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# Cytopathology of pericardial effusions

## Experience from a tertiary center of cardiology

Pericardial effusion (PE) is a common clinical condition that can develop as a result of systemic or cardiac diseases. PE has a broad spectrum starting from mild asymptomatic effusion to tamponade. It may develop slowly or suddenly [1–3] with infectious or noninfectious etiology [4].

Any condition that creates an inflammatory process causes increased production of pericardial fluid and may lead to the formation of exudative fluid. Other alternative mechanisms such as increased systemic venous pressure secondary to congestive heart failure and pulmonary hypertension lead to decreased reabsorption and thereby transudative effusion [5]. The most common causes of PE are infections (viral, bacterial, e.g., tuberculosis), cancer, connective tissue diseases, pericardial injury syndromes (postpericardiotomy syndromes, post-traumatic pericarditis, postmyocardial infarction effusions), metabolic causes (hypothyroidism, renal insufficiency), and myopericardial diseases. Moreover, PE may develop as a result of the opening of an aortic dissection into the pericardium or the use of drugs such as minoxidil. PE may occur after hypoalbuminemia, which develops secondary to hydropericardium, noninflammatory transudative PE, heart failure, cardiac cirrhosis, or nephrotic syndrome [5].

The cause of PE is found to be idiopathic in nearly 50% of cases in developed countries [6]. The other observed causes are: 10–25%, cancer; 15–30%, pericarditis and infectious causes; 15–20%, iatrogenic causes; and 5–15%, connec-

tive tissue diseases [6]. More than 60% of PE is caused by tuberculosis in developing countries and in areas where tuberculosis is endemic [6]. In the case of pericarditis with PE, malignant or infectious causes vary between 15 and 50% [7].

Data on the pericardial cytology of PE are limited. We therefore aimed to report the results of pericardial cytology in patients who underwent pericardiocentesis owing to PE.

### Patients and methods

Patients who underwent primary percutaneous pericardiocentesis between 2007 and 2016 were enrolled in the study retrospectively. Patients in whom surgical pericardial window placement was performed were excluded from the study as were patients with iatrogenic PE. All samples were sent to the pathology laboratory for cytological examination.

### Pathology

Fresh pericardial fluid specimens were delivered to the pathology laboratory. The specimens were centrifuged at 1,500 rpm for 15 min. One drop of sediment was placed in the cytospin chamber. Two cytospin slides and a cell block were prepared for each specimen. Of the two cytospin slides, one was air-dried and the other was fixed in 95% alcohol. The air-dried slide was stained using May-Grünwald-Giemsa (MGG) staining and the 95% alcohol-fixed slide with Papanicolaou (PAP)

staining. Immunohistochemical staining was performed on the cell block in selected cases. The cytological microscopic interpretation was divided into three general categories: “benign,” “malignant,” and “atypical.” The presence of reactive mesothelial cells, acute and chronic inflammatory cells, and/or blood without evidence of malignant cells was considered as benign. The benign category included nonspecific (neutrophilic and lymphocytic) inflammation and specific (rheumatoid) inflammation. The presence of malignant cells with/without reactive mesothelial cells, inflammatory cells, and/or blood was considered as malignant. For the malignant cases, tumor type and/or favored primary tumor site were stated based on cytomorphologic characteristics and immunohistochemical staining performed on the cell block. Specimens that included rare cells with atypical cytological features, and when a definitive diagnosis (benign versus malignant) could not be made, were considered as atypical.

### Statistical analyses

Continuous variables are presented as mean ± standard deviation or median (interquartile range), while categorical variables are presented as numbers and percentages. Categorical variables were compared using chi-square or Fisher's exact tests when appropriate. A two-sided *p* value of less than 0.05 was considered significant in all analyses. The collection and statistical analysis of data were

**Table 1** Cytological diagnoses

	Patients, n (%)
Benign pericardial effusion	219 (77.4%)
Malignant pericardial effusion	44 (15.5%)
Atypical pericardial effusion	20 (7.1%)

performed using SPSS 11.5 (SPSS Inc., Chicago, Ill.).

