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Neoplastic Pericardial Disease

Mitja Letonja
Medical Faculty Maribor, General Hospital Ptuj, Slovenia

1. Introduction

Malignant pericardial disease represents a common cause of morbidity and mortality in patients with cancer. Malignant tumours of the pericardium may occur as primary or secondary tumours. Primary tumours of the pericardium occur rarely, and secondary involvement of the pericardium constitutes the majority of the cases of malignant disease of the pericardium. In necropsy series, the pericardium is involved in 5 to 40% of patients with malignant disease (1-3). Autopsy studies overestimate the clinical problem because they mostly include terminally ill patients and also identify microscopic metastases even without pericardial effusion. For the majority of patients, a clinical manifestation of neoplastic pericarditis is absent or remains unrecognised during their lifetime. In a study comparing clinical and pathologic features of pericardial metastases, 60%-70% were clinically non significant (4). Clinically, neoplastic pericarditis presents itself as acute pericarditis, pericardial effusion, effusive-constrictive pericarditis or cardiac tamponade (5). In their retrospective analysis from the years 1979 to 2000, the Mayo Clinic reported a decrease of the prevalence of cancer among symptomatic pericardial effusion, mainly due to an increase of pericardial effusion due to postoperative procedures or perforations from invasive procedures, rather than to a decrease of malignant pericarditis cases (6). A Spanish study observing the years 1998-2002 and an Italian study observing the years 1996-2003, report a neoplastic etiology among pericardial effusion in 13% and 7.3%, respectively (7,8). The relative proportions of neoplastic pericarditis in particular population depends on the prevalence of cancer and the prevalence of other causes of effusion in particular populations.

2. Clinical picture

Clinically, neoplastic pericarditis can be presented as acute pericarditis where at least 2 criteria of the following 4 should be present: 1. characteristic chest pain; 2. pericardial friction rub; 3. suggestive electrocardiographic changes; and 4. new or worsening pericardial effusion (9). Neoplastic pericarditis is also manifested as effusive-constrictive pericarditis where the diastolic filling is limited by the by restricted inelastic pericardium, which is inflamed, scarred, or calcified and thicker than normal. Two other clinical pictures are pericardial effusions and cardiac tamponade (4,10). In rare cases, pericardial effusion is the initial manifestation of malignancy, and the first review of 29 isolated cases of cancer first manifested with pericardial effusion was published by Fraser in 1974

(11,12). Reports of cardiac tamponade as an initial presentation of malignancy are even much less prevalent, but we report a patient with cardiac tamponade as the first manifestation of lung cancer, although the occurrence of malignant cardiac tamponade is underestimated due to non-specific signs and symptoms (13,14). Acute dyspnea is the most commonly presented symptom in a review of malignant tamponade pooling several series with an incidence of 78%. The other reported symptoms were cough (46%), chest pain (27%), orthopnea (26%), and weakness (19%). On physical examination the most frequently detected findings are sinus tachycardia (50%), jugular venous distention (45%), hepatomegaly (36%) and peripheral edema (35%). Classical findings of pericardial tamponade such as pulsus paradoxus, pericardial rub and Kussmaul's sign – occurred in only 30%, 12% and 5%, respectively (13-15). Despite the assumption that patient presented with tamponade have a worse prognosis than the patient with pericardial effusion without tamponade, no data are available to allow the stratification of the prognosis based on clinical presentation.

