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## CARDIAC TAMPONADE RESEMBLING AN ACUTE MYOCARDIAL INFARCTION AS THE INITIAL MANIFESTATION OF METASTATIC PERICARDIAL ADENOCARCINOMA

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### Abstract

Pericardial malignancies are uncommon, usually metastatic, linked to terminal oncology patients, and rarely diagnosed premortem. A very small number of patients will develop signs and symptoms of malignant pericardial effusion as initial clinical manifestation of neoplastic disease. Among these patients, a minority will progress to a life-threatening cardiac tamponade. It is exceedingly rare for a cardiac tamponade to be the unveiling clinical manifestation of an unknown malignancy, either primary or metastatic to pericardium. We present the case of a 50-year-old male who was admitted to the emergency department with an acute myocardial infarction diagnosis that turned out to be a cardiac tamponade of unknown etiology. Further studies revealed a metastatic pericardial adenocarcinoma with secondary cardiac tamponade. We encourage considering malignancies metastatic to pericardium as probable etiology for large pericardial effusions and cardiac tamponade of unknown etiology.

### Introduction

Pericardial neoplastic disease (PND) usually is metastatic, and by the time of detection it frequently has a previously diagnosed primary tumor. Metastatic malignancies affecting the pericardium are associated with terminal cancer patients, with the vast majority of cases not being detected premortem due to a classic absence of clinical manifestations.<sup>1</sup>

With cancer patients living longer due to improvements in diagnostic and treatment options, PND is increasing in prevalence. However, it is commonly unsuspected and thus very often misdiagnosed when any related symptom appears.<sup>2</sup> The disease initially could cause an acute pericarditis, malignant pericardial effusion (MPE), effusive constrictive pericarditis, and occasionally cardiac tamponade; in addition, pericardial effusion can be the first sign of several diseases. Slow progression of symptoms is the rule among MPE patients although the severity of clinical onset varies;<sup>3</sup> a plateau phase or spontaneous regression could be observed as well.<sup>4</sup>

Both MPE and related cardiac tamponade are rarely diagnosed and, as symptoms of metastatic PND, are considered terminal events in cancer patients. We describe a case of cardiac tamponade presenting as the initial sign of metastatic pericardial adenocarcinoma in a 50-year-old male brought to our institution with sudden onset of chest pain and cardiac symptoms that were misdiagnosed as acute myocardial infarction (AMI).

### Case Report

A 50-year-old Hispanic male was transferred from an outpatient clinic with the diagnosis of AMI. Upon admission, he complained of shortness of breath (SOB) over the past 3 days and nausea with occasional vomiting. Immediately prior to his arrival to the emergency department, he experienced increased SOB and the onset of moderate chest pain. The patient, a nonsmoker, was

diabetic, recently diagnosed with renal insufficiency, and had a history of high blood pressure. According to his relatives, he experienced a 10-pound weight loss within an 8-week period; family history was unremarkable.

Upon physical examination he was hemodynamically stable, with a blood pressure of 110/70 mm Hg, a heart rate of 80 bpm, and a respiratory rate of 20 rpm; he was under distress, pale, and diaphoretic, with a trace of edema in both lower limbs.

An electrocardiogram (ECG) showed changes suggestive of acute ST-elevated myocardial infarction involving the inferior and lateral leads along with low QRS voltage in the precordial leads. Cardiac markers troponin T and proBNP were elevated at 0.14 ng/mL and 450 pg/mL, respectively. ST-Segment Elevation Myocardial Infarction (STEMI) protocol was activated, and he was taken to the cardiac catheterization laboratory. During the procedure, he was found to have no evidence of coronary artery disease. An echocardiogram showed a large pericardial effusion with tamponade physiology. The patient was taken to the operating suite and underwent an emergent pericardial exploration, pericardial drainage, and pericardial window creation. Approximately 600 mL of bloody pericardial fluid was evacuated, and a large BLAKE<sup>®</sup> silicon drain (Ethicon, Inc., Bridgewater, NJ) was placed into the posterior pericardial recess.

A pericardial fluid sample sent for cytology review was negative for bacteria, fungus, virus, or malignancy. A pericardium biopsy analyzed by pathology evidenced scattered groups of atypical cells within the pericardial fibrous stroma, with round to elongated nuclei, nuclear hyperchromasia, coarse chromatin, irregular nuclear membranes, and indistinct amphophilic cytoplasm. Apoptotic bodies were also identified. An immunohistochemical study demonstrated nests and gland-like groups of atypical epithelial cells showing an immunophenotypic pattern consistent with adenocarcinoma, possibly a

pancreatobiliary or upper gastrointestinal tract metastasis to the pericardium, which is indicative of a malignant etiology for the patient's cardiac tamponade.