## Results

The study comprised 283 patients whose mean age was  $60.0 \pm 16.6$  years; 162 (57.2%) patients were male and 121 (42.8%) were female. The cytological diagnoses of the patients are listed in **Table 1**. The vast majority of PE specimens (219 cases; 77.4%) were classified as benign. Only 20 cases (7.1%) were classified as “atypical” in terms of cytology, and malignant cells were present in the PE specimens of 44 cases (15.5%). The most common diagnosis was benign PE.

The cytological diagnoses of benign PE are shown in **Table 2**. Of 219 benign PE cases, 52 (23.7%) were acute nonspecific pericarditis, 166 (75.7%) were chronic nonspecific pericarditis, and one (0.45%) was cholesterol pericarditis (rheumatoid inflammation) according to the clinical, radiologic, biochemical, immunologic, and microbiologic background of the patient. The most prevalent type of pericarditis was chronic nonspecific pericarditis in the benign group.

The cytological diagnoses of malignant PE are shown in **Table 3**. Of 44 malignant PE cases, four (9.1%) were mesothelioma and 40 (90.1%) were metastasis (two hematologic malignancy and 38 carcinomas). Examining the primary origins of metastatic carcinomas indicated that 24 originated from the lung (24 adenocarcinoma), three from the upper gastrointestinal tract (one signet ring gastric carcinoma and two cases of esophageal cancer), one from

**Table 2** Cytological diagnoses of benign pericardial effusion

	Patients, n (%)
<i>Nonspecific pericarditis</i>	
Acute nonspecific pericarditis	52 (23.7%)
Chronic nonspecific pericarditis	166 (75.7%)
<i>Specific pericarditis</i>	
Cholesterol pericarditis (rheumatoid inflammation)	1 (0.45%)

the breast, one from the cervix, and one from the kidney. The primary origins of the other eight cases were indefinite. The most commonly encountered malignancy was lung cancer. Adenocarcinoma was detected in all patients with lung cancer. The second most common malignancy was cancer of unknown primary origin and the third was mesothelioma.

The cytological diagnoses of serous and hemorrhagic effusion are shown in **Table 4**. Chronic nonspecific pericarditis was identified as the most common cause in both the serous and hemorrhagic groups. The rate of malignancy was found to be 1.9% in the serous group and 24% in the hemorrhagic group ( $p < 0.001$ ).

## Discussion

In our study, benign PE was the most frequently observed cytological diagnosis of PE. Chronic nonspecific pericarditis was detected as the most frequent pericarditis in the benign group. Lung adenocarcinoma was the most frequently detected malignancy in the malignant PE group. The rate of malignancy was significantly higher in the hemorrhagic group than in the serous group.

Guidelines on pericardial disease differentiate between acute and chronic pericarditis according to the clinical duration, starting from the onset of disease [8]. In our study, the benign PE group was divided into three groups according to cytology findings as: (a) acute nonspecific pericarditis, (b) chronic nonspecific pericarditis, and (c) specific cholesterol pericarditis (rheumatoid inflammation). We think that nonspecific pericarditis may include all of the diseases mentioned in the guidelines in both groups.

**Table 3** Cytological diagnoses of malignant pericardial effusion

	Patients, n (%)
<i>Primary cancer of the pericardium</i>	
Malignant mesothelioma	4 (9.1%)
<i>Secondary or metastatic tumors of the pericardium</i>	
a) Carcinomas	
Lung adenocarcinoma	24 (54%)
Upper GIS carcinoma	3 (6.8%)
Breast cancer	1 (2.2%)
Cervical cancer	1 (2.2%)
Renal cancer	1 (2.2%)
Malignancy of unknown primary	8 (18.1%)
b) Hematologic malignancies	
Acute lymphoblastic leukemia	1 (2.2%)
Large B cell lymphoma	1 (2.2%)
GIS gastrointestinal system	

However, in our study, we did not specify the clinical features because our main aim was to report on the cytological data. There are different reports in the literature regarding the cytology study results of PE. In the pericardial cytology study of Dragoescu and Liu, 74.2% of patients had benign PE [9]. In a single-center study with 6-year pericardial cytology data of 116 patients with PE, the rate of malignancy was higher [10]. In our study, 77.4% of the effusions were detected as benign. There was one case of cholesterol pericarditis in our study [11]. Cholesterol pericarditis is an uncommon condition, characterized by increased levels of cholesterol in the pericardial fluid [12, 13]. Although it is usually idiopathic, it may develop secondary to some systemic diseases such as rheumatoid arthritis, tuberculosis, and hypothyroidism [14].

