Diagnosis of malignant pericarditis: a single centre experience

Anna Pawlak-Cieślik¹, Monika Szturmowicz¹, Anna Fijałkowska¹, Juliusz Gątarek², Renata Gralec³, Katarzyna Blasińska-Przerwa⁴, Ewa Szczepulska-Wójcik⁵, Agnieszka Skoczylas⁶, Anna Bilska¹, Witold Tomkowski³

¹Department of Internal Medicine, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
²Department of Thoracic Surgery, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
³Cardiopulmonary Intensive Care Unit, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
⁴Department of Radiology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
⁵Department of Pathology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
⁶Medical Centre Puławska, Warsaw, Poland

Abstract

Background: Malignancy is the most common cause of effusive pericarditis with a haemodynamically significant amount of pericardial fluid. Early diagnosis and management of malignant pericarditis may significantly improve outcomes.

Aim: To evaluate retrospectively the rate and clinical presentation of malignant pericarditis among patients undergoing invasive treatment, with a view to identification of optimal diagnostic modalities to distinguish this group among other patients.

Methods: We studied 191 patients (100 men and 91 women, median age 57 years, range 19–88 years) with effusive pericarditis who underwent invasive treatment in the National Institute of Tuberculosis and Lung Diseases in Warsaw in 1982–2008 due to a significant amount of pericardial fluid and/or echocardiographic evidence of cardiac tamponade. Pericardiocentesis was performed in 93 cases, pericardioscopy in 61 cases, and substernal pericardiotomy in 37 cases. Pericardial fluid was sent for examination in all patients, and a pericardial specimen was obtained in 96 patients. The patients were divided into 3 groups: Group 1 included patients with malignant pericarditis (malignant cells found in the cytological examination of the pericardial fluid and/or neoplastic infiltration in the histological examination of the pericardial specimen), Group 2 included patients with probable malignant pericarditis (pericardial fluid without malignant cells with histologically confirmed malignancy at some other location), and Group 3 included patients with non-malignant pericarditis (negative cytological examination of pericardial fluid and histological examination of the pericardial specimen, with no evidence of malignancy during hospitalization and one-year follow-up).

Results: Malignancy was found in 111 (58%) of 191 patients, including 66 (35%) patients with definite malignant pericarditis and 45 (23%) patients with probable malignant pericarditis. Lung cancer, including adenocarcinoma, was the most common type of malignancy, present in 44 (67%) patients. Non-malignant pericarditis was found in 80 (42%) patients. Among patients with the diagnosis of malignancy (Groups 1 and 2), a positive result of the cytological examination of the pericardial fluid was obtained in 52 cases (sensitivity of 46%). Among patients without malignancy, a negative result of the cytological examination of the pericardial fluid was obtained in all 80 cases (specificity of 100%). Malignant infiltration was found in 20 of 44 patients with the diagnosis of malignancy (sensitivity of 46%) and in none among 52 patients without malignancy (specificity of 100%). Compared to patients with non-malignant pericarditis, patients with malignant pericarditis significantly more commonly presented with tachycardia of > 100 bpm in a resting electrocardiogram (ECG) (in 77% of patients with malignant pericarditis vs. 43% of patients with non-malignant pericarditis, p = 0.01), low QRS amplitude (52% vs. 34%, respectively, p = 0.03), electrical alternans (19% vs. 3%, respectively, p = 0.001), echocardiographic evidence of cardiac tamponade (67% vs. 34%, respectively, p = 0.0001), enlarged mediastinal lymph nodes by chest computed tomography (CT) (90% vs. 29%, respectively, p = 0.0001).

Address for correspondence:
prof. Monika Szturmowicz, Department of Internal Medicine, National Institute of Tuberculosis and Lung Diseases, ul. Płocka 26, 01–138 Warszawa, Poland, e-mail: monika.szturmowicz@gmail.com
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p < 0.00001), pericardial thickness > 8 mm by chest CT (62% vs. 16%, respectively, p < 0.0001), and bloody pericardial effusion (94% vs. 43%, respectively, p < 0.0001). Levels of carcinoembryonic antigen (CEA) and cytokeratin fragment-19 (CYFRA 21-1) in the pericardial fluid were higher in patients with malignant pericarditis compared to patients with non-malignant pericarditis, with median values of 40.8 ng/mL vs. 0.9 ng/mL, p < 0.0001, and 162.85 ng/mL vs. 13.35 ng/mL, p < 0.0001, respectively.

