Characteristics of Pericardial Biopsy: 100 Cases in a Single Center

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ABSTRACT: **Background:** Pericardial biopsies are rarely performed during the diagnosis and management of pericardial diseases. The circumstances and clinical profile of patients undergoing pericardial biopsies are largely uncharacterized.

Objectives: To examine the circumstances in which pericardial biopsies are obtained and to evaluate their diagnostic yield.

Methods: We studied a total of 100 cases (71% males, mean age 60.8 years, range 8.1–84.5 years) of surgically resected pericardium specimens obtained from 2000 to 2015 at Sheba Medical Center, the largest medical center in Israel. Patients were classified into groups according to four major histological etiologies: idiopathic pericarditis, constrictive pericarditis, malignant pericarditis, and post-cardiac injury syndrome (PCIS). The clinical history and course, laboratory, echocardiography, and histological results were reviewed retrospectively.

Results: Causes of pericarditis according to histological definitions included idiopathic pericarditis (29%), constrictive pericarditis (29%), PCIS (9%), and malignant pericarditis (26%). Overall sensitivity of the pericardial biopsy in patients with malignancy was 57.7%. During the study period, we found a trend toward an increased number of biopsies due to constrictive pericarditis and PCIS, along with a decrease in the number of biopsies performed in patients with malignant or idiopathic pericarditis. The diagnosis following biopsy did not change for any of the patients.

Conclusions: Our findings suggest a low diagnostic yield from pericardial biopsies, especially in malignant pericarditis. This conclusion, along with novel therapies, resulted in the infrequent use of pericardial biopsy in recent years.

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KEY WORDS: autoimmunity, biopsy, malignancy, pericardium, pericarditis

Pericardial diseases may present as isolated diseases or as part of systemic disorders. These diseases manifest in several ways, including pericarditis (acute, sub-acute, recurrent, chronic), pericardial effusion, cardiac tamponade, constrictive pericarditis, and pericardial masses [1,2]. Various tools are used in the diagnosis of pericardial diseases, including echocardiography and cardiac magnetic resonance imaging. Invasive procedures, including pericardiocentesis and pericardial biopsies, are seldomly used as a diagnostic tool in pericardial diseases.

Pericardial biopsy is usually carried out as part of a surgical therapeutic procedure in cases of worsening pericarditis despite treatment or in selected cases of bacterial or neoplastic pericarditis [2,3].

Many studies have described pericardial fluid analysis following pericardiocentesis in different pericardial diseases; however, less is known about the etiologies and characteristics of pericardial biopsy. In fact, only a few published articles have described pericardial specimens of different etiologies and their clinical course. The studies that have been conducted included small sample sizes, were based solely on patients with pericardial effusion, or involved outdated methods [4]. Perhaps scant research is conducted on pericardial biopsies because of the relatively low diagnostic yield [5] or due to the infrequent use of therapeutic procedures to obtain such biopsies. In addition, these procedures are seldom indicated by guidelines [2]. To the best of our knowledge, the only large consecutive series concerning the histopathology of pericardial specimens in different diseases was conducted almost 18 years ago by the Mayo Clinic group in 1993–1999 (344 cases) [6]. Since then, no study has examined the span and yield of pericardial biopsies.

In this study, we evaluated all pericardial biopsies conducted from 2000 to 2015 in a tertiary medical center in Israel. We aimed to examine the circumstances in which pericardial biopsies were obtained and to evaluate their diagnosis yield.

*The first and second authors contributed equally to this study

PATIENTS AND METHODS

STUDY GROUP

All parietal pericardial specimens surgically excised at Sheba Medical Center from 2000 to 2015 were reviewed, and 100 cases were identified. Ninety-three cases were classified into one of four categories based on clinical features: idiopathic pericarditis, constrictive pericarditis, malignant pericarditis, and post-cardiac injury syndrome (PCIS). The remaining seven patients were classified as other.

The vast majority of the biopsies were obtained during pericardial window or pericardiectomy procedures. All biopsy results were reviewed and approved by a senior pathologist (R.K.H.).

The clinical history and course, as well as laboratory, echocardiography and histological results, were reviewed retrospectively by accessing the hospital's medical files and electronic databases. The institutional review board approved this study.

HISTOPATHOLOGICAL FEATURES

Surgical pathology reports and corresponding microscopic slides were reviewed for each case. The following, if present, were also recorded: calcification (gross or microscopic), inflammation (acute or chronic, graded semiquantitatively as mild, moderate, or marked), granulomas (caseating or non-caseating, with the results of special stains for organisms), fluid retention, and fibrosis. If malignant cells were present, a diagnosis of malignant pericarditis was established.

