Large Hemorrhagic Pericardial Effusion

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ABSTRACT: **Background:** Establishing the etiology of a large pericardial effusion is of crucial importance since it is likely the result of a serious underlying disease. However, there is a paucity of literature on the diagnostic management of patients with large hemorrhagic effusions.

Objectives: To analyze the management of patients with large hemorrhagic pericardial effusion.

Methods: We reviewed seven cases of large hemorrhagic pericardial effusions hospitalized in Soroka University Medical Center in 2010.

Results: All seven patients underwent a comprehensive evaluation followed by pericardiocentesis. Six of the seven cases demonstrated echocardiographic signs of tamponade. Large amounts of hemorrhagic pericardial effusion (› 600 ml) were aspirated from each patient. A pericardial window was performed in two of the seven patients. The causes for the hemorrhagic effusions were malignancy, streptococcal infection, familial Mediterranean fever exacerbation, and idiopathic. Four patients completely recovered. The condition of one patient improved after initiation of chemotherapy for lung cancer, and two patients with progressive malignancies passed away shortly after discharge. Two cases of massive pulmonary embolism were diagnosed and resolved spontaneously without anticoagulation therapy after the effusion was treated.

Conclusions: All cases of pericardial effusion resolved after rapid diagnosis and initiation of specific treatment. Pulmonary embolism in situ may be a complication of large pericardial effusions that does not require anticoagulation treatment after the effusion resolves.

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KEY WORDS: large hemorrhagic pericardial effusion, pericardiocentesis, pericardial window

Pericardial disease and a variety of systemic disorders may lead to the development of pericardial effusion. Establishing the etiology of pericardial effusion is important for prognosis (e.g., malignancy), treatment (e.g., acute pericarditis, autoimmune disease, tuberculosis), or both (dissection of the ascending aorta, iatrogenic causes). The etiology of pericardial effusion varies in published reports, depending in part on geographic location, patient population, and the indications for pericardiocentesis [1-4]. The cause of pericardial effusion is often recognized by the clinical context in which it occurs [1], and the likelihood of establishing a specific diagnosis appears to increase with larger effusions (90% of cases) [2].

Establishing the etiology of a large pericardial effusion is of crucial importance because it can be life-threatening; it is more likely the result of a serious illness, and the diagnosis can be made relatively easily and safely [3]. Most cases of "acute idiopathic pericarditis" with small effusions are of short duration and have a low mortality rate [3,5]. Therefore, pericardiocentesis of small effusions is of less diagnostic importance. The most common causes of moderate to large pericardial effusions are iatrogenic, infection, malignancy, chronic idiopathic effusion, post-acute myocardial infarction, autoimmune disease, radiation, renal failure with uremia, and hypothyroidism [1,3,4,6]. A comprehensive systemic evaluation in combination with fluid and tissue analysis following subxiphoid pericardiotomy yields a diagnosis in the majority of patients with large pericardial effusions [2]. Rapid diagnosis of these diseases may lead to earlier therapy and improved survival.

Patients with hemorrhagic pericardial effusions have a somewhat different distribution of etiologies, although the overlap with serous effusions is significant. The most frequent causes of bloody pericardial effusions are: malignancy, post-procedural (transcatheter interventions and pacemaker insertion), post-pericardiotomy syndrome, complications of myocardial infarction, idiopathic, uremic, aortic dissection, and trauma [6,7]. In addition, tuberculosis is a frequent cause of hemorrhagic effusion in endemic areas [7-10].

Pericardial fluid can be sampled or drained either by closed needle pericardiocentesis or via surgical incision. The 2004 European Society of Cardiology guidelines on the diagnosis and management of pericardial diseases recommended percutaneous pericardiocentesis in patients with tamponade. Surgical intervention was recommended only in patients with very large chronic effusions in whom repeated pericardiocentesis was not effective. An open surgical procedure is required for pericardial biopsy [11].