Malignant invasion of the pericardium can be seen in about 10% of all cancer patients, and one third of these patients die as a result of this involvement. Primary tumors of the pericardium are very rare, whereas secondary or metastatic tumors of the pericardium are quite common; lung cancer, breast cancer, melanoma, and hematological malignancies constitute the majority of the latter [15–18]. Dragoescu and Liu indicated that peri-

cardial fluid cytology is better than pericardial biopsy for detecting malignancy [9]. The diagnosis of malignant PE is made on the basis of positive results from cytological examinations of pericardial fluid. Although pericardial fluid cytology is specific, its sensitivity varies. Despite the frequent examination of tumor markers after pericardiocentesis, their diagnostic use has not been well established [19]. In a study including 140 Chinese patients undergoing pericardiocentesis, malignancy and tuberculosis were detected as the most common cause of moderate and large effusion. Lung cancer was the most common cause among the malignancies [20].

In a series including 322 patients with moderate and severe PE, idiopathic pericarditis was found in 20%, iatrogenic causes in 16%, cancer in 13%, and chronic idiopathic PE in 9% of the patients. In 192 (60%) of the patients, the cause of the effusion was a known medical condition [21]. In a single-center study examining the 6-year pericardial cytology data of 116 patients with PE, 74 patients had malignancy clinically, 39 patients did not have malignancy, and in three patients no diagnosis could be made. Lung cancer was the most common cause among the patients with malignancy [10]. In a pericardial cytology study conducted by Dragoescu and Liu that included 128 patients, 95 (74.2%) patients had benign PE, 31 (24.2%) patients had malignant PE, and two patients had severe atypical cells. The benign etiology included 23.1% of cases of neoplasia, 19% of cases with an idiopathic cause, 14.7% of cases with an infectious cause, and 12.6% of cases of connective tissue disease. The most commonly detected cancer was lung adenocarcinoma. Lung cancer was the most commonly seen malignancy in both genders, 75% of men and 52.2% of women. In women, breast cancer (39.1%) was the second most common tumor [9]. In this study, the main point to be emphasized was that the differentiation of benign and malignant could be made easily via cytological examination in 98.4% of the specimens. Sometimes cytological examination cannot distinguish malignant mesothelial cells from reactive mesothelial cells or metastatic cells. These differ-

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## Cytopathology of pericardial effusions. Experience from a tertiary center of cardiology

### Abstract

**Background.** Pericardial effusion (PE) is a common clinical condition that can develop as a result of systemic or cardiac diseases. Here, we report the results of cytology for patients who underwent pericardiocentesis for PE.

**Methods.** The study comprised 283 patients who underwent primary percutaneous pericardiocentesis between 2007 and 2016. The mean age of the patients was  $60.0 \pm 16.6$  years; 162 (57.2%) were male and 121 (42.8%) were female. The presence of reactive mesothelial cells, acute and chronic inflammatory cells, and/or blood without evidence of malignant cells was considered as benign. The presence of malignant cells with/without reactive mesothelial cells, inflammatory cells, and/or blood was considered as malignant.

**Results.** The vast majority of PE specimens (219 cases; 77.4%) were classified as benign. Only 20 cases (7.1%) were classified as

atypical, and malignant cells were present in the PE specimens of 44 cases (15.5%). The most common diagnosis was benign PE. The most commonly encountered malignancy was lung cancer. The rate of malignancy was 1.9% in the serous group and 24% in the hemorrhagic group, which was statistically significant.