RESULTS

Table 1 displays the etiologies of the pericardial diseases in the 100 patients in our series. Of these, 93 patients were classified into four major groups:

- Group 1: Idiopathic pericarditis was diagnosed 29 patients, 69% males, mean age 61.1 years (range 8.1–84.5) [Figure 1A]
- Group 2: Constrictive pericarditis was diagnosed in 29 patients, 96.6% males, mean age 66.6 years (range 23.0–81.5) [Figure 1B and C]
- Group 3: Malignant pericarditis was diagnosed in 26 patients, 57.7% males, mean age 55.2 years (range 17.7–82.8) [Figure 1D–F]
- Group 4: Inflammatory PCIS was diagnosed in 9 patients, 55.6% male, mean age 61.7 years (range 19.5–81.6) [Figure 1G–I].

The remaining seven patients had other etiologies. Four patients had purulent pericarditis, one presented with pericarditis due to an autoimmune disease, one had amyloidosis with pericardial involvement, and one presented with hemorrhagic pericardial effusion following irradiation therapy.

The characteristics of these patients and the clinical course of their disease, echocardiography, and laboratory and histopathologic results are described in Table 2.

HISTOPATHOLOGICAL FINDINGS OF THE 100 BIOPSIES

Fibrosis: Fibrosis was evident in 71% of all specimens collected, most prominent in the constrictive (93.1%) and idiopathic (79.3%) groups. PCIS was the only group in which the majority of the biopsies did not contain fibrosis (22.2%).

Pericardial effusion: Pericardial effusion was found in 65.9% of the specimens collected, most prominently in the PCIS group, in which 88.9% of the biopsies contained fluid.

Inflammation: Inflammatory cells were found in two-thirds of the biopsies, mostly in the idiopathic pericarditis group (86.2%).

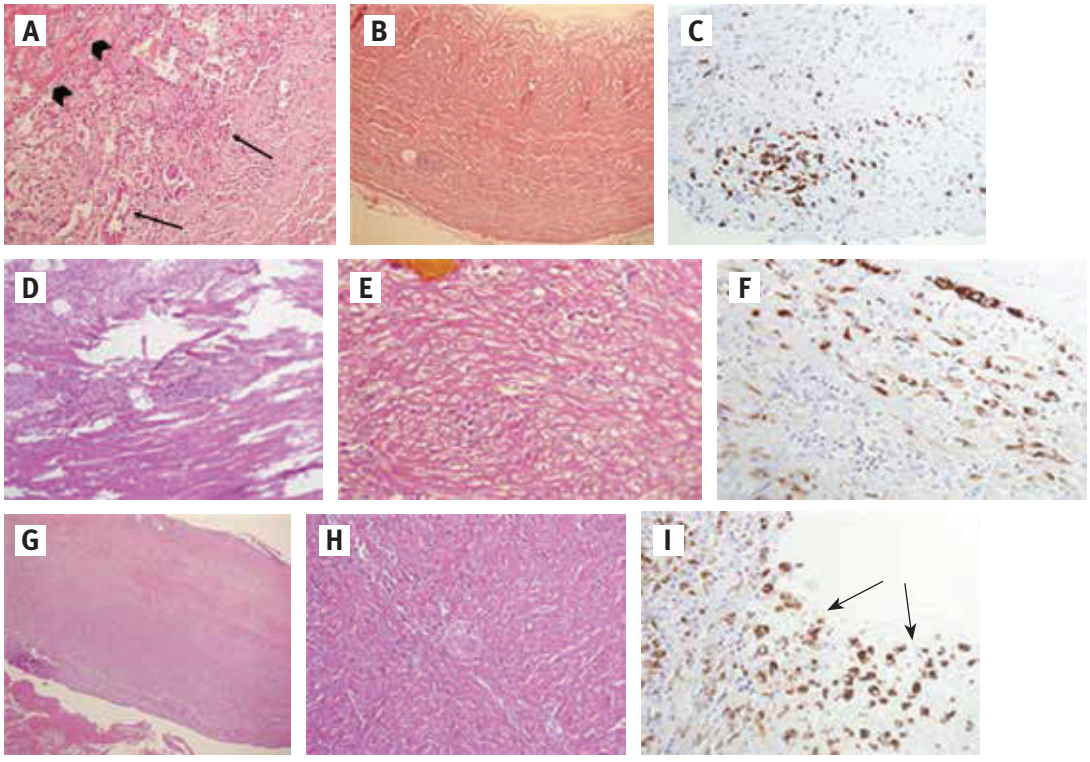
Table 1. Etiologies of pericardial diseases among patients with pericardial specimens