A chest, abdomen, and pelvis computed tomography scan showed bilateral pleural effusion and extensive retroperitoneal periaortic lymphadenopathy extending down to the aortic bifurcation and the right common iliac chain. Serum tumor markers were revised, with only CA 19-9 having an elevated serum level of 457 U/mL.

The patient's stay was uneventful. He was widely informed about his diagnosis and decided to leave against medical advice, refusing to receive further medical assessment or treatment. He was strongly encouraged to maintain a medical oncology and gastroenterology follow-up visit for further studies to determine staging and receive proper treatment.

## Epidemiology

Cardiac and pericardial neoplasms, either primary or secondary, appear in one to three of every 10,000 autopsies,<sup>5</sup> and PND has been revealed in 5% to 15% of autopsies in terminal cancer patients,<sup>1</sup> although some authors state that metastasis to the pericardium could complicate up to 21% of all neoplasms.<sup>6</sup> The cardiac site most commonly affected by metastasis is the pericardium followed by the myocardium, but myocardial involvement confers an 8.5% probability of pericardial involvement as well.

Secondary neoplasms of the pericardium account for 95% of all PND.<sup>7</sup> Metastatic involvement of the pericardium represents a leading cause of pericardial disease in hospitalized patients,<sup>8</sup> with the most common primary tumors being lung and breast cancer<sup>9</sup> since both metastasize via hematogenous and lymphatic routes and also by direct extension. These two primaries along with leukemia, melanoma, Hodgkin's and non-Hodgkin's lymphoma are the etiology of 75% of all diagnosed MPE;<sup>10</sup> specifically, lung, breast, and hematologic cancers will cause 33%, 25%, and 15% of all MPE, respectively.<sup>11</sup> In men, carcinoma of the esophagus represents the primary tumor in 28.7% of all cases of metastatic PND.<sup>7</sup> Some other malignancies that metastasize to pericardium are sarcomas and gastrointestinal neoplasms.<sup>12</sup> Metastatic carcinoma from an unknown primary site represents 10% to 15% of all PND diagnosed pre-mortem.<sup>13</sup>

## Pericardial Effusion and Cardiac Tamponade

Like PND, only 5% to 8% of MPE detected in autopsies are diagnosed pre-mortem;<sup>14</sup> the rest are comprised of small effusions that remain asymptomatic during the patient's lifetime, leading to an apparent low incidence and prevalence. MPE becomes symptomatic when pericardial fluid accumulates significantly, increasing the risk of cardiac tamponade, which is commonly caused by neoplastic pericarditis.<sup>15</sup>

While malignancies are one of the main causes of pericardial effusion in the United States,<sup>16</sup> it must be emphasized that in most cancer patients with pericardial effusion, there will not be a malignant invasion to the pericardium; in fact, one of every three cases of MPE is due to infection or radiation pericarditis.<sup>17</sup> Regardless of pericardial neoplastic involvement, pericardial effusions are increasingly observed in terminal cancer patients.<sup>18</sup>

## Etiology and Pathophysiology

Pericardium metastatic involvement can occur through three main routes: hematogenous, lymphatic, and local extension.<sup>12</sup> For

many years, the hematogenous pathway has been considered the main spread route by some authors, although others, like Warren and Kline, consider the lymphatic system as the most common metastatic pathway.<sup>19</sup>

PND can lead to pericardial effusion through different mechanisms, such as a decrease in pericardial fluid drainage due to local obstruction of lymphatic and venous flow that increases hydrostatic pressure; pericardial fluid overproduction secondary to direct leakage produced by tumor implantation in the serosal surfaces or fluid exudation due to inflammatory processes; or a decrease of oncotic pressure with fluid transudation into the pericardial sac, usually produced by indirect tumor effects such as malnutrition, hypoalbuminemia, and cachexia.

Not all pericardial effusions seen in cancer patients are malignant; other causes are chemotherapeutic drugs, uremic, idiopathic, and paraneoplastic pericardial effusions, and radiotherapy. Therefore, determining the cause of pericardial effusions in cancer patients is essential.<sup>20</sup>

Besides PND, other diseases related to large pericardial effusions are tuberculosis, cholesterol pericarditis, uremic pericarditis, myxedema, and parasitoses.<sup>21</sup> Severe pericardial effusions and acute cardiac tamponade are usually related to more serious entities,<sup>22</sup> such as AMI complicated with disruption of the ventricular wall.<sup>8</sup>

