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CASE REPORT

ADVANCED

CLINICAL CASE SERIES

Primary Malignant Pericardial Mesothelioma

A Clinical Case Series Illustrating the Necessity of a Multidisciplinary Approach

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ABSTRACT

Primary malignant pericardial mesothelioma is a rare cardiac neoplasm. The authors evaluated risk factors, clinical presentation, and outcomes by reviewing all biopsy-confirmed cases at one institution. The use of multimodality imaging, detailed hemodynamic assessment for the presence of an effusive-constrictive profile, and cytology evaluation can support the diagnosis. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:202–7) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In the scope of cardiovascular diseases, malignancies of the heart are uncommonly encountered. Nevertheless, knowledge and awareness of these entities in relation to their presentations and natural history are important for prompt management and ultimately prognostication. With respect to cardiac malignancies, most occur as metastatic disease to the heart, which can be present in up to 18% of stage IV cancers. Primary malignant diseases, in contrast, comprise <1% of all cardiac malignancies (1).

Among primary pericardial malignancies, primary malignant pericardial mesothelioma (PMPM) is the most common, accounting for approximately 3% of primary cardiac and pericardial tumors.(2,3). Despite pathologic description of PMPM, data for clinical presentation and outcomes have thus far been limited. This study sought to define clinical characteristics, including echocardiographic and clinical presentation, of the largest single clinical cohort of patients with PMPM and evaluate outcomes as they related to the treatment modalities used.

LEARNING OBJECTIVES

- Understand the most frequent clinical presentations of primary pericardial mesothelioma.
- Recognize the importance of multidisciplinary approach to the diagnosis and management of primary pericardial mesothelioma.
- Evaluate current outcomes in primary pericardial mesothelioma in the context of historical data.

MATERIALS AND METHODS

A retrospective review was performed, which sought to identify all patients with a diagnosis of PMPM at a single institution. A search algorithm using an internal clinical data repository for keywords or diagnoses (1999 to present) was used. All matches were reviewed for the definite diagnosis of

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PMPM; a cohort of 6 patients with PMPM was identified between 2001 and 2015. The Mayo Clinic Institutional Review Board approved the present study.

Demographic characteristics were reviewed: pathologic diagnosis, including subtype; clinical presentation of pericardial disease; initial imaging findings and laboratory evaluation; putative oncologic risk factors; echocardiographic appearance and hemodynamic features; medical comorbidities; surgical or chemotherapeutic treatments administered; and long-term outcomes. Descriptive statistics were used, given the small sample size.