Conclusions: 1. Malignancy was found in 58% of patients undergoing invasive treatment due to large pericardial effusion. 2. Cytological examination of the pericardial fluid and histological examination of a pericardial specimen showed high specificity (100%) but low sensitivity (46%) in the diagnosis of malignant pericarditis. 3. The most important predictors of malignant pericarditis included tachycardia of > 100 bpm as revealed by the physical examination and ECG, echocardiographic evidence of cardiac tamponade, presence of enlarged mediastinal lymph nodes (> 1 cm) and thickened pericardium (> 8 mm) by chest CT, bloody pericardial effusion, and elevated levels of CEA (> 5 ng/mL) and CYFRA 21-1 (> 50 ng/mL) in the pericardial fluid.

Key words: pericarditis, lung cancer, malignancy, diagnosis, computed tomography, cardiac tamponade, carcinoembryonic antigen, cytokeratin
RESULTS

Malignant pericarditis: 66 (35%) patients, including 28 women and 38 men, median age 53 (range 26–81) years. Malignant cells were found in the pericardial fluid in 46 patients, malignant infiltrate was identified in the pericardial specimen in 14 patients, and in 6 patients, the diagnosis of a malignancy was confirmed in the examination of both the pericardial fluid and the pericardial specimen. Lung cancer was the most common cause of malignant pericarditis, noted in 44 (67%) cases, including adenocarcinoma in 26 (39%) cases. Of the remaining patients, pleural mesothelioma and primary pericardial mesothelioma were found in 4 patients each, breast cancer in 3 patients, and kidney cancer, stomach cancer, ovarian cancer, colon cancer, pancreatic cancer, uterine cancer, and lymphoma were found in 1 patient each. In 4 cases, we were unable to identify the origin of a disseminated malignancy.

Probable malignant pericarditis: 45 (23%) patients, including 19 women and 26 men, median age 55 (range 18–77) years. Cytological examination of the pericardial fluid yielded a negative result in all patients in this group. Malignancy identified at a distant location included lung cancer in 24 (53%) patients, breast cancer in 3 patients, pleural mesothelioma in 3 patients, ovarian cancer in 2 patients, and oesophageal cancer. colon cancer, thymoma, lymphoma, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, and malignant melanoma in 1 patient each. Adenocarcinoma was diagnosed in 6 cases, but the origin of the malignancy could not have been identified due to a disseminated disease.

Non-malignant pericarditis: 80 (42%) patients, including 44 women and 36 men, median age 62 (range 21–88) years. Malignant cells were identified in the cytological examination of the pericardial fluid in none of these patients. Histological examination of a pericardial specimen was performed in 52 patients, and identified unspecific inflammatory infiltrate in 20 patients, fibrous tissue in 24 patients, fragments of pericardial tissue with ecchymoses in 5 patients, a fragment of normal pericardium in 2 patients, and a tuberculous granuloma in 1 patient. The final diagnosis in this group included idiopathic pericarditis in 21 (26%) patients, tuberculous pericarditis in 21 (26%), bacterial pericarditis in 13 (16%), viral pericarditis in 10 (13%), pericarditis related to a collagen vascular disease in 6 (8%), Dressler syndrome in 5 (6%), mycobacteriosis-related pericarditis in 1 (23%), uраemic pericarditis in 1 (1%) patient, and pericarditis related to hypothyroidism in 1 (1%) patient.

Diagnostic value of the cytological examination of the pericardial fluid and histological examination of the pericardial specimen in the diagnosis of malignant pericarditis. Among 111 patients with the diagnosis of a malignancy (Groups 1 and 2), a positive result of the cytological examination was obtained in 52 cases. A negative result of the cytological examination of the pericardial fluid was obtained in all 80 patients without the diagnosis of a malignancy (sensitivity 46%, specificity 100%, positive predictive value [PPV] 100%, negative predictive value [NPV] 58%). Histological examination of a pericardial specimen was performed in 96 cases, including 44 patients with the diagnosis of a malignancy and 52 patients without a malignancy. Malignant infiltrate was identified in 20 of 44 patients with the diagnosis of a malignancy and in none of the patients without a malignancy (sensitivity 46%, specificity 100%, PPV 100%, NPV 68%).

