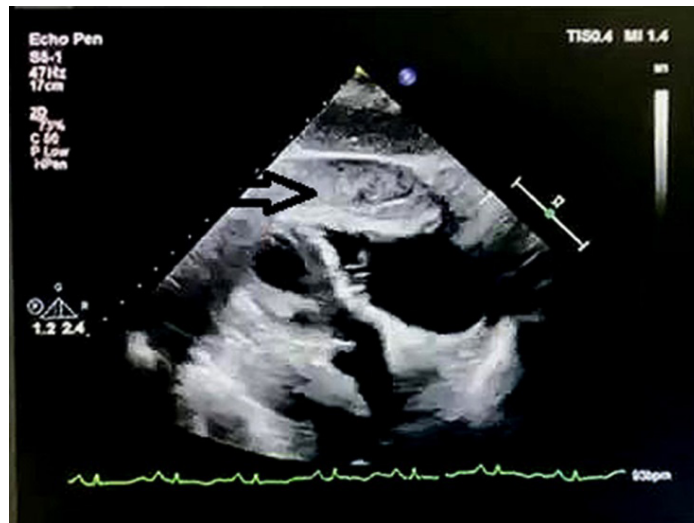


Figure 3. TTE at 22 months: Obvious oval capsular mass (white arrow)

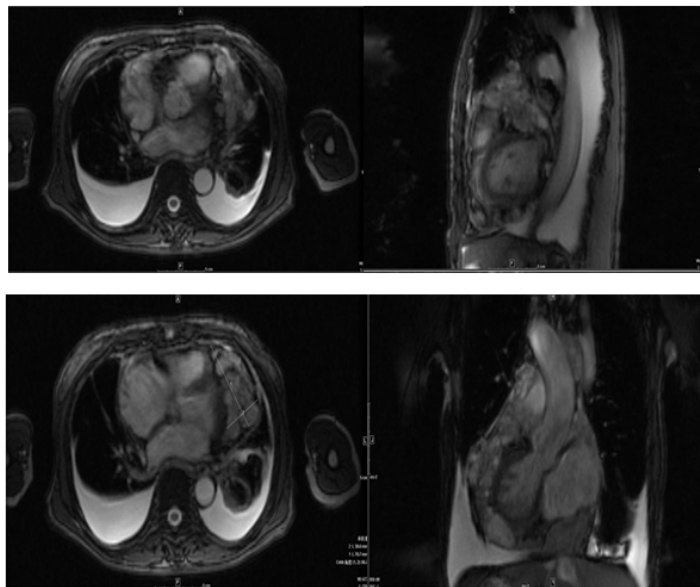


Figure 4. CMR at 22 months

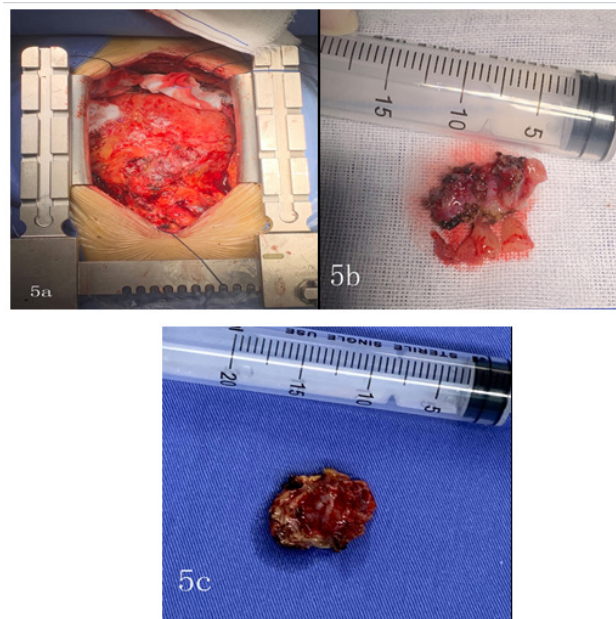


Figure 5. a) During operation; b) Cut section of PMPM; c) Gross pathology of PMPM

