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The Diagnostic Value of Pericardial Fluid and Pericardial Biopsy: Single Center Experiences

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ABSTRACT

Background: Patients with recurrent pericardial effusion and pericardial tamponade are usually treated in thoracic surgery clinics by VATS (video-assisted thoracoscopic surgery) or open pericardial window operation. The diagnostic importance of pathological evaluation of the pericardial fluid and tissue in the same patients has been reported in few studies. We reviewed pathological examination of the pericardial tissue and fluid specimens and the effect on the clinical treatment in our clinic, and compared the results with the literature.

Methods: We retrospectively analyzed 174 patients who underwent pericardial window operation due to pericardial tamponade or recurrent pericardial effusion. For all patients both the results of the pericardial fluid and pericardial biopsy specimen were evaluated. Clinicopathological factors were analyzed by using descriptive analysis.

Results: Median age was 61 (range, 20-94 years). The most common benign diagnosis was chronic inflammation (94 patients) by pericardial biopsy. History of malignancy was present in 28 patients (16.1%) and the most common disease was lung cancer (14 patients). A total of 24 patients (13.8%) could be diagnosed as having malignancy by pericardial fluid or pericardial biopsy examination. The malignancy was recognized for 12 patients who had a history of cancer; 9 of 12 with pericardial biopsy, 7 diagnosed by pericardial fluid. Twelve of 156 patients were recognized as having underlying malignancy by pericardial biopsy (n = 9) or fluid examination (n = 10), without known malignancy previously.

Conclusion: Recurrent pericardial effusion/pericardial tamponade are entities frequently diagnosed, and surgical interventions may be needed either for diagnosis and/or treatment, but specific etiology can rarely be obtained in spite of pathological examination of either pericardial tissue or fluid. For increasing the probability of a specific diagnosis both the pericardial fluid and the pericardial tissues have to be sent for pathologic examination.

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INTRODUCTION

The etiology of pericardial effusion and cardiac tamponade is metastatic invasion of pericardium by cancer cells in cancer patients, or inflammation or infection caused by chronic diseases like tuberculosis, congestive heart failure, metabolic or autoimmune diseases [Wagner 2011; Karatolios 2013]. Drainage of pericardial fluid can be performed by pericardiocentesis or pericardial window operation to relieve symptoms, or for diagnosis. Recurrent symptomatic pericardial effusion and pericardial tamponade can cause hemodynamic instability and can indicate unrecognized underlying malignancy.

The diagnosis of the etiology of recurrent pericardial effusion or cardiac tamponade is often challenging. There is no consensus in the prevalence of malignancy in patients who present with pericardial effusion and the diagnostic value of pericardial fluid and biopsy examination. Pericardial fluid sensitivity for malignancy was reported as 54%-90% in the literature [Ben-Horin 2006; Gibbs 2000; Meyers 1997; Wilkes 1995]. Pericardioscopy with targeted pericardial biopsy increases sensitivity in malignant etiology, but this method was not widespread especially after video-assisted thoracoscopic surgery (VATS) replaced it [Maisch 1994; Maisch 2010]. Patients presenting with recurrent symptomatic pericardial effusion with a negative history of cancer require extensive study in respect to excluding malignancy.

The importance of pericardial fluid and/or pericardial biopsy examination for distinction of benign or malignant disease is not well known. Herein we evaluated the pathological results of pericardial fluid and pericardial biopsy to diagnose malignant or benign disease for patients with or without previous malignancy history.

MATERIALS AND METHODS

We retrospectively analyzed 174 patients who had undergone pericardial window operation in Siyami Ersek Thoracic Surgery Department from May 2007 and December 2013. Each operation was performed by VATS (124 patients, 71.2%) or open approach (left anterior mini thoracotomy) (50 patients, 28.8%). Subxyphoid approach was not preferred in any of our cases. In all cases at least 8 cm2 of pericardial tissue was resected from both the anterior and posterior sides