Assessment of the value of specific diagnostic methods in predicting malignant pericarditis. History and physical examination findings are shown in Figure 1. Among patients with malignant pericarditis, cough and tachycardia > 100 bpm were found to be significantly more common compared to the patients with non-malignant pericarditis.

Results of the imaging studies are shown in Table 1. Chest X-ray showed pleural involvement and parenchymal lung lesions significantly more commonly among patients with malignant pericarditis than among those with non-malignant pericarditis. Compared to the patients with non-malignant pericarditis, patients with malignant pericarditis also presented significantly more frequently with tachycardia > 100 bpm, low QRS amplitude and electrical alternans in the electrocardiogram (ECG), and evidence of cardiac tamponade in the echocardiographic examination.

Chest computed tomography (CT) findings are shown in Table 2 and Figure 2. Among patients with malignant pericarditis, enlarged mediastinal lymph nodes (> 10 mm) and pericardial thickening > 8 mm were found more frequently compared to the patients with non-malignant pericarditis.

The evacuated pericardial effusion was bloody in 94% of patients with malignant pericarditis and 43% of patients with non-malignant pericarditis (p < 0.0001).

Median CEA level in patients with malignant pericarditis was significantly higher compared to the patients with non-malignant pericarditis (40.8 ng/mL [range 0–305] vs. 0.9 ng/mL).
Table 1. Chest roentgenogram, electrocardiography, and echocardiography findings in the examined patient groups

<table>
<thead>
<tr>
<th>Examen</th>
<th>Malignant pericarditis</th>
<th>Non-malignant pericarditis</th>
<th>Probable malignant pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged cardiac silhouette</td>
<td>61/64 (95%)</td>
<td>72/77 (94%)</td>
<td>41/44 (93%)</td>
</tr>
<tr>
<td>Pleural involvement</td>
<td>49/64 (77%)*</td>
<td>44/77 (57%)*</td>
<td>36/44 (82%)</td>
</tr>
<tr>
<td>Parenchymal lung lesions</td>
<td>37/64 (58%)**</td>
<td>30/77 (39%)**</td>
<td>20/44 (45%)</td>
</tr>
<tr>
<td><strong>Electrocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia &gt; 100 bpm</td>
<td>49/64 (77%)*</td>
<td>34/79 (43%)*</td>
<td>25/45 (56%)</td>
</tr>
<tr>
<td>Low QRS amplitude</td>
<td>33/64 (52%)*</td>
<td>27/79 (34%)*</td>
<td>19/45 (42%)</td>
</tr>
<tr>
<td>Electrical alternans</td>
<td>12/64 (19%)†</td>
<td>2/79 (3%)†</td>
<td>6/45 (13%)</td>
</tr>
<tr>
<td>Non-specific ST-T changes</td>
<td>50/64 (78%)</td>
<td>52/79 (66%)</td>
<td>36/45 (80%)</td>
</tr>
<tr>
<td>Arrhythmia and conduction disturbances</td>
<td>23/64 (36%)</td>
<td>36/79 (46%)</td>
<td>20/45 (44%)</td>
</tr>
</tbody>
</table>

| Echocardiography                 |                         |                             |                                 |
| Maximum fluid thickness [mm]: median (range) | 27 (6–55) | 25 (4–60) | 32 (7–50) |
| Evidence of cardiac tamponade    | 44/60 (67%)@           | 28/77 (34%)@                | 23/45 (51%)                     |