3. Diagnosis

The ECG changes were suggestive of pericardial involvement in some patients. There are reports of sinus tachycardia which is usual in terminal malignancy, but should also be considered as an important sign of cardiac involvement. The presence of low voltage in limb leads, non-specific T-wave abnormalities, ST-segment elevation, atrial fibrillation and electrical alternans are neither common nor specific findings for malignant pericardial effusion (5). The chest x-ray showed non-specific cardiomegaly and indicates at least 200 ml of pericardial fluid (16). Pleural effusion is presented in more than half of the patients in literature (5). The echocardiogram documented the presence and magnitude of pericardial effusion which is detected as an echo-free space between the left ventricular posterior wall and the lung. As effusion grows in size, we observed besides the echo-free space the swinging of the heart, and abnormal septal motion. Echocardiography differentiates cardiac tamponade from other causes of systemic venous hypertension and arterial hypotension, including constrictive pericarditis, cardiomyopathy and right ventricular infarction. Typical echocardiographic findings in tamponade include late diastolic collapse of the right atrium and early diastolic collapse of the right ventricle when the intrapericardial pressure exceeds intracavitary pressure. Left atrial collapse, which can occur in tamponade, is very specific but is not sensitive for tamponade. Abnormal septal motion is described with bulges of the intraventricular septum during inspiration into the left ventricle due to an increased systemic venous return to the right ventricle and a limited expansion of the right ventricular free wall due to the increase in intrapericardial pressure. With expiration, the transmitral pressure gradient increases and the systemic venous return decreases and we observe a reversal of diastolic flow in the hepatic veins (17). Echocardiography also guides pericardiocentesis (18). Cardiac computed tomography (CT) and cardiac magnetic resonance imaging (CMR) are increasingly being used in the diagnosis of pericardial diseases. Both imaging modalities are very sensitive in the detection of generalised or loculated effusions and can also be used to measure the pericardial thickness (19).

Pericardial effusions in patients with cancer are not always due to malignancy. Other causes of pericardial effusion are radiation-induced, idiopathic, hypoalbuminemic, drug-related or uremic (5). Defining the cause of a pericardial effusion in a patient with cancer is of vital

importance. The gross appearance of the pericardial fluid is not useful in differentiating malignant from non-malignant effusion (20). A cytological examination of pericardial fluid confirmed the diagnosis of malignant pericardial effusion in 65% to 85% of cases (21). Even with accurate sampling and cytopreparatory techniques, the diagnosis is not always simple, and sometimes impossible. In cytology-negative samples of pericardial fluid the dosage of tumour markers such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), serum cytocheratin 19 fragments (CYFRA 21-1) and carbohydrate antigens CA 125, CA 15-3 and CA 19-9 may be helpful in the setting of an equivocal diagnosis (22). However, there is no tumor marker that alone has sufficient diagnostic accuracy in discriminating between malignant and benign pericardial diseases. Measuring a panel of tumor markers as was proposed for the diagnosis in pleural effusion also does not provide a much higher sensitivity. At present, for the confirmation of the diagnosis of malignant pericardial effusion, there is a firm recommendation for the assessment of CEA and CYFRA 21-1 (23-26). Open pericardial biopsy or pericardoscopy with visualisation of the pericardial surface and guided biopsies of suspicious areas can identify most of the remaining cases (5). A search for the primary tumour must be undertaken because metastases to the pericardium are much more common than the primary tumour and furthermore, primary tumors of the heart are far less common than metastatic tumours to the heart. Primary tumours of the pericardium are usually sarcomas or mesotheliomas (27,28). The metastatic cancer is most often carcinoma of the lung (40%), breast (22%), leukemia and lymphoma (15%), sarcomas (3.5%) and melanoma (2.7%) (10).

The reason for the heart and the pericardium not being affected by primary cancer, and cardiac tissue mostly being invaded by the metastatic process can probably be explained with the concept of immune privilege which was first proposed in the 1940s by the Nobel laureate, P.B. Medawar and colleagues. At present, the eye, brain and reproductive organs are endowed with immune privilege where inflammation is self-regulated so as to preserve organ functions (29,30). There are also a lot of reports which might indicate self-regulated inflammation of the heart and pericardium as well. The reaction of cardiac tissue to acute injury involves interacting cascades of cellular and molecular responses that encompass inflammation, hormonal signalling, extracellular matrix remodelling, and compensatory adaptation of cardiomyocytes. There is a significant importance of acute inflammation occurring during acute myocardial infarction where the infarct scar is a dynamic tissue: cellular, vascularised, metabolically active and contractile. Although the induction of pro-inflammatory mediators is important for the clearance of the wound from dead cardiomyocytes and matrix debris, the activation of inflammatory pathways is transient and followed by the repression of inflammatory gene synthesis and the resolution of the leukocytic infiltrate (31). There is also evidence of heart specific cardiomyocytes apoptosis and changes in interstitial tissue of the heart in the progression of heart failure, as in hypertension, myocarditis and after myocardial infarction. Ongoing inflammation is of great importance in chronic heart failure. The marker of inflammation, the C-reactive protein (CRP), is elevated in chronic heart failure and is produced by the liver in response to cytokines such as IL-1, IL-6, and TNF-alpha. Inflammatory cytokines and chemokines plays an active role in cardiac deterioration in chronic heart failure through the induction of endothelial dysfunction and apoptosis of cardiomyocytes (32,33). Therefore, a chronic inflammatory response in heart and vessels also produces different end stage complications compared to other tissue and due to their close interaction with angiogenesis, apoptosis and

