

Pericardial Disease in Patients with Cancer

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Abstract

Pericardial effusion can develop in patients with acute pericarditis or in association with a wide variety of systemic diseases and is characterized as transudative, exudative, pyopericardium, or hemopericardium. Large effusions are usually related to tuberculous or neoplastic effusions. Primary pericardial tumors are rare, with the vast majority of cases resulting from secondary tumors. Pericardial effusion may be present in 7% to 53% of patients with cancer and is correlated with an advanced stage of the disease. The main types of cancer related to pericardial involvement are lung, breast, blood, and gastrointestinal cancers. The clinical presentation is variable; some patients are asymptomatic, whereas up to one-third may develop cardiac tamponade. In general, the severity of pericardial effusion ranges from moderate to significant, and the diagnostic process should focus mainly on the search for the primary disease and on the hemodynamic condition. The presence of pericardial effusion portends a grave prognosis, and treatment depends on the malignancy. Interventional treatments in patients with cancer include pericardiocentesis, pericardial window, and surgical pericardiectomy.

Introduction

The pericardial space consists of a potential cavity between the visceral and parietal peritoneum, which contains approximately 15 mL to 50 mL of plasma ultrafiltrate. The pathological accumulation of fluid in the pericardial space is called pericardial effusion (PE). PE is a common disease with a broad clinical spectrum, ranging from small asymptomatic effusions to cardiac tamponade.^{1,2} The main pericardial syndromes are acute or chronic pericarditis, PE, and constrictive pericarditis.

PE etiology basically depends on the clinical presentation of the patient. The main causes include infections (viral,

tuberculosis), cancer (lung, breast, lymphoma), rheumatic diseases (lupus, rheumatoid arthritis), metabolic diseases (uremia, hypothyroidism), aortic dissection, and postcardiac injury syndromes (postinfarction, postpericardiotomy).³ In addition, the increasing number of invasive procedures has led to an increase in the rates of iatrogenic strokes, which result from myocardial perforation during pacemaker implantation, radiofrequency ablation, or cardiac catheterization.⁴

Etiology Pericardial Effusion

Corey et al.⁵ evaluated 57 patients with PE > 10 mm and reported that the most frequent etiology was infectious (27%), followed by neoplastic (23%). In a study of 322 patients with PE > 10 mm,⁶ the most frequent etiology was idiopathic (29%), followed by iatrogenic (16%) and neoplastic (13%); 37% of participants developed cardiac tamponade. A study by Levy et al.⁷ evaluated 204 patients with PE, and the most frequent etiologies were idiopathic (48%), infectious (16%), and neoplastic (15%). In our study of 254 patients with PE, the most common etiology was idiopathic (33.1%), followed by postsurgical (19.3%), neoplastic (16.9%), and postprocedural (8.7%).⁴

The clinical context in which PE occurs provides important diagnostic clues, such as the presence of cancer, collagenosis, tuberculosis, myocardial infarction, acute pericarditis, hypothyroidism, or renal failure.⁷

In patients with small PEs and no hemodynamic repercussions, inflammatory signs, or suspected potentially treatable systemic diseases, etiological investigation is usually unnecessary. In these cases, clinical evaluation and serial echocardiography are sufficient.²

Epidemiology

Primary pericardial tumors are rare, with the vast majority of cases resulting from secondary tumors. PE may be present in 7% to 53% of patients with cancer and is correlated with an advanced stage of the disease.^{8,9} Related mechanisms are implantation of tumor cells in the pericardium by direct extension, hematogenous or lymphatic dissemination of the primary tumor, chemotherapy- or radiotherapy-induced toxicity, and opportunistic infection related to cytotoxic immunosuppression and rapid immune response.¹⁰⁻¹²

In most cases, PE is secondary to a primary tumor. Cancers more typically associated with pericardial involvement are lung, breast, blood (mostly lymphoma and leukemia), and gastrointestinal cancers.¹³ Similarly, cardiac tamponade could be present in 32% of cases, with a recurrence rate of 10%.¹⁴

Keywords

Etiology Pericardial Effusion

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In our series, the most frequent type was lung cancer, followed by lymphoma and breast cancer.¹⁵

PE in patients with cancer has prognostic value. According to the results of the study by Wagner et al.,¹⁶ carried out in a tertiary care center for patients with cancer, 11% of those with PE undergoing surgical drainage had hemodynamic instability (pressor-dependent hypotension requiring intensive care unit admission), which portends a grave prognosis with a median survival of 35 days after the procedure.