Pericardial effusions may persist for extended periods and can also recur. The management in these settings is based on the treatment of the underlying disorder. Percutaneous drainage of the effusion is reserved for hemodynamically significant or persistently symptomatic effusions [12].

PATIENTS AND METHODS

The purpose of our study was to assess the management of patients with large hemorrhagic pericardial effusion. We performed a retrospective cohort study that included all patients with large hemorrhagic pericardial effusion who were hospitalized in 2010 at the Soroka University Medical Center, the only tertiary academic medical center serving the southern part of Israel.

All patients included in the study were hospitalized in the medical or thoracic surgery department of the medical center. Each patient was assessed by a comprehensive systemic evaluation followed by pericardiocentesis according to the recommendations of the 2004 European Society of Cardiology guidelines for the diagnosis and management of pericardial disease [11]. Large amounts of hemorrhagic pericardial fluid were aspirated from each patient and samples were sent for laboratory analysis.

Pericardiocentesis was performed by experienced medical personnel: thoracic surgeon or invasive radiologist. The pericardial window was performed by a thoracic surgeon according to accepted guidelines for this procedure. Patients' records, radiology and laboratory studies, and pathology specimens of pericardial fluid were reviewed. Patient follow-up was performed 6 months after discharge from the hospital. The study was approved by the Institutional Review Board prior to its initiation. Confidentiality was maintained throughout the study.

RESULTS

In 2010 in our medical center pericardiocentesis was performed in 24 patients with large pericardial effusion. Seven of the patients who had a hemorrhagic pericardial effusion were included in the study.

Our cohort consisted of five men and two women with

Table 1. Clinical and demographic characteristics of the study patients

Patient	Age (yrs)	Gender	Clinical history prior to hospitalization	Comorbidities	Treatment prior to admission
1	58	M	Chest pain and fever for 1 month	None	None
2	77	M	Chest pain, effort dyspnea, edema of the legs, syncope for 3 wks	• IHD • PAF (without anticoagulation) • DM type 2 • CRF • HTN	Hydrochlorothiazide Lercanidipine Alfuzosin Dutasteride Omeprazole Isosorbide dinitrate Metformin Enalapril Aspirin
3	43	F	Productive cough and dyspnea for several months	Heavy smoking (100 pack/yrs)	None
4	68	M	Dry cough for 2 wks Fever 3 days prior to presentation	• FMF • Gout • PAF (with anticoagulation) • HTN • s/p CVA • s/p nephrectomy due to hypernephroma (2000) • Renal transplantation (2006)	Colchicine Warfarin Amiodarone Tacrolimus Mycophenolic acid Prednisone Aspirin Allopurinol Ramipril Valsartan Carvedilol Doxazosin
5	73	M	Palpitations and effort dyspnea for 2 months Recurrent pericardial effusion	• HTN • TB in the past	Valsartan Hydrochlorothiazide Aspirin
6	53	F	Dyspnea and weakness for several weeks	• HTN • Heavy smoker • (100 pack/yrs)	Atenolol Hydrochlorothiazide
7	53	M	Progressive dyspnea Recurrent pericardial effusion s/p Pericardial window for 2 months	• NSCLCA (2 year history, s/p chemotherapy) • CIHD • HTN • Major depression	Omeprazole Escitalopram Simvastatin Alprazolam Lamotrigine Mirtazapine Oxycodone Prednisone Aspirin

IHD = ischemic heart disease, PAF = paroxysmal atrial fibrillation, DM = diabetes mellitus, HTN = arterial hypertension, CRF = chronic renal failure, CVA = cerebrovascular accident, TB = tuberculosis, NSCLCA = non-small cell lung cancer, CIHD = chronic ischemic heart disease