ABBREVIATIONS AND ACRONYMS

LV = left ventricle

PMPM = primary malignant pericardial mesothelioma

RESULTS

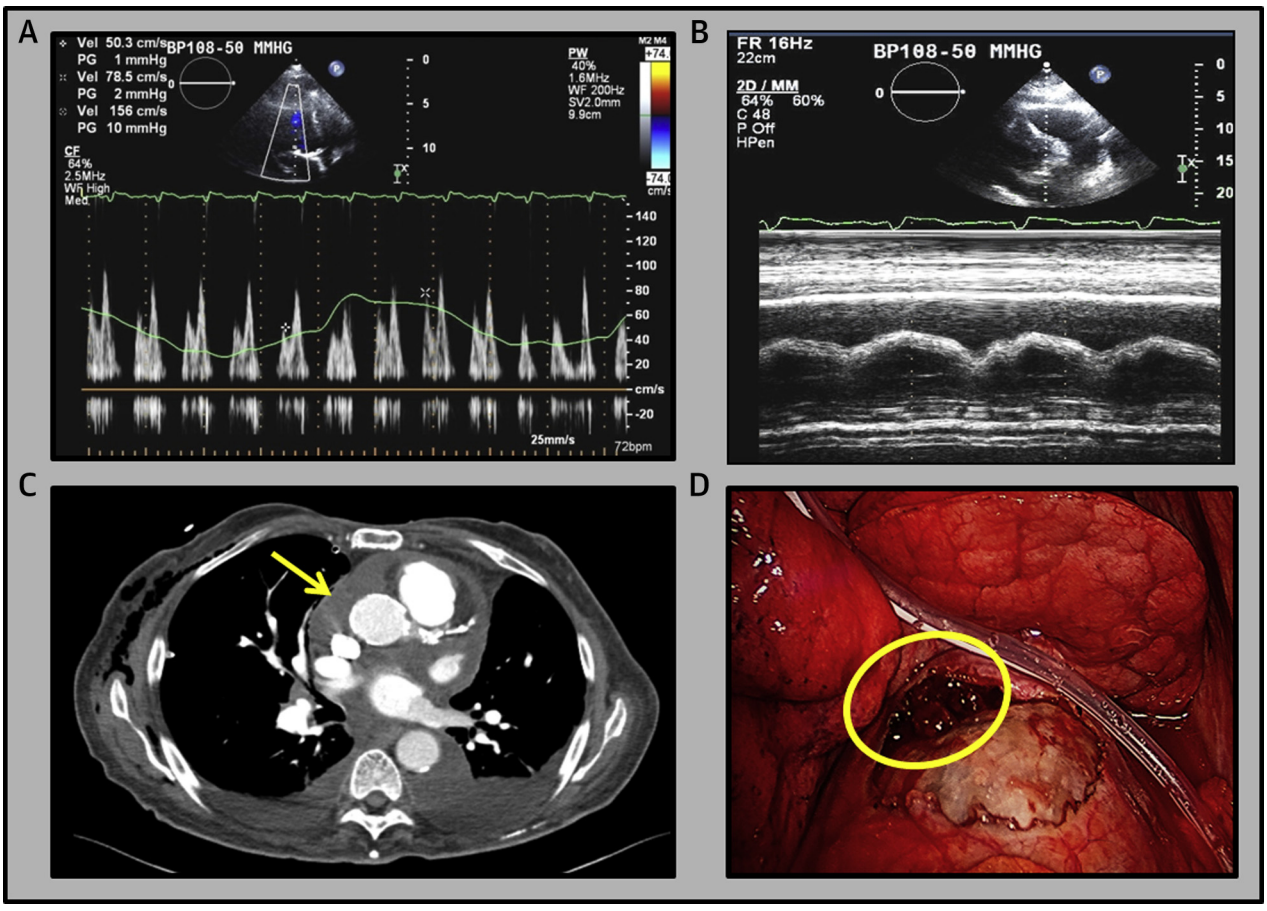
A thorough characterization of each patient within the cohort is shown in Table 1. Overall, the mean age at diagnosis was 50 years (range: 23 to 71 years). Half of the patients had a previous diagnosis of coronary

TABLE 1 Characteristics and Initial Presentation of Patients With PMPM

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
Age, yrs, sex	44 F	50 F	53 M	71 M	60 F	23 F
Time to diagnosis from onset of attributable symptoms, months	15	(1) (asx)	28	26	24	12
Diagnosis (PMPM subtype)	Biphasic/mixed	Biphasic/mixed	Biphasic/mixed	Epithelial	Epithelial	Biphasic/mixed
Comorbidities						
Coronary artery disease	(+)	(0)	(0)	(+)	(+)	(0)
Atrial fibrillation	(0)	(0)	(0)	(+)	(0)	(0)
History of VT/VF	(0)	(0)	(0)	(0)	(0)	(0)
Diabetes	(0)	(+)	(0)	(+)	(0)	(0)
COPD	(0)	(+)	(0)	(0)	(0)	(0)
Cirrhosis	(0)	(+)	(0)	(0)	(0)	(0)
Anemia	(0)	(+)	(0)	(0)	(+)	(+)
Putative risk factors						
Prior malignancy	Hodgkin disease	(0)	(0)	Hodgkin disease	(0)	(0)
Prior radiation therapy	(+)	(0)	(0)	(+)	(0)	(0)
Smoking history, pack-years	0	60	35	70	26	0
Asbestos exposure	(0)	(0)	(+)	(0)	(0)	(0)
Family history of thoracic malignancy	(0)	(0)	(0)	(0)	(0)	(0)
Notable laboratory studies at diagnosis						
Serum creatinine, mg/dl	1.2	0.7	0.9	1.6	0.9	0.9
BUN, mg/dl	95	12	22	28	17	23
Alkaline phosphatase, U/l	164	49	388	75	445	61
Total serum bilirubin, mg/dl	1.5	0.8	2.5	0.9	0.3	
NT-proBNP, pg/ml		524		3,321		
Hgb, g/dl	10.6	10	17.2	11.7	11.5	10.5
ESR, mm/h	39		0		11	48
Echocardiographic clinical presentation	Effusive-constrictive pericarditis	Normal pericardial space	Effusive-constrictive pericarditis	Effusive-constrictive pericarditis	Effusive-constrictive pericarditis	Constrictive pericarditis
Pericardial thickening	(0)	(0)	(+)	(0)	(+)	(+)
Pericardial mass	(0)	(0)	(+)	(0)	(0)	(0)
LVEF	56	75	55	25	55	46
Significant valvular heart disease (moderate or greater valve lesion)	(0)	(0)	(0)	AS, MS	(0)	(0)
Clinical management						
Pericardial therapy	Pericardial window	None	Pericardiectomy	Pericardial window	Pericardiectomy	Pericardiectomy
Follow-up effusion	None	NA	None	Trivial	None	None
Chemotherapy	Cisplatin/pemetrexed × 2 cycles; Carboplatin/pemetrexed × 3 cycles	None	None	None	None	Cisplatin/pemetrexed × 4 cycles; Gemcitabine/oxaliplatin × 2 cycles
Days from diagnosis to death	837	279	30	30	627	235