## Clinical Findings

For any malignant disease, regardless of its location, it is unusual for malignant cardiac tamponade to be the initial manifestation; nonetheless, its incidence could be underestimated due to unspecific symptoms and lack of clinical suspicion that are ultimately viewed as signs of simple pericardial effusion.<sup>23</sup> Cardiac tamponade should be considered in every cancer patient with sudden dyspnea, and each case of undetermined etiology should be considered a possible malignancy. One in every three cases of cardiac tamponade could be secondary to PND.<sup>24</sup> There usually will not be a large primary whenever cardiac tamponade appears as the first manifestation of pericardial metastatic disease.<sup>25</sup>

In patients with malignant cardiac tamponade, Kussmaul's sign, pericardial rub, and pulsus paradoxus are observed in only 5%, 12%, and 30%, respectively.<sup>26</sup> According to several malignant series of cardiac tamponade, the most common presenting symptom is dyspnea (78%); other common symptoms are cough (46%), chest pain (27%), orthopnea (26%), and weakness (19%).<sup>1</sup> The most common signs seen on physical examination in order of frequency are sinus tachycardia, jugular venous distention, hepatomegaly, and peripheral edema.<sup>1</sup> Cardiac tamponade lacking two or more inflammatory signs such as diffuse ST elevation, fever, typical chest pain, and pericardial rub are more likely associated with malignancies. Pericardial friction rub is not as common in MPE as in pericardial effusions of a different etiology.

Pericardial constriction may occur in patients with PND as well, with clinical manifestations very similar to those seen in malignant cardiac tamponade. Pericardial constriction due to PND is more often seen among lung cancer patients.<sup>27</sup>

As evidenced by the findings in our case report, cardiac tamponade could resemble an AMI, especially due to sudden onset where the only clinical signs and symptoms observed are chest tightness, severe SOB, and dizziness. In the most severe cases, increased intrapericardial pressure leads to direct compression and collapse of epicardial coronary arteries, which results in diminished perfusion, abnormal distribution of blood flow to the

myocardium, and compromised ventricular systolic function.<sup>8</sup> In addition, AMI complicated with cardiac rupture is among the possible causes of cardiac tamponade, which is more likely to occur in lateral myocardial infarctions; these patients usually will not survive the resultant mechanical dissociation.

Pericardial effusion is seen in one of every five cases of transmural AMI, mainly in those located in the anterior wall.<sup>28</sup> In those patients with large pericardial effusions, the ECG will depict a low QRS voltage in limb leads, PR segment depression, ST-T changes, bundle branch block, and electrical alternans. The latter constitutes a finding only observed in cardiac tamponade;<sup>22</sup> electrical alternans is not common in patients with MPE, and ECG is not sensitive enough for a cardiac tamponade diagnosis.<sup>29</sup>

Echocardiography allows one not only to document the presence and severity of cardiac tamponade but also to easily discard differential diagnoses such as cardiomyopathy, constrictive pericarditis, and myocardial infarction in those patients with arterial hypotension and venous hypertension.<sup>30</sup> However, magnetic resonance imaging is superior for complete visualization of the pericardial cavity and tissue contrast, thereby improving the evaluation of the pericardial sac and obtaining a better assessment.<sup>5</sup>

Since physical examination and imagenology provide inconclusive findings, a more invasive approach, such as obtaining pericardial fluid and biopsies for cytology and histology, is usually required.

Some authors have suggested that a pericardial fluid cytology should be done in all patients presenting with cardiac tamponade.<sup>25</sup> The sensitivity for malignant cell detection in a single pericardial fluid sample ranges between 67% and 92%,<sup>31</sup> a variation too wide to rule out PND. Cytology is useful to establish some other pericardial effusion etiologies as viral, bacterial, tuberculosis, fungal, and cholesterol.<sup>22</sup>

The histology features observed in pericardial carcinoma typically are detached cell clusters with fibrinous/hemorrhagic exudates. The two most common histology types seen in pericardial malignancies are adenocarcinoma and large cell carcinoma. The most common diagnosis is carcinoma of the lung (90%), although in some cases the primary site will not be defined with certainty.<sup>32</sup>

A false negative pericardial fluid cytology and pericardium biopsy are likely to occur in patients with a nondiffuse PND such as those arising through direct extension from contiguous thoracic malignancies. In these cases, pericardioscopy enables an adequate inspection of parietal and visceral pericardium, allowing procurement of guided biopsies by identifying areas of abnormal macroscopic appearance. According to Seferovic et al., the diagnostic value of pericardioscopy-guided biopsies increases whenever an extensive sampling is accomplished.<sup>33</sup>

## Treatment

Current literature shows a controversial MPE therapy. Treatment selection is based on a patient's life expectancy, tumor type, tumor response to chemotherapy and radiotherapy, and the presence or absence of cardiac tamponade at the moment of diagnosis. The main treatment options are pericardiocentesis, pericardial sclerosis, systemic chemotherapy, radiotherapy, and surgical treatment. The latter shows a failure rate of less than 5%.<sup>3</sup>