*p = 0.015, **p = 0.026, *p = 0.01, *p = 0.031, †p = 0.001, ‡p = 0.0001

Table 2. Chest computed tomography in the examined patient groups

<table>
<thead>
<tr>
<th>Chest computed tomography</th>
<th>Malignant pericarditis</th>
<th>Non-malignant pericarditis</th>
<th>Probable malignant pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>29</td>
<td>48</td>
<td>22</td>
</tr>
<tr>
<td>Maximum fluid thickness [mm]: median (range)</td>
<td>21 (1–70)</td>
<td>35 (10–60)</td>
<td>20 (5–50)</td>
</tr>
<tr>
<td>Pericardial thickness [mm]: median (range)</td>
<td>10 (2–55)</td>
<td>4 (2–50)</td>
<td>4 (2–10)</td>
</tr>
<tr>
<td>Pericardial thickness &gt; 8 mm: number of patients (%)</td>
<td>16/26 (62%)*</td>
<td>7/43 (16%)*</td>
<td>4/21 (19%)</td>
</tr>
<tr>
<td>Mediastinal lymph nodes &gt; 10 mm</td>
<td>26/29 (90%)**</td>
<td>14/48 (29%)**</td>
<td>14/22 (64%)</td>
</tr>
<tr>
<td>Parenchymal lung lesions</td>
<td>19/29 (66%)†</td>
<td>14/48 (29%)*</td>
<td>10/22 (45%)</td>
</tr>
<tr>
<td>Pleural involvement (fluid or infiltrate)</td>
<td>23/29 (79%)*</td>
<td>21/48 (44%)*</td>
<td>20/22 (91%)</td>
</tr>
</tbody>
</table>

*p < 0.0001, **p < 0.00001, †p < 0.0001, ‡p < 0.0005

Figure 2. L.M., a 62-year-old women. Chest computed tomography with contrast enhancement, mediastinal window; A. Lung tumour in the left upper lobe. Enlarged mediastinal nodes are also seen (*); B. Pericardial effusion (**)
In our study, malignancy was found in 58% of patients undergoing invasive treatment for effusive pericarditis. Malignancy was thought to be a definite cause of pericardial effusion in 35% of patients, and considered a probable cause in 23% of patients, as malignant cells were not identified in the pericardial fluid, and malignant infiltrate was not found in the pericardial specimen. In other studies, malignancy was reported as the aetiology of pericarditis in 20–76% of patients with pericardial effusion [1, 2, 13], mostly in patients with large effusions (> 2 cm) and more commonly among patients treated in 1970–2000 compared to those hospitalised after 2000 [2]. Studies by Maisch et al. [13] and Posner et al. [14] suggest that in 30–50% of patients with established malignancy and pericardial effusion, effusive pericarditis may have a non-malignant nature. In such cases, causes include radiation-induced pericarditis, and infective pericarditis complicating malignancy [13, 14].

In our study population, adenocarcinoma of the lung was the predominant cause of effusive pericarditis, similarly to other reports [1, 3]. Of note, primary pericardial mesothelioma was diagnosed in 4 patients, a rare neoplasm that might pose particular diagnostic and therapeutic problems [15].

Among non-malignant causes of effusive pericarditis in our study population, tuberculous pericarditis was diagnosed in 26% of patients. This rate is much higher compared to that reported in most European countries and the United States, where tuberculous pericarditis is identified in about 4–7% of patients with a haemodynamically significant effusion [1]. However, incidence of tuberculosis in the Polish population (19.7/100,000 in 2010) [16] is higher compared to the United States (3.6/100,000) [17]. As recently reported by Kuś et al. [18], the proportion of subjects infected with tuberculosis in the population of the Mazovian voivodeship, as determined by a positive result of the Quantiferon-TB Gold In-Tube test, was 23%.

Sensitivity of the cytological examination of the pericardial fluid and histological examination of the pericardial specimen for the diagnosis of malignant pericarditis in our study population was similar at 46%. According to other authors, sensitivity of the cytological examination of the pericardial fluid was 41–75%, depending on the histological type of the malignancy [19], and sensitivity of the histological examination was 24–85%, depending on the number of obtained specimens and collection technique [1, 13].