(+) = presence of finding; (0) = absence of finding; AS = aortic stenosis; asx = asymptomatic; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; ESR = erythrocyte sedimentation rate; Hgb = hemoglobin; MS = mitral stenosis; NT-proBNP = N-terminal pro-brain natriuretic peptide; PMPM = primary malignant pericardial effusion; VF = ventricular fibrillation; VT = ventricular tachycardia.

FIGURE 1 Clinical Features of PMPM With Imaging Correlation



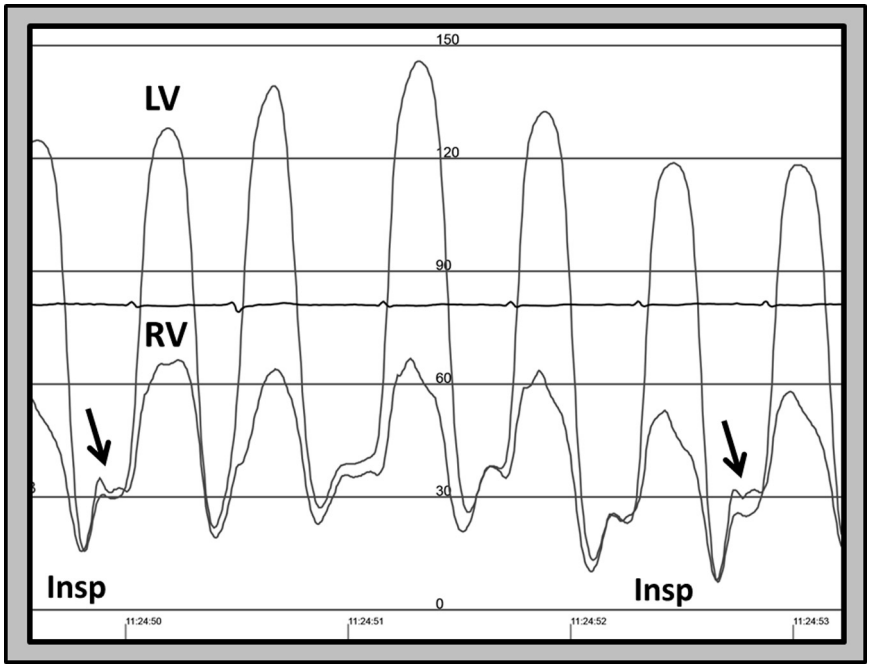
(A) Transmitral pulsed-wave Doppler showing A-wave-predominant mitral inflow with significant respirophasic E-wave variability, consistent with interventricular interdependence and intracardiac-intrathoracic pressure dissociation. **(B)** Parasternal right ventricular inflow view shows prominent diastolic right ventricular free wall collapse, consistent with cardiac tamponade. **(C)** Cardiac-gated CT scan shows a large globular mass anterior to the superior vena cava **(arrow)**. **(D)** Intraoperative view saved during video-assisted thoracoscopy for pericardial window and biopsy of soft tissue mass. The **yellow circle** highlights is the globular mass located just anterior to the superior vena caval-atrial junction (Patient #4). CT = computed tomography; PMPM = primary malignant pericardial mesothelioma.

artery disease. Anemia, prior malignancies, and diabetes were all common. Of note, no patients presented with a history of ventricular arrhythmia. Diagnosis was delayed by 21 ± 7 months from onset of symptoms (15 to 28 months).

Among conventional oncologic risk factors, tobacco use was present in 4 patients (67%) with an average of 48 pack-years (range: 26 to 70 pack-years). Previous radiation therapy for another malignancy was present in 2 patients (33%). Asbestos exposure was clearly identified in only 1 patient. No patients had a family history of thoracic malignancy or mesothelioma. One patient had previous exposure to tuberculosis, a potential risk factor.