Table 1. Patient Characteristics

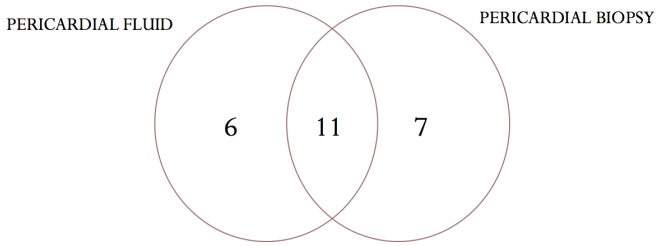
	n	%
Age		
<50	47	27
>50	127	73
Sex		
Female	88	50.6
Male	86	49.4
Pericardial fluid		
Malignant	17	9.8
Benign	154	88.5
Atypical	3	1.7
Pericardial biopsy		
Malignant	18	10.3
Benign	156	89.7
History of malignancy		
Present	28	16.1
Absent	146	83.9

of the phrenic nerve. The indications of pericardial window operation were therapeutic intervention for recurrent pericardial effusion after pericardiocentesis or pericardial tamponade that couldn't be drained by pericardiocentesis. Patients were excluded if one of the results of biopsy or fluid examination could not be achieved. Patients with pericardial effusion occurring after major cardiac surgery in the early period were also excluded (first 30 days after operation). This study is a retrospective, observational and review-based study of medical records of patients. Clinical information about age, sex, malignancy, other chronic disease history, and clinicopathological features were obtained from patients' charts after written informed consent had been obtained from the patients or their relatives. In all cases samples were acquired to be sent for microbiologic examination for cultures, but as the extent of this study is to evaluate the importance of pathologic results, these results were not discussed in this paper.

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA) software. Clinicopathological parameters were described by using descriptive analysis. The relationship between the results of pericardial fluid and pericardial biopsy based on malignancy history and malignancy diagnosis were analyzed by Pearson chi-square test and Fisher exact test. All P values were two-sided in tests and P values less than or equal to .05 were considered statistically significant.

RESULTS

A total of 174 patients with the pathological results of both pericardial fluid and biopsy obtained during pericardial window operation were retrospectively analyzed. Nearly half of the patients were male (49.4%). The median age was 61



Malignancy was diagnosed totally in 24 patients.

Table 2. Etiology of the Pericardial Fluid and Pericardial Biopsy

	Pericardial Biopsy		Pericardial Fluid	
	n	%	n	%
Malignant				
Carcinoma	14	77.8	15	75
Mesothelioma	2	11.1	1	5
Other	2	11.1	1	5
Atypical cells	0	0	3	15
Benign		154	100	
Fibrosis	42	27		
Granulomatous	6	3.8		
Chronic inflammation	97	62.5		
Mature fat	10	6.7		

(range, 20 to 94 years). Forty-seven patients were younger than 50 years (27%). The history of malignancy was present in 28 patients (16.1%) and these malignancies were lung cancer (n = 14), breast cancer (n = 4), lymphoma (n = 4), mesothelioma (n = 1), melanoma (n = 1), nasopharyngeal cancer (n = 1), cervix cancer, (n = 1), osteosarcoma (n = 1), and renal cell carcinoma (n = 1) in order of frequency. On the other hand, 8 patients had history of cardiac disease, like prior aorto-coronary bypass surgery (2 patients), and congestive heart failure (6 patients). Two patients had anamnesis of tuberculosis and 3 had hypothyroidism. The results of the patients' characteristics are shown in Table 1. In total 24 patients (13.8%) could be diagnosed with malignancy either by pericardial fluid or pericardial biopsy examination, or by both. While 17 of the patients (9.8%) could be diagnosed with malignancy by pericardial fluid, pericardial biopsy recognized malignancy in 18 patients (10.3%) (Table 2; Figure). There were no uncertain diagnoses by pericardial biopsy, but 3 atypical cells without diagnosis were achieved by pericardial fluid examination. The etiology of the malignancies that were diagnosed by pericardial biopsy was 77.8% carcinoma infiltration (n = 14), 11.1% mesothelioma (n = 2) and 11.1% other (n = 2). On the other hand, 15 carcinoma cells (75%), 3 atypical cells (15%), 1 mesothelioma cells (5%),

Table 3. Diagnostic Value of Pericardial Fluid and Biopsy

	Malignancy		
	Present (%)	Absent (%)	*P*
Pericardial fluid			<.001
Malignant	17 (70.8)	0 (0)	
Benign	5 (20.8)	149 (99.3)	
Atypical	2 (8.4)	1 (0.7)	
Pericardial biopsy			<.001
Malignant	18 (75)	150 (100)	
Benign	6 (25)	0 (0)	