The most significant difference between the study groups was the presence of enlarged mediastinal lymph nodes in chest CT in 90% of patients with malignant pericarditis, as compared to 27% of patients with non-malignant pericarditis. In 2010, Sun et al. [20] reported enlarged mediastinal lymph nodes in chest CT in 60.7% of patients with malignant pericarditis and only 6.5% of patients with non-malignant pericarditis. Until that publication, the only report regarding the diagnostic value of enlarged mediastinal lymph nodes in malignant pericarditis was published by our group [12]. In 2003, Cherian et al. [21] reported enlarged mediastinal lymph nodes in 100% of patients with tuberculous pericarditis but none of the patients with viral pericarditis and postcardiotomy syndrome. It may be thus suspected that the higher proportion of tuberculous pericarditis among patients with non-malignant pericarditis, the lower is the specificity of this finding. In our study population, similarly to a study by Prakash et al. [22], chest CT showed significantly increased pericardial thickness among patients with malignant pericarditis compared to those with non-malignant pericarditis. However, this observation should be interpreted with caution, as our study population included a relatively large number of patients with mesothelioma which is associated with marked pericardial thickening.

In our study population, patients with malignant pericarditis were characterised by a significantly higher CEA level in the pericardial fluid compared to patients with non-malignant pericarditis. High diagnostic value of CEA level in the pericardial fluid was initially reported by Koh et al. [23], and later confirmed in a study published previously by our group [24].

In the present study, CYFRA 21-1 level in the pericardial fluid was also found to be significantly higher among patients with malignant pericarditis as compared to those with non-malignant pericarditis. Elevated CYFRA 21-1 levels in the serum and pleural fluid were reported in patients with lung cancer and pleural mesothelioma [25]. Evaluation of CYFRA 21-1 level in the pericardial fluid reported in the present study is a novel approach. Apart from reports published by our group in 2005 and 2006 [12, 24], no data have been reported on this subject in the available scientific literature.
CONCLUSIONS

1. Malignancy was found in 58% of patients undergoing invasive treatment due to large pericardial effusion.
2. Cytological examination of the pericardial fluid and histological examination of a pericardial specimen showed high specificity (100%) but low sensitivity (46%) in the diagnosis of malignant pericarditis.
3. The most important predictors of malignant pericarditis included tachycardia of > 100 bpm as revealed by the physical examination and ECG, echocardiographic evidence of cardiac tamponade, presence of enlarged mediastinal lymph nodes (> 1 cm) and thickened pericardium (> 8 mm) by chest CT, bloody pericardial effusion, and elevated levels of CEA (> 5 ng/mL) and CYFRA 21-1 (> 50 ng/mL) in the pericardial fluid.

Conflict of interest: none declared

References

Rozpoznawanie nowotworowego zapalenia osierdzia — doświadczenie jednoośrodkowe

Anna Pawlak-Cieslik1, Monika Szturmowicz1, Anna Fijałkowska1, Juliusz Gątarek2, Renata Gralec3, Katarzyna Blasińska-Przerwa4, Ewa Szczepulska-Wójcik5, Agnieszka Skoczyńska6, Anna Bilska1, Witold Tomkowski3


Streszczenie

Wstęp: Najczęstszą przyczyną wysiękowego zapalenia osierdzia (ZO), przebiegającego ze znaczącą hemodynamicznie objętością płynu, jest choroba nowotworowa. Wczesne rozpoznanie i leczenie nowotworowego ZO może istotnie poprawić rokowanie.

Cel: Celem pracy była retrospektywna ocena częstości i obrazu klinicznego nowotworowego ZO wśród chorych leczonych zabiegowo i próba określenia optymalnych metod diagnostycznych pozwalających odróżnić tę grupę chorych od pozostałych.