Echocardiographic findings were notable for a diffusely thickened pericardium in 3 patients (50%) and with an epicardial mass effect in 1 patient. Two patients (33%) presented with cardiac tamponade requiring pericardiocentesis (Figure 1). Two patients (33%) also presented with a coexistent cardiomyopathy (left ventricular [LV] ejection fraction of 25% in 1 patient and 46% in another). There was minimal valvular heart disease aside from 1 patient with moderate aortic and mitral stenosis, suspected to be related to prior chest irradiation for Hodgkin disease. Cardiac computed tomography revealed the presence of a pericardial complex mass in 1 patient (Figure 1). Definitive diagnoses were achieved through open surgical biopsy (Figure 1D) in all 6 patients.

FIGURE 2 **Hemodynamic Catheterization in a Patient With PMPM**



Mixed restrictive and constrictive hemodynamics in Patient #1, who had undergone radiation therapy to the chest for Hodgkin disease and current PMPM. Note the subtle increase in RV pressure as LV pressure falls with inspiration (especially the last beat), consistent with ventricular interdependence. Higher RV end-diastolic pressure (**arrows**) than LV is seen during inspiration is consistent with intrinsic myocardial disease with a dip and end-diastolic pressure plateau of approximately 30 mm Hg, consistent with superimposed restrictive hemodynamics. Insp = inspiration; LV = left ventricular; PMPM = primary malignant pericardial mesothelioma; RV = right ventricular.

Four patients (67%) presented with an effusive-constrictive pericarditis. Combined left and right heart catheterization were available for 1 patient (Figure 2), showing the presence of interventricular interdependence and intrinsic myocardial restrictive physiology. Pericardial fluid analysis in both cases was indeterminate for malignancy, as both revealed atypical mesothelial cell proliferation (Figure 3). PMPM was biphasic/mixed in 2 patients (33%) and epithelioid in 4 (67%) (Figure 3). No sarcomatous PMPMs were identified.

Clinical and surgical therapies are also shown in Table 1. Two patients underwent partial or complete pericardiectomies; however, complete resection of the PMPM tumor burden was not possible in either case. No recurrent effusions developed, and no distant metastases were identified, although no patients within the cohort underwent autopsy. Two patients underwent platinum-based chemotherapeutic regimens. Median survival was 8.4 months (257 days; range: 30 to 837 days) after diagnosis.

To our knowledge, this cohort is the largest contemporary series of clinically diagnosed PMPM published to date. Several findings were identified that contributed to an enhanced understanding of the clinical syndrome associated with PMPM and variety of presentations. Based on the array of modalities used in these challenging cases, collaboration among cardiovascular imaging experts, hemodynamic experts, cardiovascular pathologists, and cardiac surgeons was critical to achieving the diagnosis and instituting appropriate therapies.

With respect to demographics and risk factors, in this cohort of 6 patients, there was an equal distribution of sexes, compared to prior reports suggesting a male predominance (4). Conventional oncologic risk factors were common: most had a significant tobacco history, and 2 patients underwent prior radiation therapy to the chest. Data do not provide any definitive link between asbestos exposure and PMPM as only 1 patient in the cohort was exposed; therefore, this link remains controversial (4).

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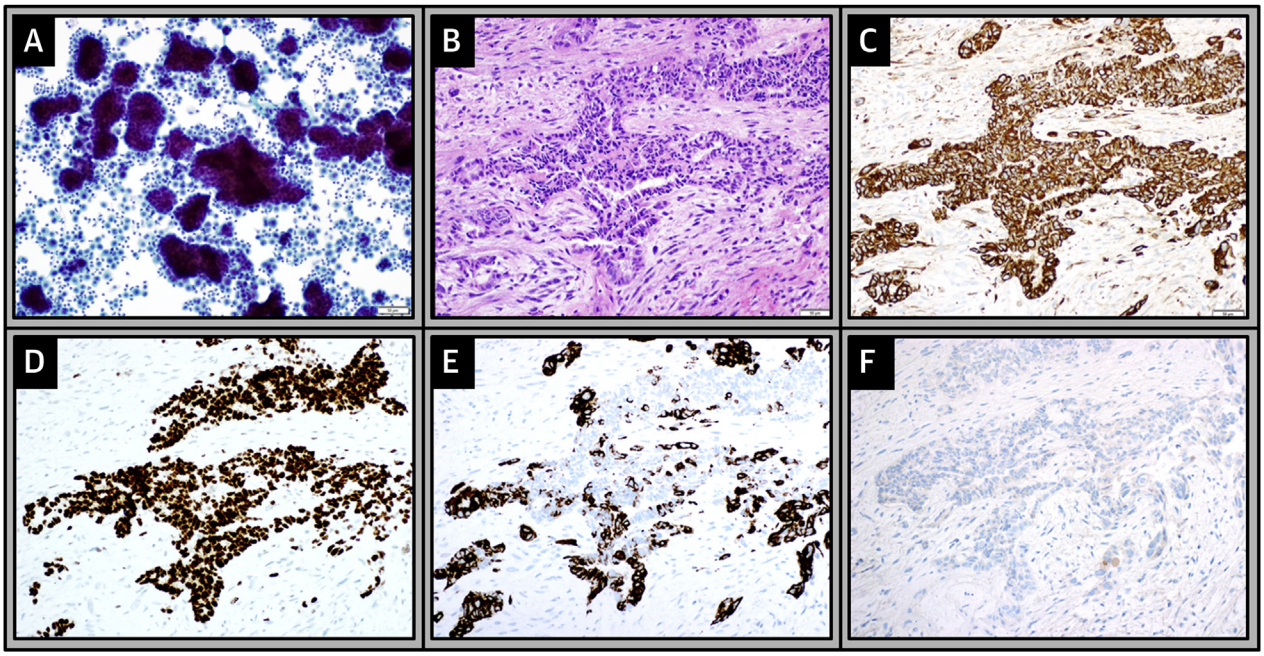
FIGURE 3 Pathologic Evaluation of PMPM