Table 4. Correlation between Malignancy History and Histopathological Diagnosis

Diagnosis	History of malignancy		
	Present (n = 28) (%)	Absent (n = 146) (%)	
Pericardial fluid			*P* < .001
Malignant	7 (25)	10 (6.8)	
Benign	19 (67.8)	135 (92.4)	
Atypical	2 (7.2)	1 (0.8)	
Pericardial biopsy			*P* < .001
Malignant	9 (35)	9 (6.1)	
Benign	19 (65)	137 (93.9)	

and 1 (5%) other were found in pericardial fluid examination (Table 3). The most common benign diagnoses were chronic inflammation (62.5%), fibrosis (27%), mature fat (6.7%), and granulomatous reaction (3.8%) by pericardial biopsy.

Malignancy was recognized in 12 patients who had history of cancer, 9 out of 12 with pericardial biopsy, and 7 diagnosed by pericardial fluid. Both pericardial fluid and pericardial biopsy were positive for malignancy in 4 patients. Underlying malignancy was determined in 12 of 156 patients by pericardial biopsy (n = 9) or fluid examination (n = 10), although they had no known malignancy previously. Both procedures were positive for cancer in 10 patients (Table 4). The diagnosis was more common by pericardial biopsy compared with pericardial fluid in patients with previously known malignancy ($P < .001$).

The pathological examination of both fluid and biopsy were correlated with previous malignancy history. While lung and breast cancer could be diagnosed as carcinoma cells in pleural fluid and carcinoma infiltration in pleural biopsy, melanoma could be seen as melanoma cells in fluid and infiltration in biopsy, and also mesothelioma defined as atypical mesothelium cells in fluid and mesothelioma infiltration in the biopsy specimen (Table 5).

DISCUSSION

Pericardial effusions are commonly caused by a variety of pathological conditions, including infectious, metabolic, malignant, and autoimmune diseases [Karatolios 2013]. The specific diagnosis of pericardial effusion is often challenging. The underlying cause of pericardial fluid may be an unrecognized malignant disease so the therapeutic approach can be changed. In contrast to pleural fluid, there are no biochemical markers like LDH or protein that can be helpful for separation of exudative or transudative fluid. By pericardiocentesis, pericardial fluid effusion can be analyzed histopathologically and sensitivity for malignancy is variable, ranging 30-90% [Karatolios 2013; Meyers 1997]. We analyzed specimens from 174 patients who presented with pericardial tamponade or recurrent pericardial effusion and underwent pericardial window operation.

The aim of our study was to evaluate the importance of the pathological examination of pericardial fluid and biopsy at the same time. In total 30 patients (17.2%) could be diagnosed specifically, 24 (13.8%) malignancy and 6 (3.4%) granulomatous infections were detected by pericardial fluid or pericardial biopsy examination. In total 17 by pericardial fluid and 18 pericardial biopsy were positive for malignancy; on the other hand malignancy was detected in 11 patients by both fluid and biopsy specimens. As shown in the Figure, if we had sent only a pericardial fluid or biopsy specimen our diagnosis rate would have been much lower.

Surgical pericardial window operation is reported as a successful method in preventing recurrence of pericardial effusions [Vaitkus 1994]. Rafique et al analyzed 157 patients with recurrent pericardial effusion who underwent pericardiocentesis and pericardial catheter drainage [Rafique 2011]. They excluded surgical pericardiotomy. One fifth of their patients had recurrent pericardial tamponade at 1 year. In the literature, surgical pericardiotomy and pericardiocentesis with extended drainage was compared in 88 patients with pericardial tamponade because of malignancy. Recurrence rate and diagnostic yields were no different between the two procedures [Patel 2013]. We performed pericardial window operation because of recurrent pericardial fluid without any serious complications. We couldn't report the recurrence rate or follow-up data because these patients has been followed-up in cardiology or oncology clinics and were submitted to our thoracic surgery department for surgery.