Etiology		Number of patients (%)		Males (%)		Age, years			
						Mean		Range	
Idiopathic	Idiopathic	19 (19)	29 (29)	68.4	69.0	62.4	61.1	28.3–82.0	8.1–84.5
	Idiopathic recurrent	10 (10)		70		58.6		8.1–84.5	
Constrictive	Idiopathic constrictive	25 (25)	29 (29)	96.0	96.6	65.5	66.6	17.7–82.8	17.7–82.8
	PCIS constrictive	4 (4)		100		73.9		68.7–76.7	
Malignant	Biopsy positive for malignant cells	15 (15)	26 (26)	46.7	57.7	58.6	55.2	35.1–81.5	23.0–81.5
	Biopsy negative for malignant cells	11 (11)		72.7		50.5		23.0–74.5	
PCIS		9 (9)		55.6		61.7		19.5–81.6	
Purulent		4 (4)		50		60.9		39.6–78.3	
Autoimmune	Systemic lupus erythematosus	1 (1)		0		28.7			
Amyloidosis		1 (1)		100		69.5			
Irradiation		1 (1)		0		47			
Total		100				60.8		8.1–84.5	

PCIS = post-cardiac injury syndrome

Figure 1. Histopathological findings from the different pericardial etiologies

[A] Idiopathic pericarditis: The pericardium is partially covered by fibrin (arrow heads) and shows an acute inflammatory process consisting of neutrophilic infiltration into the soft tissue, vascular congestion, edema, and early organization. There is focal mesothelial reactive hyperplasia (arrows). **[B] [C] Constrictive pericarditis:** The pericardium shows thickening due to collagen fibrosis with foci of hyalinization. There are occasional thick walled blood vessels and minimal chronic inflammation (as seen in Figures B, E, and H). There is mild chronic inflammation, and the predominant inflammatory cell identified is the T cytotoxic lymphocyte (immunohistochemical stain CD8) **[C]**. **[D] [E] [F] Malignant pericarditis:** The pericardium is extensively infiltrated by a neoplastic process composed of epithelial tumor cells arranged in single cell files and small groups. They occasionally show a perivascular infiltrative pattern, and there is a desmoplastic reaction with acute and chronic inflammation. The tumor cells have large irregular vesiculated nuclei with occasional small nucleolus [As seen in Figures D, E, H]. On immunostain, the mouse monoclonal cytokeratin antibody [MNF116] **[F]** highlights the single cell files and small group cell infiltrative pattern. **[G] [H] [I] Inflammatory PCIS:** The surface of the pericardium is partially covered by a fibrinous exudate with partial loss of the normal pericardial mesothelial lining [G]. There is a chronic inflammatory infiltrate consisting of lymphocytes, plasma cells and macrophages with occasionally multinuclear giant cells [As seen in Figures E, G, H]. On immunostains there is a predominance of T cytotoxic lymphocytes (CD8) and macrophages **[I]**. The macrophages are mostly seen at the surface of the pericardial exudate as illustrated with immunostain CD68 **[I]**, arrows



Calcifications: Of the specimens,12% contained calcifications, almost exclusively in the constrictive group, both in the pericardial specimens and in the echocardiogram results.

Of note, following the biopsy results, none of the patients had a change in the primary diagnosis.

Of the 26 patients with malignancies, 13 were diagnosed with lung cancer (50%), 10 had a pericardial biopsy positive for malignant cells, and 3 had negative samples (sensitivity of 76.9%). Four patients had breast cancer (15.4%) and all four presented with a pericardial biopsy negative for malignant cells. Two patients had lymphoma, both with pericardial biopsy negative for malignant cells. Two patients had leukemia, only one of whom showed pericardial biopsy with evidence of leukemia involvement. One patient had thymus cancer with negative biopsy for malignant cells. Four patients had biopsies positive for neoplastic involvement of the pericardium, including stomach cancer, colon cancer, renal cell carcinoma, and one of unknown primary site.

In our sample population, the diagnostic value of pericardial biopsy in metastatic neoplasms of the pericardium had an overall sensitivity of 57.69%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 87.06%.