Table 2. Diagnostic evaluation of the study patients

Patient	Imaging (X-ray, CT study)	Echo study	Pericardiocentesis	Pericardial fluid analysis	Laboratory studies
1	Cardiomegaly, large pericardial effusion, right pleural effusion	Large pericardial effusion with tamponade	800 ml hemorrhagic fluid	Elevated CRP and ASLO	Pleural fluid culture positive for *Streptococcus viridans*
2	Cardiomegaly, small left pleural ffusion, segmentary PE	Large pericardial effusion with tamponade	800 ml hemorrhagic fluid	Blood	Non-contributory
3	Cardiomegaly SOL of lung	Large pericardial effusion with tamponade	850 ml hemorrhagic fluid	Large pleomorphic malignant epithelial cells and positive for CK7, CEA and TTF1	Non-contributory
4	Cardiomegaly	Large, postero-lateral pericardial effusion with borderline tamponade	1000 ml hemorrhagic fluid	Reactive mesothelial cells, blood	Elevated CRP, positive CA 19-9
5	Pericardial and small left pleural effusion	Large pericardial effusion without tamponade	1000 ml hemorrhagic fluid	Blood and many lymphoid cells. Few reactive mesothelial cells. CD 68 positive	Negative studies for TB including pericardial biopsy
6	Large pericardial effusion SOL of the Rt. lung Small bilateral PE	Large pericardial effusion with diastolic collapse of the Rt. ventricle	600 ml hemorrhagic fluid	Groups of cells with features suggestive of adenocarcinoma	Lung needle biopsy: adenocarcinoma of lung
7	Multiple lung metastases Bilateral pleural and pericardial effusion	Large pericardial effusion with partial signs of tamponade	800 ml hemorrhagic fluid	Blood, large malignant cells	Pericardial biopsy: metastatic adenocarcinoma of lung origin

CRP = C-reactive protein, ASLO = antistreptolysin O, SOL = solid occupational lesion, PE = pulmonary embolism, TB = tuberculosis

a mean age of 60.7 years. Their clinical characteristics are detailed in Table 1. All patients in our study were symptomatic on presentation. The initial clinical presentation was subacute or chronic. Five patients had subacute clinical presentation prior to hospitalization. Their clinical picture included cardiac symptoms (chest pain, palpitations, pitting edema of the legs, syncope), respiratory symptoms (dyspnea, cough) and/or general symptoms (fever, weakness). Two patients had chronic symptoms with slow progressive dyspnea and cough for several months prior to hospitalization. Both of these patients had been previously diagnosed with a lung malignancy. Six patients had been on chronic drug therapy for various medical conditions prior to hospitalization. One patient was free of any chronic disease or treatment. The diagnostic evaluation of the study patients is shown in Table 2.

All patients had cardiomegaly on chest X-ray. Computed tomography scan revealed a space-occupying lesion of the lung in two patients and metastatic lung disease in another. In addition, two cases of pulmonary embolism were revealed on CT. All patients were assessed by echocardiography and signs of cardiac tamponade were revealed in six of the seven patients.

Large amounts (600–1000 ml) of hemorrhagic pericardial fluid were aspirated from each patient and samples were sent for laboratory analysis. The pericardial fluid analysis helped to establish a diagnosis in five of the seven patients. Three patients had a malignant effusion, one patient a streptococcal infection and one patient an exacerbation of familial Mediterranean fever. In two of the seven patients a diagnosis was not established and these patients were thought to have an idiopathic pericardial effusion. Diagnosis, management and outcomes of the study patients are shown in Table 3.

Pericardial window by thoracotomy was performed in two of the seven patients. Four patients completely recovered, the condition of one patient with malignant effusion improved after initiation of chemotherapy for lung cancer, and two patients with advanced-stage lung cancer expired shortly after being discharged from the hospital.

DISCUSSION

Large pericardial effusion may be the result of a variety of disease processes. The clinical presentation can be quite variable, ranging from asymptomatic effusions discovered incidentally to a life-threatening emergency where the patient presents with cardiac tamponade [1,2,4,13]. In our study the clinical presentation in the majority of patients (five of seven) was subacute and in two the presentation was chronic. Both of these patients suffered from advanced-stage lung cancer and it is probable that the pericardial effusion developed very slowly, which explains the chronic clinical presentation.