Metody: Badaną grupę stanowiło 191 chorych (100 mężczyzn i 91 kobiet, mediana wieku 57 lat, zakres 19–88 lat) z wysiękowym ZO, poddanych leczeniu zabiegowemu w Instytucie Gruźlicy i Chorób Płuc w Warszawie w latach 1982–2008 z powodu znaczącej ilości płynu w worku osierdziowym i/lub echokardiograficznych cech tamponady serca. W 93 przypadkach wykonano zabieg perikardiocentezy, w 61 — perikardioskopii i w 37 — perikardiotomii podmostkowej. W wszystkich chorych uzyskano płyn osierdziowy do badań, w 96 przypadkach pobrano wycinek osierdziowy. Pacjentów podzielono na 3 grupy: 1 — nowotworowe ZO (komórki nowotworowe w badaniu cytologicznym płynu z osierdzia i/lub naciek nowotworowy w badaniu histologicznym wycinków z osierdzia), 2 — prawdopodobnie nowotworowe ZO (wysięk w osierdziu bez komórek nowotworowych w płynie oraz obecność potwierdzonego histologicznie nowotworu o innym umiejscowieniu), 3 — nienowotworowe ZO (negatywne badanie cytologiczne płynu osierdziowego i histologiczne wycinka pobranego z osierdzia, bez choroby osierdzowej w czasie hospitalizacji i rocznej obserwacji odległej).

Wyniki: Spóśród 191 pacjentów chorobę nowotworową stwierdzono w 111 (58%) przypadkach. U 66 (35%) osób była ona pewną przyczyną wysięku osierdziowego, a u 45 (23%) — przyczyną prawdopodobną. Wśród przyczyn nowotworowego ZO dominował rak płuca — 44 (67%) przypadki, w tym podtyp gruczolakoraka. Nienowotrowe ZO stwierdzono u 80 (42%) osób. Wśród chorych ze zdiagnozowanym nowotworem (grupa 1 i 2) dodatni wynik badania cytologicznego płynu osierdziowego uzyskano w 52 przypadkach (czułość 46%). Wśród pacjentów bez choroby nowotworowej w wszystkich 80 przypadkach uzyskano ujemny wynik badania cytologicznego płynu osierdziowego (swoistość 100%). Naciek nowotworowy stwierdzono u 20 spośród 44 chorych ze zdiagnozowanym nowotworem (czułość 46%) i u żadnego spośród 52 pacjentów bez choroby nowotworowej (swoistość 100%). W grupie chorych z nowotworowym ZO istotnie częściej niż w grupie chorych z nienowotrowym ZO stwierdzano: tachykardię > 100/min w badaniu EKG (odpowiednio 77% i 43%; p = 0,01), niski woltaż zespołów QRS (odpowiednio 52% i 34%; p = 0,03), naprzemiennece węzły chłonne śródpiersia w badaniu TK klatki piersiowej (odpowiednio 90% i 29%; p < 0,00001) i grubość osierdzia > 8 mm w badaniu TK klatki piersiowej (odpowiednio 62% i 16%; p < 0,0001), krwisty płyn osierdziowy (odpowiednio u 94% i 43%; p < 0,0001). Stężenie antygenu rakowo-płodowego (CEA) i fragmentów cytokeratyny 19 (Cyfra 21-1) w płynie osierdziowym było istotnie wyższe u chorych z nowotworowym ZO niż nienowotrowym, a mediany wynosiły odpowiednio: 40,8 ng/ml i 0,9 ng/ml (p < 0,0001) oraz 162,85 ng/ml i 13,35 ng/ml (p < 0,0001).

Wnioski: 1. Wśród chorych leczonych zabiegowo z powodu dużej objętości płynu w worku osierdziowym u 58% stwierdzono chorobę nowotworową. 2. Badanie cytochalagiczne płynu osierdziowego i badanie histopatologiczne wycinka z osierdzia wykazały wysoką swoistość (100%), a niższą czułość (46%) w rozpoznawaniu nowotworowego ZO. 3. Elementami szczególnie istotnymi w przewidywaniu nowotworowego etiologii wysięku osierdziowego były: tachykardia > 100/min w badaniu przedmiotowym, cechy tamponady serca, obecność powiększonych (> 1 cm) węzłów chłonnych śródpiersia i grubość osierdzia > 8 mm w badaniu TK klatki piersiowej, krwisty płyn osierdziowy, podwyższone stężenie CEA (> 5 ng/ml) i Cyfra 21-1 (> 50 ng/ml) w płynie osierdziowym.

Słowa kluczowe: zapalenie osierdzia, rak płuc, nowotwory, diagnostyka, tomografia komputerowa, tamponada serca, antygen rakowo-płodowy, cytokeratyny