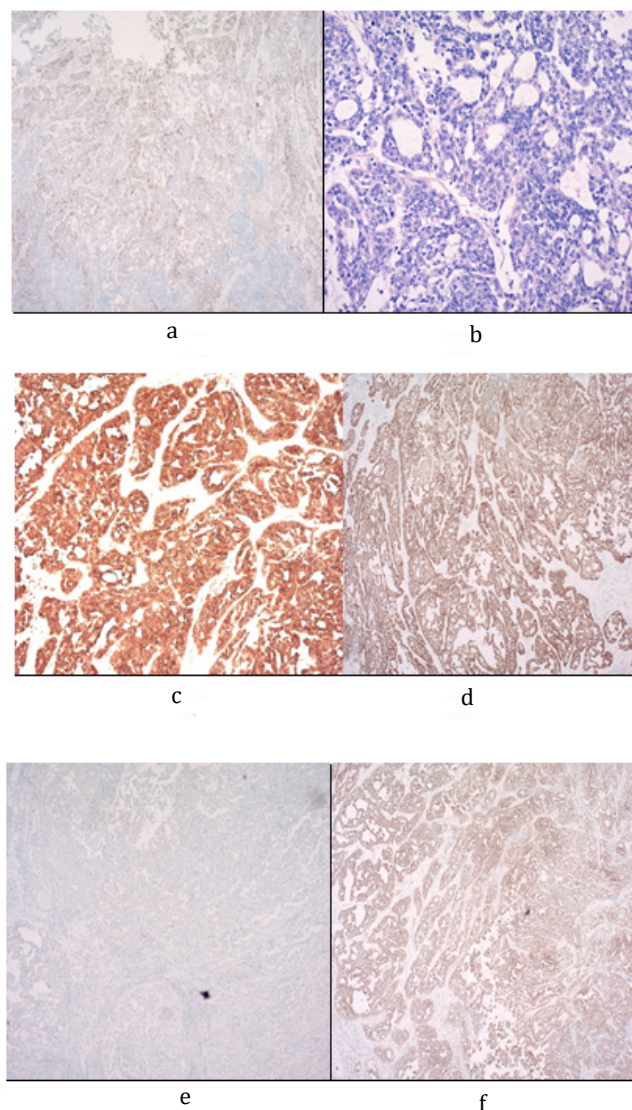


Figure 6. a) Histopathology: Mesothelial (+); b) Histopathology: AE3 (+) 200 ×; c) Histopathology: Calretinin (+); d) Histopathology: CK-67(+); e) Histopathology: CK-56(+); f) Histopathology: D240(+)

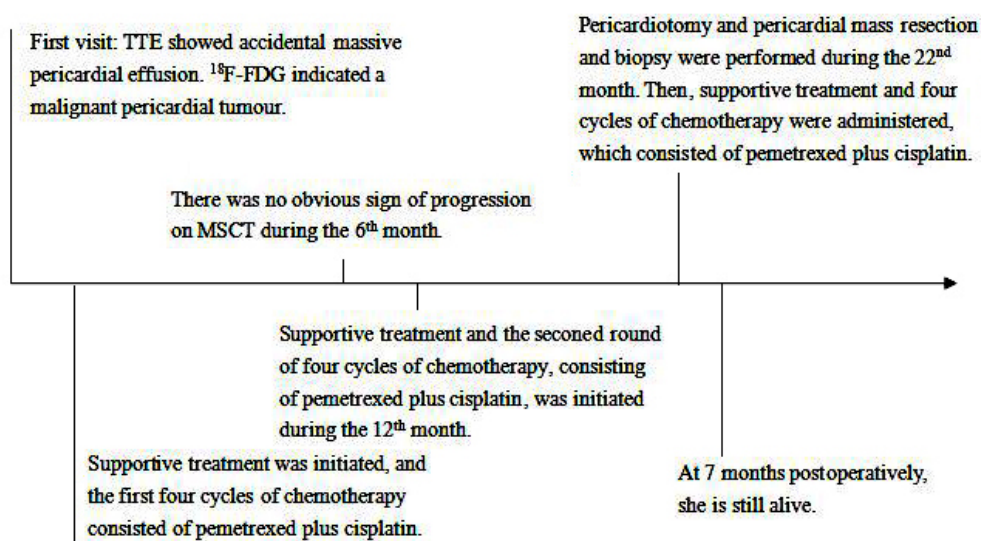


Figure 7. Medical evidence for the development of relevant guidelines

Outcome and follow-up

After the surgery, the patient was administered conventional cardiotoxic, diuretic and other symptomatic treatments. Her overall condition had improved, and TTE evaluation showed that her cardiac ejection fraction was 60%. The patient then continued the previous chemotherapy regimen, pemetrexed at a dose of 125 mg/m² plus cisplatin at a dose of 18.75 mg/m² for four cycles. Follow-up PET/CT did not show any recurrence or distant metastasis at 7 months postoperatively. Further follow-up will continue.