Clinical presentation

The clinical presentation of PE is variable, ranging from asymptomatic patients to patients with nonspecific complaints and those with systemic symptoms typical of the underlying cancer, such as weight loss, asthenia, cough, palpitations, hemoptysis, malaise, weakness, fatigue, and nausea and vomiting. Up to one-third of patients may develop cardiac tamponade with clinical presentation of jugular distention, muffled heart sounds, hypotension, and paradoxical pulse (a drop in systolic blood pressure of 10 mm Hg during inspiration). Other possible symptoms are tachycardia, pericardial friction rub, arrhythmia, ascites, and peripheral edema.^{12,17}

Diagnostic tests

Electrocardiogram

Although electrocardiographic findings are usually normal, the most frequent changes found in patients with cancer and PE are sinus tachycardia and low QRS voltage in the presence of cardiac tamponade (61% of cases), which is defined as amplitude < 0.5 mV in limb leads. Occasionally, new-onset atrial fibrillation and electrical alternans may also be found.^{10,17}

Chest radiography

Although chest radiography is not highly specific, it may show an enlarged heart, which is suggestive of significant PE. It may also show other findings, such as pleural effusion and abnormalities in the lung parenchyma.¹⁸

Echocardiogram

Transthoracic echocardiography is the most available and efficient method for diagnosing PE and is useful for managing pericardiocentesis. PE can be identified on m-mode by the presence of an echo-free space between the epicardium and parietal pericardium; the presence in both systole and diastole suggests PE > 50 mL. Likewise, PE can be distinguished from pleural effusion by analyzing the parasternal window on 2D short-axis view, which shows the PE between the descending aorta and the heart. PEs are classified as small (50 to 100 mL), moderate (100 to 500 mL), or large (> 500 mL).

On the echocardiogram, signs of cardiac tamponade include “swinging heart”, diastolic collapse of the right atrium and ventricle, left atrial compression, increased respiratory changes in tricuspid and mitral flow velocities, and inferior vena cava regurgitation.¹⁹

Tomography and cardiac magnetic resonance imaging

Tomography and cardiac magnetic resonance imaging (CMRI) are quite useful in the differential diagnosis of PE. They may show enlargement of the inferior vena cava and hepatic veins, compression of the cardiac chambers, septal bounce, and reflux of contrast material into the azygos vein or inferior vena cava. These methods can also be used to evaluate pericardial thickening or calcifications, cysts, and masses, as well as to provide information on the possible nature of PE based on attenuation measurements. On CMRI, hemorrhagic fluid is characterized by low intensity signals on T1-weighted images and high intensity signals on cine images with steady-state free precession.^{12,19,20}

Other imaging methods

Right-sided cardiac catheterization contributes to the diagnosis of cardiac tamponade because it provides important information, such as increased right atrial pressure and equalization of pressures between multiple chambers (right atrium, right ventricle, and pulmonary capillary wedge pressure).²¹

The diagnosis of effusive-constrictive pericarditis is made when right atrial pressure does not fall by 50% or to a level lower than 10 mmHg after pericardiocentesis, when other causes that may elevate right atrial pressure, such as right ventricular failure or tricuspid regurgitation, have been excluded. Such condition may be found in patients undergoing radiation.