DISCUSSION

During a period of 16 years, only 100 pericardial biopsies were performed in our 1700-bed tertiary hospital, an average of fewer than 10 biopsies per year. This low number highlights the

Table 2. Clinical features of 100 patients with pericardial specimen, including clinical course, echocardiography, laboratory and histopathologic results

Patients		All	Group 1	Group 2	Group 3	Group 4
Number		100	29	29	26	9
Clinical course	Past pericardiocentesis, N (%)	41 (41)	15 (515.7)	0	17 (65.4)	6 (66.7)
	Tamponade, N (%)	14 (14)	3 (10.3)	0	8 (30.8)	3 (33.3)
Echocardiogram findings	Pericardial effusion, N (%)	60 (65.9)	20 (76.9)	8 (28.6)	18 (85.7)	8 (88.9)
	LV systolic diameter (cm), median (IQR)	2.6 (2.3–3.0)	2.8 (2.3–3.4)	2.6 (2.3–2.9)	2.9 (2.0–3.0)	2.5 (2.3–3.0)
	LV diastolic diameter (cm), median (IQR)	4.5 (4.0–4.8)	4.8 (4.2–5.3)	4.4 (4.1–4.8)	4.4 (3.9–4.8)	4.0 (3.8–5.0)
	EF (%), median (IQR)	60 (53–60)	57.5 (48.3–60)	55 (50–60)	60 (57.5–65)	60 (58.8–60)
Laboratory results: blood serum	Creatinine (mg/dl), median (IQR)	1.0 (0.9–1.3)	1.0 (0.9–1.6)	1.1 (0.9–1.4)	0.9 (0.7–1.0)	1.1 (0.9–1.5)
	Uric acid (mg/dl), median (IQR)	5.5 (4.1–7.2)	5.0 (4.5–7.0)	6.8 (5.4–8.0)	4.2 (3.4–6.1)	6.3 (3.5–10.4)
	Ferritin (ng/ml), median (IQR)	194.7 (68.6–396.2)	305.5 (159.7–546.3)	146.0 (33.1–330.4)	972.7 (217.7–2001.0)	53.8 (31.8–91.6)
Histopathology results of biopsies	Fibrosis, N (%)	71 (71)	23 (79.3)	27 (93.1)	16 (61.5)	2 (22.2)
	Fluid, N (%)	63 (63)	23 (79.3)	6 (20.7)	21 (80.8)	8 (88.9)
	Malignancy, N (%)	15 (15)	0	0	15 (57.7)	0
	Inflammation, N (%)	68 (68)	25 (86.2)	17 (58.6)	13 (50)	7 (77.8)
	Calcification, N (%)	12 (12)	1 (3.4)	10 (34.5)	0	0

*The laboratory results were recorded for 98 patients (creatinine), 97 patients (uric acid) and 32 patients (ferritin)
EF = ejection fracture, LV = left ventricle, PCIS = post-cardiac injury syndrome

negligibility and the low diagnostic yield of these procedures in the various pathologies involving the pericardium.

In most case reports [6], like ours, the biopsies were obtained as part of a therapeutic procedure, such as pericardial window or pericardiectomy. The procedures were conducted to treat conditions such as recurrent pericardial effusion, tamponade, constrictive pericarditis, or failure to respond to medical therapy. However, the diagnostic contribution of pericardial biopsies to the clinical management of patients is considered controversial [3,5,7,8].

Our findings suggest that there was no diagnostic value in the pericardial biopsies performed in our series. The various etiologies for pericardial disease in the 100 patients included in our study were established by imaging methods, laboratory findings, pericardial effusion evaluation, and clinical data. Biopsy analysis did not alter the diagnosis in any of the patients included.

The most common etiology in our study was idiopathic pericarditis in 29% of all patients. In a previous study, idiopathic etiology was reported in 78–86% of patients [9]. The smaller portion of idiopathic etiology that we found, compared to other researchers, may suggest that these patients required less surgical intervention. Patients with idiopathic or viral pericarditis often present with a self-limited disease and respond well to medication [9,10]. They have a good prognosis compared to specific known etiologies, and rarely encounter complications such as cardiac tamponade, constriction, or recurrences [11].

Malignancy is a frequent cause of pericardial effusion, often associated with a poor prognosis. Surgical drainage of pericardial fluid in the majority of these patients who present with advanced stages of malignancy is palliative and has no effect on long-term survival [12]. However, in selected patients it may provide a symptom-free interval for further aggressive treatment [12].