Although pericardial effusion is a very common clinical problem, there is a lack of consensus regarding the approach to both diagnosis and treatment [2]. However, in patients presenting with a large symptomatic pericardial effusion accompanied

Table 3. Diagnosis, management and outcomes

Patient	Diagnosis	Management	Outcome
1	*S. viridans* polyserositis	Pericardiocentesis and antibiotic therapy	Recovered
2	Idiopathic large hemorrhagic pericardial effusion	Pericardiocentesis, symptomatic therapy	Recovered
3	Adenocarcinoma of lung, stage IV	Pericardiocentesis. Patient refused specific carcinoma treatment	Patient died several months later
4	FMF exacerbation	Pericardiocentesis, symptomatic therapy	Recovered
5	Recurrent massive pericardial effusion due to idiopathic pericarditis	Pericardial window by thoracotomy	Recovered
6	Adenocarcinoma of lung, stage IV	Chemotherapy	Recovered
7	Adenocarcinoma of lung, stage IV	Pericardial window by thoracotomy	Patient died 3 weeks after discharge from hospital

FMF = familial Mediterranean fever

by signs of cardiac tamponade it is of crucial importance to take an aggressive diagnostic and therapeutic approach including pericardiocentesis, since it can quickly lead to hemodynamic compromise and a life-threatening condition [2,13].

Establishing the etiology of a large pericardial effusion is of crucial importance [1,3,4,6]. Pericardiocentesis helped establish a specific etiologic cause in the majority of our patients, and the early initiation of appropriate therapy in patients with streptococcal infection, FMF exacerbation and lung cancer was crucial for their management. Although the most common cause of hemorrhagic effusion in patients with signs or symptoms of cardiac tamponade is iatrogenic [7], all patients in our study had a large hemorrhagic pericardial effusion of non-iatrogenic cause. Malignancy of the lung and idiopathic pericarditis are common well-known causes of hemorrhagic pericardial effusion. However, streptococcal infection and FMF are very rare causes. To the best of our knowledge there are no previous reports describing massive hemorrhagic pericardial effusion due to *Streptococcus viridans* infection. In patient # 1 in our study, a previously healthy 58 year old man, a right pleural effusion and massive pericardial effusion with tamponade were demonstrated on CT and echocardiographic studies. Pleural fluid culture was positive for *Streptococcus viridans*. Pericardial fluid was hemorrhagic with elevated C-reactive protein (0.8) and antistreptolysin O > 600. After pericardiocentesis and an appropriate course of antibiotic therapy this patient fully recovered.

FMF = familial Mediterranean fever

It is crucial that tuberculosis be excluded in every patient with a bloody effusion [7-10]. In our study, patient # 5 had had tuberculosis in the past. This patient was diagnosed with recurrent pericardial effusion., but all diagnostic procedures including pericardial biopsy were negative for tuberculosis. Therefore, he was diagnosed with recurrent massive hemorrhagic pericardial effusion due to idiopathic pericarditis. He recovered after a pericardial window was performed by thoracotomy.

Patient # 4 had many comorbid diseases, including FMF, gout, paroxysmal atrial fibrillation with warfarin therapy, renal cell carcinoma with nephrectomy and renal transplantation in the past maintained on immunosuppressive treatment. It is important to note that since the international normalized ratio in this patient was consistently in the therapeutic or subtherapeutic range¸ anticoagulant therapy does not explain a hemorrhagic effusion. Moreover, there was no recurrence of renal malignancy. However, prolonged fever, elevated acute-phase reactants in the blood and in the pericardial fluid, and a good response to increased doses of steroids suggest the inflammatory nature of pericardial effusion and, in particular, FMF.