(A) Cytospin of a pericardial effusion shows atypical mesothelial proliferation (original magnification ×200) with clusters of epithelioid cells demonstrating scalloped community borders. Scattered single atypical mesothelial cells are present in the background (Patient #3). **(B, C)** Biphasic PMPM. Histologic sections of a surgical biopsy show both epithelioid and spindled (sarcomatoid) mesothelial cells infiltrating the pericardium (**[B]** hematoxylin and eosin stain; **[C]** cytokeratin AE1/AE3; original magnification ×200, both) (Patient #4). **(D, E)** Immunohistochemistry discloses a mesothelial phenotype with immunoreactivity for WT-1 and CK5/6 (original magnification ×200) (Patient #4). **(F)** Lack of immunoreactivity with MOC-31 further supports the histologic diagnosis of malignant mesothelioma (original magnification ×200) (Patient #4). PMPM = primary malignant pericardial mesothelioma.

The distribution of clinical presentations was variable, which reflects the variety of case reports. The insidious onset of symptoms was highlighted by delay in diagnosis, which, while significantly protracted at 21 months in this cohort, was consistent with prior data. An effusive-constrictive hemodynamic profile has been previously described, but this was common in the present population (5). Interestingly, no patients presented with significant dysrhythmia, and no ventricular arrhythmia or sudden death events were seen. As shown in **Figure 1**, the use of multimodality imaging is highlighted, and cardiac magnetic resonance can yield additional insights through imaging characterization.

Cytology from pericardial fluid may not yield a definitive diagnosis. As was demonstrated in both of the patients who underwent cytology evaluation, differentiating malignant from reactive mesothelial cells can be challenging (6). Nevertheless, novel ancillary methodologies have facilitated identification of mesothelioma in effusion cytology. Immunohistochemical evaluation of the tumor suppressor gene *BRCA1*-associated protein 1 (BAP1), which is frequently lost in epithelioid mesotheliomas of the pleural and peritoneum, has thus far been highly specific for the diagnosis (7). Moreover, loss of p16 (evaluated by fluorescence in situ hybridization) has reliably distinguished benign from malignant mesothelial populations (8). Although touted for their specificity, neither test portends a high degree of sensitivity, and data for their performance in PMPM is limited (9).

With regard to treatment, and in contrast to some prior reports, chemotherapy did not seem to offer a survival advantage in our cohort. Outcomes in PMPM are poor, and the present data indicate little improvement in the last 25 years, despite advancement in chemotherapeutic regimens with the addition of pemetrexed (10). Complete or partial pericardiectomy was also not associated with any long-term benefit.

The current study is limited by the small size of the cohort in question. The rarity of the disease process does not lend well to developing strong conclusions

from single-center analyses, but the present cohort is the largest pre-mortem clinical cohort in contemporary reports. The data were not collected prospectively, and therefore, only information, particularly regarding the presence of risk factors, available in the medical record could be reviewed. Additionally, as advanced disease is common at diagnosis in PMPM, therapies offered and outcomes are often affected by performance status and general health factors. Therefore, any true effect of therapy cannot be ascertained in this study due to selection bias and the small cohort of patients studied.

The study report describes the largest clinical pre-mortem cohort of patients with a diagnosis of PMPM. Although PMPM is a challenging diagnosis to establish, the use of multimodality imaging, detailed hemodynamic assessment for the presence of an effusive-constrictive profile, and novel cytology evaluation can provide clues to this elusive diagnosis, which highlights the importance of multidisciplinary collaboration. Unfortunately, despite advances in chemotherapeutics, clinical outcome remains poor.

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