We found no primary pericardial malignancies in our series, as may be expected considering the extremely low prevalence of primary pericardial neoplastic diseases [13]. In our series, lung and breast cancers were the most common neoplastic etiologies. Other less frequent neoplastic etiologies were lymphoma, leukemia, and renal cell carcinoma, as well as stomach, colon, and thymus cancer [Table 3].

When examining the yield of pericardial biopsy performed because of malignancy, our results point to a negligible diagnostic value. All 26 patients with malignant etiology underwent the biopsy as part of a therapeutic procedure, with a previously established diagnosis of malignancy. In one patient with cancer of unknown primary origin, pericardial biopsy did not reveal the primary tumor; moreover, in a considerable proportion of the patients with a widespread metastatic disease, the biopsy was negative for malignant cells.

Thus, we found that in the presence of malignancy, the sensitivity of pericardial biopsy was only 57.69%. This finding concurs with previous studies [14], which showed that although the diagnostic value has improved over the years due to new, more advanced techniques, such as pericardioscopy [15,16], pericardial biopsy still remains inadequate in terms of its diagnostic yield for malignancies [8,16,17]. Furthermore, previous studies suggest that in this setting, pericardial fluid

cytology may prove to be sufficient or even superior to tissue histology [5,17]. Nevertheless, some studies point to the diagnostic advantage of performing targeted pericardial biopsies collected during pericardioscopy [15], as well as using a combination of cytology and histological, epicardial, or pericardial biopsy, compared to cytology or histology alone [18].

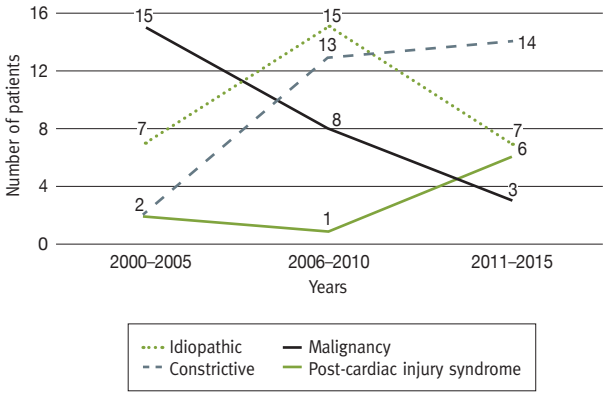
One possible explanation for the relatively low yield of pericardial biopsies in the setting of malignancy relates to the most common route of metastatic spread to the heart, which is through retrograde lymphatic migration. Since lymphatic tumor progression is first to the visceral pericardium and pericardial fluid and only then to the parietal pericardium, which is sampled in biopsies, this method may be less sensitive than pericardial fluid aspiration [17,19].

Figure 2 shows the increasing number of surgical procedures for PCIS and constrictive pericarditis, probably due to the experience gained by the surgeons in our hospital and the evolving field of percutaneous intracardiac procedures with regard to PCIS [20]. However, the number of surgical procedures in patients with idiopathic etiology increased at the beginning of this trend, but later decreased. This change may be explained by the introduction of novel therapies, including anti-interleukin-1, azathioprine, and by better use of colchicine in resistant cases of idiopathic recurrent pericarditis. As for malignant pericarditis, surgical procedures do not assist in the diagnosis; however, in the development of new therapies and the availability of pericardiocentesis, the procedure of pericardial biopsy has become almost redundant.

LIMITATIONS OF THE STUDY

We found no data regarding the specific surgical techniques used to obtain the biopsies. Using advanced technology, such as pericardioscopy, increases the probability of obtaining disease-specific results [4]. Furthermore, different pathologists examined the specimens, which might have resulted in intra- and inter-observer variation. Nevertheless, we believe that this did not affect the diagnosis or the trends in this study.

Figure 2. Trends in the number of pericardial biopsies surgically excised over time according to the major etiologies of pericardial diseases



CONCLUSIONS

To the best of our knowledge, this study is the only one that examined the yield of pericardial biopsies in the last 20 years in Israel, which included all pericardial biopsies conducted in a tertiary hospital over a 16 year period. Our findings suggest a low diagnostic yield from pericardial biopsies, especially in malignant pericarditis, where pericardial biopsy should not be relied on as a single diagnostic tool. This technique, in addition to novel therapies, resulted in the infrequent use of pericardial biopsies in recent years. We suggest avoiding pericardial biopsies for diagnostic purposes, and rather reserving them for therapeutic use only.

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