Leading indications for pericardiocentesis are the need for immediate relief of symptoms and mechanical restraint of large pericardial effusions and cardiac tamponade.<sup>10</sup> However, this procedure has a low MPE control rate (31%-38%), and there is

typically reaccumulation of pericardial fluid within 48 hours following the initial intervention.<sup>31</sup> Because of its simplicity and low complication and mortality rates (2.9% and 0.7%, respectively), pericardiocentesis may be the ideal treatment option for terminal cancer patients with short life expectancy who develop MPE and cardiac tamponade.<sup>34</sup>

Thoracoscopy, median sternotomy, left anterior thoracotomy, or a subxiphoid approach can all be considered for surgical treatment of MPE and malignant cardiac tamponade. Thoracoscopy and open-thoracic approaches allow better access to loculated pericardial effusions and both pericardial and pleural cavities, thus permitting the assessment of synchronous pericardial and pleural effusions in cancer patients. Still, these approaches significantly increase morbidity and mortality due to the need for general anesthesia,<sup>35</sup> making the subxiphoid approach the procedure of choice since it only requires local anesthesia. The surgical approach is usually dependent on the experiences of individual institutions and practitioners.

MPE and malignant cardiac tamponade patients may be treated with a simple subxiphoid pericardiotomy, which is a safe, effective, and low-cost procedure with a low morbidity rate. However, long-term management for these pericardial diseases remains open to discussion. Medical literature favors the creation of a pericardial window using any of the aforementioned surgical approaches.<sup>1,36</sup> A pericardial window is considered by some authors as the standard treatment for long-term drainage due to acceptable effectiveness, low complication rate, and pericardial effusion control rate ranging between 86% and 92%.<sup>3,12,34</sup> Total pericardiectomy is no longer advised due to an excessive operative risk.<sup>1</sup>

Radiotherapy has proven to be effective against leukemia and lymphoma PND, with a response rate of 50% to 60%,<sup>34</sup> although the observed improvement is limited and effusion recurrence is frequent.<sup>37</sup> These malignancies have good response to chemotherapy and should precede radiotherapy if feasible. At present, radiotherapy is not considered an advisable treatment for PND.<sup>12</sup>

Intrapericardial instillation of a sclerosing and chemotherapeutic agent is increasingly used in Europe as a long-term palliative treatment for MPE; the most widely studied agent for this treatment modality is tetracycline, which achieves successful long-term control of MPE although it is associated with chest pain, fever, and arrhythmias.<sup>12</sup> Thiotepea seems to be effective in suppressing MPE as it provides both antineoplastic and sclerosing effects without chest pain, myelosuppression, or ECG changes.<sup>38</sup> Many other agents have been proposed for this purpose: doxycycline, mitomycin C,<sup>14</sup> cisplatin,<sup>2</sup> carboplatin, vinblastine, mechlorethamine hydrochloride, 5-fluorouracil, talc, and bleomycin, among others.

In the United States, this treatment option has been neglected due to the associated side effects. Furthermore, true efficacy of this treatment cannot be established as most of the related data are case reports. The reported failure rate is usually as high as 20%, and an effusion recurrence may be observed within the 30 days after treatment.<sup>34</sup>

## Prognosis

Patients with metastatic involvement of the pericardium usually have a poor prognosis;<sup>11</sup> therefore, determining the etiology of a pericardial effusion becomes crucial in cancer patients. The histologic type of the underlying malignancy, along with neoplasm extension, is a central factor in determining expected survival and quality of life.<sup>39</sup> There is a very limited life expectancy whenever

cardiac tamponade appears as the first manifestation of PND.<sup>1</sup> Malignant cardiac tamponade represents a life-threatening situation and, when not treated appropriately, invariably results in acute cardiac failure for terminal patients. Life expectancy for patients with PND is less than 4 months at diagnosis,<sup>7</sup> and regardless of the therapy selected, less than half of all cases will survive more than 2 months whenever sudden cardiac tamponade constitutes the initial manifestation.<sup>40</sup>

## Conclusion

Cardiac tamponade rarely constitutes the initial clinical manifestation of pericardial malignancy in cancer patients, and it is exceedingly rare as a very first manifestation of neoplastic disease not previously diagnosed, whether primary or metastatic to pericardium. However, as we report, sudden manifestation of large pericardial effusions and cardiac tamponade secondary to malignant processes may occur, with the patient initially displaying symptoms that suggest AMI, such as severe shortness of breath, dizziness, and chest tightness.

Malignancy should always be considered in every patient with pericardial effusion or cardiac tamponade of unknown etiology, and cytology analysis of pericardial fluid along with pericardial biopsy should be performed.

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