Results and Discussion

In clinical work, various questions arise for surgeons: What kind of imaging examination should be used to make an early and accurate diagnosis? Which treatment is better? What surgical treatment will confer the most benefit to the patient? The latest guidelines do not include specific recommendations for malignant pericardial tumours [5]. Thus, this paper describes the diagnosis and treatment of a case of PMPM to provide guidance for clinicians in making decisions regarding treatment planning.

It is challenging to diagnose pericardial tumours using only the patient's medical history, clinical signs, cardiac X-ray and TTE. TTE, MSCT and CMR have their own unique advantages and disadvantages [6], but diagnosis still depends on histopathology. PMPM patients do not present dyspnoea—the most common symptom—or other nonspecific symptoms when massive pericardial effusion and pericardial thickening are occasionally found by TTE. Because MSCT and CMR do not provide any more discriminating information than TTE, PET/CT was performed, which indicated the possibility of a malignant pericardial tumour. This cautiously suggests that when the patient is suspected of pericardial malignancy but does not accept or cannot undergo histopathological examination, the use of PET/CT may aid in making an accurate diagnosis [7,8].

In 1997, Basso et al. pointed out that surgery is the first and only choice for PMPM [9]. The recent cases in the literature provided evidence to support the use of combined therapy—pericardiectomy-assisted radiotherapy and/or chemotherapy for patients with limited PMPM and pericardial perfusion chemotherapy after fenestration and drainage for patients with diffuse PMPM—in patients who do not meet the criteria for complete resection. This combination therapy can alleviate pain and prolong the survival time [10]. Despite many new advances in the diagnosis and treatment of PMPM, its prognosis is dismal, with a median survival

time of six months [11,12]. Standard treatment for diffuse PMPM has not been well established. It has been reported that pemetrexed plus cisplatin, the only approved first-line treatment for patients with unresectable malignant pleural mesothelioma, is also effective in the short term for localised PMPM [13]. At the time of accidental discovery, the tumour was diffuse and could not be completely resected. Thus, chemotherapy and supportive treatment were provided. Due to manifestations of haematotoxicity and gastrointestinal toxicity, the dosage of the chemotherapy regimen was adjusted twice. After one and one-quarter of four cycles of chemotherapy, owing to the poor nutritional status and the reoccurrence of haematotoxicity and gastrointestinal toxicity, chemotherapy was suspended, and the patients received best supportive treatment. After 10 months of supportive treatment, patient's general condition had improved, but she suffered disease progression, and her condition was similar to constrictive pericarditis. Excluding pleural effusion, it was determined that her symptoms were caused by a narrowed pericardium. Surgery was performed promptly, and symptoms were significantly relieved. The patient's cardiac ejection function was 60% after surgery, and the previous chemotherapy regimen was resumed. The patient was treated with comprehensive treatment for 22 months before the operation. After 7 months postoperatively, she remains alive and continues to receive best supportive care 29 months after the first clinical manifestation. This proves that our treatment is effective.

In 1994, Thomason et al. presented a case report and reviewed 27 cases of primary pericardial mesothelioma that appeared in English literature from 1972 to 1992 [14]. Ase Nilsson, et al. reviewed 29 cases reported in the English literature from 1993 through 2008 in which a diagnosis of primary pericardial mesothelioma was established. In the available literature, we found twelve cases of PMPM (four males and eight females) diagnosed between 2009 and 2020 (Table 1). The mean age at the time of diagnosis was 47.92 ± 14.15 years. Dyspnoea was the most common clinical symptom, which was reported in 12 cases (8/12, 66.67%). We did not find any patients with a history of asbestos exposure among these cases, consistent with the current mainstream opinion. The histologic type of 2 patients was not mentioned; 4 were the biphasic type (33.33%) and 6 were the epithelial type (50.00%). Seven of the 12 cases were treated with chemotherapy in combination with surgery; the longest survival time was 27 months, and the shortest survival time was 3 months.

Table 1. Summary of literature involving primary malignant pericardial mesothelioma from 2009 to 2020.