Interestingly, two patients (# 2 and 6) were diagnosed with pulmonary embolism by computed tomography. Neither of these patients had a previous history of thromboembolic incidences, and no deep vein thrombosis or other obvious cause was found that could have explained a pulmonary embolism. All other investigations for establishing a hypercoagulability state in these patients did not reveal an alternative origin for pulmonary embolism. Although we cannot rule out all possible etiologies of thrombotic events in these patients (such as a tumor leading to both a pulmonary embolism and pericardial effusion or a drug effect), we suggest that hypostasis due to a large pericardial effusion constricting the right heart may explain the organization of a thrombus in situ in the pulmonary artery in such cases. Therefore, we avoided anticoagulation in these patients and they recovered spontaneously after drainage of the large pericardial effusion.

It is possible that an aggressive therapeutic approach with pericardiocentesis for patients with large pericardial effusion and tamponade should be undertaken not only for possible hemodynamic compromise, but also for prevention of pulmonary embolism due to hypostasis and possible in situ thrombus organization in the pulmonary arteries.

CONCLUSIONS

A large symptomatic pericardial effusion is a serious clinical condition that requires an aggressive diagnostic and therapeutic approach including pericardiocentesis. This approach has been largely accepted for prevention of hemodynamic compromise due to tamponade. However, we suggest that this aggressive approach may be necessary for prevention of

pulmonary embolism as well, which may originate in a thrombus in situ in the pulmonary artery due to hypostasis. In our cohort the etiologies for the non-iatrogenic large hemorrhagic pericardial effusion were malignancy, streptococcal infection, possible FMF exacerbation, and idiopathic.

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You can't separate peace from freedom because no one can be at peace unless he has his freedom

Malcolm X (1925-1965), African-American Muslim minister and human rights activist. A controversial figure, he was viewed by his admirers as a courageous advocate for the rights of African Americans, and by his detractors as a racist preaching black supremacy, antisemitism, and violence. He has been called one of the greatest and most influential African Americans in history

Capsule

Prion-like behavior and tau-dependent cytotoxicity of pyroglutamylated amyloid-β DOI:

Extracellular plaques of amyloid-β and intraneuronal neurofibrillary tangles made from tau are the histopathological signatures of Alzheimer's disease. Plaques comprise amyloid-β fibrils that assemble from monomeric and oligomeric intermediates, and are prognostic indicators of Alzheimer's disease. Despite the importance of plaques to Alzheimer's disease, oligomers are considered to be the principal toxic forms of amyloid-β. Interestingly, many adverse responses to amyloid-β, such as cytotoxicity, microtubule loss, impaired memory and learning, and neuritic degeneration, are greatly amplified by tau expression. Amino-terminally truncated, pyroglutamylated (pE) forms of amyloid-β are strongly associated with Alzheimer's disease, are more toxic than amyloid-β, residues 1–42 (Aβ1–42) and Aβ1–40, and have been proposed as initiators of Alzheimer's disease pathogenesis. Nussbaum and co-researchers report a mechanism by which pE-Aβ may trigger Alzheimer's disease. Aβ3(pE)–42 co-oligomerizes with excess Aβ1–42 to form metastable low-n oligomers (LNOs) that are structurally distinct and far more cytotoxic to cultured neurons than comparable LNOs made from Aβ1–42 alone. Tau is required for cytotoxicity, and LNOs comprising 5% Aβ3(pE)–42 plus 95% Aβ1–42 (5% pE-Aβ) seed new cytotoxic LNOs through multiple serial dilutions into Aβ1–42 monomers in the absence of additional Aβ3(pE)–42. LNOs isolated from human Alzheimer's disease brain contained Aβ3(pE)–42, and enhanced Aβ3(pE)–42 formation in mice triggered neuron loss and gliosis at 3 months, but not in a tau-null background. We conclude that Aβ3(pE)–42 confers tau-dependent neuronal death and causes template-induced misfolding of Aβ1–42 into structurally distinct LNOs that propagate by a prion-like mechanism. Our results raise the possibility that Aβ3(pE)–42 acts similarly at a primary step in Alzheimer's disease pathogenesis.

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Eitan Israeli

People see God every day. They just don't recognize him

Pearl Bailey (1918-1990), African-American actress and singer