cell proliferation. Cardiac tissue specific immune response may also influence carcinogenesis (34). Plausible immune privilege of the heart and pericardium can also be due to the complex structure of the lymphatic system in the heart, which is a three-tiered structure: the subepicardial, the myocardial and the subendocardial nets and drain from the heart to the mediastinum. Considering that lymphatics represent the major route to cardiac metastases, a blockade of the common lymphatic node by neoplastic cells coming from the metastasised mediastinum lymph nodes is a key event leading to the formation of metastases (35). Immune privilege might explain the relatively low incidence of secondary tumors in the heart compared with other organs.

4. Treatment

The ideal treatment for pericardial effusion ensures the complete removal of fluid, relives tamponade if present and therefore relives symptoms. Other goals in the treatment are to prevent recurrent effusion and treat the local neoplastic disease with the aim of prolonging survival.

Pericardiocentesis using the Seldinger technique is successful in removing fluid and alleviating symptoms in 97% of patients, with 3% of major complications (6,36). There is only a sporadic report on the rate of recurrence of pericardial effusion which was reported to be 40%, without additional treatment (36,37). The number of patients reported in literature not receiving any additional therapy is too small to make a firm conclusion of the spontaneous re-accumulation rate of malignant effusion after pericardiocentesis (38-41). Tsang et al. reported of reducing the rate of recurrence by extending the drainage for several days (6,37). The indwelling pericardial catheter was left in place in the study of Gatenbey et al. for 4.8 days (42), but in the majority of studies it was used in conjunction with systemic therapy or sclerosing agents.

The rationale for sclerosing therapy is to prevent the recurrence of effusion by creating adhesions of the visceral and parietal pericardium. Antibiotic agents doxycycline and previously tetracycline were first used as pure sclerosing agents for this purpose with short-term efficacy in preventing early recurrences (43,44-46). It should be noted, however, that the effusion control of tetracyclines is only due to sclerosing activity and not to specific antineoplastic action. Tetracyclines have many adverse effects and a potential for the development of the constrictive pericarditis secondary to fibrosis in long-term survivors (table 1). The OK-432, an immunomodulator available in Japan has been used in small group of patients with neoplastic pericarditis. Despite that, the OK-432 has the ability to stimulate cell-mediated immunity and besides the direct cytotoxic effect against malignant cells it has no significant advantages over other agents. The OK-432 also has common side effects (47). Bleomycin and thiotepa are anticancer agents with sclerosing properties and are used for local therapy with good results and few side effects (45,48-52).

The rationale for intrapericardial instillation of the antineoplastic drug is to provide a high and long-lasting concentration of the intrapericardial drug. Various chemotherapeutic agents have been used for local chemotherapy with the purpose to prevent recurrent effusion or prolong the effusion-free period and prolong survival. The use of intrapericardial cis-platinum was first reported in 1985 and after that drug was often used (41,53-57). Nitrogen mustard, mitomycin C, mitoxantrone and 5-fluorouracil have also been used intrapericardially (58-62). The reported experiences with sclerosing agents and

chemotherapeutic agents are summarized in table 1. Lestuzzi et al. have suggested a "tumour specific" treatment algorithm for neoplastic pericardial effusion in which he preferred cisplatin in pericardial lung carcinoma metastases and bleomycin in pericardial breast carcinoma metastases. Authors reported a low complication rate and significant effectiveness of local chemotherapy. On the basis of personal experience and the review of literature, they conclude that sclerosing therapy should not be considered as the first choice