Abdallah et al reported in their series that the most common etiology of pericardial effusions were reported as idiopathic (36%), followed by malignancy (31.4%), complications of ischemic heart disease, renal failure, chest trauma, autoimmune disease, and myxedema in 86 patients with pericardial effusions [Abdallah 2014]. In our study, a total of 148 patients with both pericardial fluid and biopsy sent for pathological examination had benign pathology, 154 with only pericardial fluid sent for pathological examination, 156 with only pericardial biopsy sent for pathological examination; cytology were benign. Pericardial biopsy was more specific detecting benign causes (especially with positive history). Chronic inflammation (62.5%) was the most common etiology, followed by fibrosis (27%), mature fat (6.7%), and granulomatous reaction (3.8%). Six patients, 2 of them who

Table 5. Subtypes of the Malignancy of Patients with History of Cancer

Patient	Type of Malignancy History	Pericardial Fluid	Pericardial Biopsy
1	NSCLC	Carcinoma cells	Benign
2	NSCLC	Carcinoma cells	Benign
3	Osteosarcoma	Carcinoma cells	Benign
4	NSCLC	Benign	Carcinoma infiltration
5	NSCLC	Carcinoma cells	Carcinoma infiltration
6	NSCLC	Carcinoma cells	Carcinoma infiltration
7	Breast cancer	Carcinoma cells	Carcinoma infiltration
8	NSCLC	Benign	Carcinoma infiltration
9	Lymphoma	Benign	Lymphoma
10	Mesothelioma	Atypical mesothelial cells	Mesothelioma
11	Melanoma	Melanoma cells	Melanoma infiltration
12	Lymphoma	Atypical lymphoid cells	Lymphoma

NSCLC indicates non-small cell lung cancer.

had known tuberculosis, were diagnosed with tuberculosis by pericardial biopsy. Although malignant etiology was similar in the literature, benign causes of pericardial effusion were different [Abdallah 2014]. We excluded the pericardial effusion occurring after major cardiac surgery. These differences may be related to regional differences, because chronic infection like tuberculosis is still an important health problem in our country.

The sensitivity of pericardial fluid and pericardial biopsy to detect malignancy was 72% and 75% respectively in our study, compatible with the literature [Karatolios 2013; Ben-Horin 2006; Meyers 1997]. Ben-Horin et al analyzed 173 patients who underwent pericardiocentesis only [Ben-Horin 2006]. Malignancy was diagnosed by pericardiocentesis in 58 (33%) patients, which is higher than our study results (24 of 174 patients). Although we used both pericardial fluid and biopsy for diagnosis. It may be related to the fact that their patients had more malignancy history than our patients (26% versus 16.1%). They performed pericardial biopsy together with pericardiocentesis in 6 patients only, and found that all cases were positive for malignancy. Cullinane et al has not found malignancy by pathological examination of pericardial biopsy in 56 patients with the absence of history of malignancy with pericardial fluid cytology [Cullinane 2004]. Furthermore, Patel et al also couldn't find any difference between diagnostic yield of malignancy between pericardial drainage and pericardial surgery [Patel 2013]. We diagnosed malignancy with only pericardial biopsy in 7 patients (29.1%) with negative pericardial fluid cytology, and also one fourth of the pericardial fluid was positive for malignancy with negative pericardial biopsy. As no proven clinical sign, symptoms or biochemical markers supported the diagnosis of malignancy presented with recurrent pericardial fluid, we performed pericardial fluid examination together with pericardial biopsy for all patients at the same time, differing from their study.

In our study the specimens of the 146 patients without history of cancer or malignancy were diagnosed in 12 patients (8.2%) with pericardial biopsy (9 patients positive with biopsy) or fluid examinations (10 patients). Unrecognized cancer, mostly lung cancer, was diagnosed in 22% of patients by pericardiocentesis in Ben-Horin's study [Ben-Horin 2006]. The retrospective analysis of pericardial window operation in 179 cancer patients revealed that lung cancer and breast cancer were the most common underlying malignancies associated with pericardial effusion [Wagner 2011]. The most commonly detected malignancy in our study was also lung cancer followed by hematologic malignancy, mesothelioma, and breast cancer.

There are some limitations in our study, as this was a small sample sized group analyzed retrospectively. Furthermore, we cannot inform about survival of the patients. On the other hand, it is noteworthy that only pericardial fluid or biopsy was positive for unrecognized malignancy, so we recommend analyzing both specimens, especially if clinically malignancy is suspected.

The correct diagnosis of pericardial effusion is important for successful treatment. Especially in patients with a negative history for cancer, pericardial fluid and biopsy examinations require extensive workup to label effusion as benign, because pericardial effusion can be the first presentation of an underlying malignant disease. To increase the probability of a specific diagnosis, both the pericardial fluid and the pericardial tissues should be sent for pathologic examination.

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