Cytological study

In patients with suspected malignant PE, cytological evaluation of pericardial fluid helps to diagnose the condition.²² Pericardial biopsy (PB) with fluid cytology helps to reach a definitive diagnosis in 48% to 93% of cases.^{23,24} However, a negative result does not rule out malignancy, given that PB typically analyzes only one sample, which could be a false negative, and results also depend on the experience of the examiner. PB can be performed through subxiphoid pericardiostomy (window) or pericardioscopy; the latter directly evaluates the pericardial space, increasing the sensitivity of the biopsy.^{5,25}

Immunohistochemistry (IHC) staining in combination with clinical and morphological characteristics provides a more specific diagnosis, which may eliminate the need for more invasive tissue sampling. IHC allows differentiating between a mesothelial or epithelial origin of isolated atypical cells and cell clusters, in addition to identifying the primary site of malignancy in patients with a history of multiple malignancies or a previously unidentified primary site.²⁶

Treatment

There is currently no defined treatment for PE in patients with cancer.^{2,27} The presence of PE portends a worse prognosis, and treatment depends on the underlying cancer.^{28,29}

In patients with cancer with PE and no secondary pericardial implants, the treatment should focus on the malignancy, with indication for pericardial intervention in symptomatic cases

(especially chest pain) and in patients with hemodynamic instability and signs of cardiac tamponade.³⁰⁻³² Many patients with cancer-related PE are asymptomatic and do not require specific treatment for PE.^{33,34}

Surgical treatments in patients with cancer include pericardiocentesis, prolonged catheter drainage, pericardial window, and pericardiectomy.^{15,35-39} In cases with recurrent PE or cardiac tamponade, pericardial window is an interesting option.^{15,38,39} It involves creating a real window by a partial pericardiectomy, thereby creating a channel to allow for long-term drainage to an adjacent space, usually the pleural cavity.⁴⁰

For patients with recurrent PE requiring multiple approaches, some options are possible. Intrapericardial instillation of cytostatic/sclerosing agents can be considered in the management of malignant PEs.^{35,36}

Several components have already been evaluated for pericardial instillation, such as tetracyclines, bleomycin, and sterile talc powder. These drugs rapidly form pericardial adhesions that obliterate the pericardial space and control effusion recurrence.³⁷ Despite the high success rate of these interventions, with a good safety profile and low morbidity,³⁶ the side effects resulting from chemical pleurodesis still limit their routine indication. The main side effects result from induced inflammation, which can lead to fever, pleuritic chest pain, and atrial fibrillation.^{15,36-39}

Conversely, pericardial injection of drugs, although effective for pericardial tamponade and recurrent PE, can only relieve symptoms temporarily.⁴⁰

Systemic chemotherapy is effective for lymphoma and small cell lung cancer, which are sensitive to chemotherapy drugs. Immunotherapy has recently shown promising results in the treatment of neoplastic PE, constituting a new treatment option for these patients.⁴⁰

Another possible line of treatment is immunomodulatory monoclonal antibodies against vascular endothelial growth factor receptors. Several recent studies have reported that, in patients with malignant PE, bevacizumab appears to be more effective than conventional chemotherapy drugs such as platinum and sclerosing agents.^{41,42}

The indication for radiotherapy is extensive pericardial infiltration of encapsulated or unresectable cardiac tumors, such as mediastinal tumors.⁴⁰

Pericardial disorders and risk of cancer

Some studies have drawn attention to an increased risk of cancer in patients diagnosed with pericardial conditions.^{8,42,43} In a population-based cohort study using data from the UK Clinical Practice Research Datalink, pericarditis was associated with an increased subsequent risk of cancer (HR 3.03, 95% CI 2.74-3.36), and this association was particularly evident within 3 months of pericarditis diagnosis.⁸

In a Danish national cohort study, of 13,759 patients with acute pericarditis, 1,550 were subsequently diagnosed with cancer during follow-up. The cancer incidence rate was 1.5 (95% CI 1.4-1.5), with increased rates of lung, kidney, and bladder cancer, lymphoma, leukemia, and unspecified metastatic cancer.⁴³

It is unclear whether this finding is related to an etiologic misdiagnosis of pericarditis in the presence of PE. Therefore, it seems reasonable to justify investigations focused on patients with cancer who present with pericarditis/PE in combination with advanced age, obesity, and need for hospitalization.

Author Contributions

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This article does not contain any studies with human participants or animals performed by any of the authors.

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