Itrapericardial treatment (references)	Chemical natures and action	Treatment success (%)	Current use	Side effects and complications
Tetracycline or Doxycyline (43-46)	Antibiotics sclerosis	73-75	–	Severe pain (15-70%) Atrial arrhythmias (9-10%) Fever (7.5-50%) Infection (0.5%) Constriction (2%)
OK-432 (47)	Immunomodulator	70	–	Fever (60%) Pain (50%)
Bleomycin (45,48,49)	Antineoplastic agent, Antibiotic Inhibits synthesis of DNA and sclerosis	71-100	++	Constriction (2.4%) Fever (18%) Atrial fibrillation (9%)
Thiotepa (50-52)	Antineoplastic agent, Alkylating agent	79-91	+	Thrombocytopenia (0.9%) Leucopoenia (0.9%)
Mitomycin C (58)	Antineoplastic agent, Antibiotic Act like an alkylating agent	70	+	Constriction after several months (5%)
Mitoxantrone (59)	Antineoplastic agent, Anthracenedione Inhibits DNA and RNA synthesis	60	+	None
Cisplatin (41,42,53-57)	Antineoplastic agent, Alkylating agent Inhibits DNA synthesis	50-100	++	Nausea (6.7%) Atrial arrhythmias (4.4%) Constriction (1.1%) Myocardial ischemia (1%)
Nitrogen mustard (60,61)	Antineoplastic agent, Alkylating agent Inhibits DNA and RNA synthesis	100	–	Pain (% no report) Nausea (% no report) Vomiting (% no report) Leucopenia (% no report) Fever (% no report)
5-Fluorouracil (62)	Antineoplastic agent, Pyrimidine analogue-Antimetabolite Interferes with DNA and RNA synthesis	100	–	Nausea (% no report) Leucopenia (% no report) Premature beats (% no report)

Table 1. ·

therapy for malignant pericardial effusion because the goal of treatment is not simply to mechanically prevent the accumulation of pericardial fluid, but trying to cure pericardial metastases (63).

Systemic chemotherapy and radiation therapy are successfully used in breast cancer and leukemia and lymphoma after the initial pericardiocentesis to prevent the recurrence of effusion and to treat primary cancer (37-39). In cases of recurrent effusion and persistent symptoms various surgical drainage procedures are available. Total pericardiectomy is seldom performed today for pericardial effusions associated with malignancy because the operative risks are too high. Recent literature favours the creation of a pericardial window either by thoracotomy, by a subxiphoid route, or by thoracoscopy (40).

The epidemiology, therapy, and prognosis of neoplastic pericarditis have changed over time. The comparison of many observational studies is misleading, since in the largest studies, different tumours and/or different treatments were analyzed together. The most important bias in the articles reporting the efficacy of various local treatments is the concomitant use of systemic chemotherapy.

5. Conclusion

Clinical suspicion of pericardial involvement is crucial for the identification of a patient with neoplastic pericarditis because of non-specific symptoms and signs and because chest x-ray, ECG and even echocardiographic findings are not 100% sensitive or specific either. Pericardiocentesis provides the diagnosis and offers this group of patients immediate relief, but trials with various chemotherapeutic agents and radiotherapy, in addition to the new surgical procedure will hopefully change the survival rate for this group of oncologic patients.

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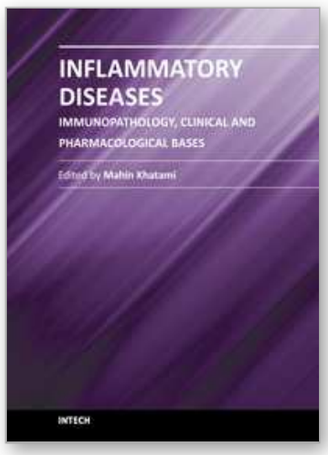

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