No.	Author, year	Age, gender	Symptoms	Asbestosis	Diagnosis methods	Tumor size(cm)	Metastases and invansion	Histologic type	Treatments	Outcomes
1	Ase Nilsson, 2009	38,M	Chest pain, dyspnea	No	TTE,CMI,PET/CT	5 × 4 × 2.5	No	Biphasic	Surgery, Pemetrexed+cispatin	15 mo without symptoms
2	Kelli Reardon, 2010	59,FM	Chest pain, dyspnea	No	X-ray, CT,CMI	7.4 × 4.8 × 4.2	Adherence to right ventricle	Biphasic	PericardialWindows,gem-citabine+cisplatin,gem-citabine+carboplatin. permextred,Radiation	50 mo without progression
3	Mohit Godar, 2013	68,M	Dyspnea	No	TTE,CT	3.5	No	Epithelial	Surgery, Pemetrexed+cispatin	Died after 27 mo
4	Weihui Gong, 2014	60,FM	Dry cough, shortness of breath	No	TTE,CT,PET/CT	11 × 9 × 2	Adherence to right ventricle	Epithelial	Pericardiocentesis,Thoracocentesis,Surgery,cisplatin+eoposide	Died after 3 mo
5	Russell Fernandes, 2014	30,FM	No	No	TTE,CT,CMI	10.2 × 5.2 × 0.6	Adherence to right ventricle	Epithelial	Surgery	Died
6	RajooRamachandran, 2014	55,FM	Dyspnea	No	TTE,CT,PET/CT	Max. thickness of 1.5	No	Biphasic	CT-guided biopsy	Not mention
7	Takeyukikurosawa, 2016	37.FM	Chest pain, dyspnea	No	TTE,CT,PET/CT	Irregular;thickened pericardium	Adherence to right ventricle	Epithelial	Surgery,carboplatin+pemetrexed	Died after 18 mo
8	SANG MI CHUNG, 2016	52,FM	Dyspnea, coughing, fever	No	X-ray, TTE,CT,C - MI	surrounding the heart	Metastased to both lung fields	Epithelial	Pericardial biopsy,pericardiocentesis,Surgery,Pemetrexed+cispatin	21 mo whitout symptoms
9	Xiaohui Li,2017	28,M	chest pain, Shortness of breath	No	X-ray, TTE,CT, - PET/CT	surrounding the heart	Bone and right atrium etastasis	Not mention	Pericardial biopsy, Surgery,Pemetrexed+cispatin	Died after 27 mo
10	Kohei Shikano, 2018	64,FM	Dyspnea	No	X-ray, TTE,CT	surrounding the heart	Invasion of myocardium, right pleura and lung	Epithelial	Pericardiocentesis,- VATS-pericardial fenestration,surgery	Died after 5 mo
11	Guang Song,2019	52,M	Chest pain, dyspnea	No	TTE,CT,PET/CT,CMI	5 × 4 × 2.5	No	Biphasic	Pericardiocentesis, surgery	Still alive after 29 mo
12	Sameh Ben Farhat, 2020	32,FM	Shortness of breath	No	X-ray, TTE,CT	surrounding the heart	No	Not mention	Pericardiocentesis,surgery,chemo+radiotherapy	Died after 4 mo

Note: CT: Computed Tomography; F: Female; M: Male; CMR: Cardiac Magnetic Resonance; PET/CT: Positron Emission Tomography/Computed Tomography; TTE: Transthoracic

Conclusion

In conclusion, comprehensive treatment, including chemotherapy and best supportive treatment, and timely surgery is effective for unrespectable PMPM. When patients present with symptoms caused by PMPM that are not relieved by medication, we recommend prioritising urgent surgery. There were no patients found with history of asbestosis. All the patients had a common symptom of dysphonia (i.e shortness in breathing). After proper examinations, With respect to the patient's condition treatment was undergone.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests in financial and non-financial.

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Authors' contributions

All authors contributed equally within the limits and beyond their speciality in accumulating knowledge, diagnosing and managing this rare condition and have approved the manuscript. CYL and BZ were involved in disease management and follow-up of the patient. CYL was involved in the thorough literature review. WWC was involved in the radiological investigations throughout the follow-up. DLM was involved in the histological evaluation of the tumour. XW was involved in the surgical management and follow up of the patient. SYZ revised the manuscript critically for important intellectual content and gave final approval for this manuscript version to be submitted.

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