**Conclusion.** Benign PE was the most frequent cytological diagnosis in our study. Chronic nonspecific pericarditis was the most frequent type of pericarditis in the benign PE group, while lung adenocarcinoma was the most frequent malignancy in the malignant PE group. The rate of malignancy was significantly higher in the hemorrhagic group than in the serous group.

### Keywords

Hemopericardium · Pericarditis · Pericardiocentesis · Pathology · Cytology

## Zytopathologie des Perikardergusses. Erfahrungen eines kardiologischen Zentrums der Maximalversorgung

### Zusammenfassung

**Hintergrund.** Ein Perikarderguss (PE) ist ein häufiges klinisches Ereignis, das infolge systemischer oder kardialer Erkrankungen auftreten kann. Im vorliegenden Beitrag wird über die zytologischen Ergebnisse von Patienten berichtet, bei denen wegen eines PE eine Perikardpunktion erfolgte.

**Methoden.** Die Studie umfasste 283 Patienten, bei denen zwischen 2007 und 2016 eine primäre Perikardpunktion durchgeführt wurde. Das Durchschnittsalter der Patienten lag bei  $60,0 \pm 16,6$  Jahren; 162 (57,2%) Männer und 121 (42,8%) Frauen. Das Vorliegen reaktiver Mesothelialzellen, akuter und chronischer Entzündungszellen und/oder von Blut ohne Anhalt für maligne Zellen wurde als benigne eingestuft. Das Vorliegen maligner Zellen mit/ohne reaktive Mesothelialzellen, Entzündungszellen und/oder Blut wurde als maligne eingestuft.

**Ergebnisse.** Die überwiegende Mehrheit der PE-Punktate (219 Fälle; 77,4%) wurde als benigne klassifiziert. Nur 20 Fälle (7,1%)

wurden als atypisch eingestuft, und in den PE-Punktaten von 44 Fällen (15,5%) lagen maligne Zellen vor. Die häufigste Diagnose war ein benigner PE. Häufigstes Malignom war das Bronchialkarzinom. Die Malignomrate betrug 1,9% in der Gruppe mit serösem PE, aber 24% in der Gruppe mit hämorrhagischem PE, was statistisch signifikant war.

**Schlussfolgerung.** Ein benigner PE war die häufigste zytologische Diagnose in der vorliegenden Studie. In der Gruppe mit benignem PE kam als häufigster Typ der Perikarditis die chronische nichtspezifische Form vor, während in der Gruppe mit malignem PE das Bronchialkarzinom das häufigste Malignom darstellte. Die Malignomrate war in der Gruppe mit hämorrhagischem PE signifikant höher als in der Gruppe mit serösem PE.

### Schlüsselwörter

Hämoperikard · Perikarditis · Perikardpunktion · Pathologie · Zytologie

**Table 4** Cytological diagnoses of serous and hemorrhagic effusion

	Serous effusion Patients, n (%)	Hemorrhagic effusion Patients, n (%)	
Acute pericarditis	23 (21.3%)	29 (16.6%)	$p < 0.001$
Chronic nonspecific pericarditis	78 (72.2)	88 (50.3%)	
Atypical pericardial effusion	4 (3.7%)	16 (9.1%)	
Malignant pericardial effusion	2 (1.9%)	42 (24%)	
Cholesterol pericarditis	1 (0.9%)	–	

ent diagnoses may include primary tumors such as mesothelioma, tumors such as angiosarcoma or rhabdomyosarcoma that originate from the pericardium, mediastinal tumors, chronic inflammation such as tuberculosis, or metastatic tumors [22–26]. In our study, in 7.1% of the patients, the differentiation between benign and malignant could not be made with cytological methods. Moreover, the primary origin of the tumor could not be determined by cytology in 18.1% of patients with malignant PE in our study.

PE formation from malignancies is a multifactorial process and can also be caused by treatment modalities, especially radiotherapy treatment, direct proliferation of the tumor in the pericardium, hematogenous or lymphatic pericardial spread, or processes such as uremia or thrombocytopenia [27]. Similar to reports to the literature, lung cancer was detected as the most frequent malignancy in our study. All of the lung cancer cases were adenocarcinoma. This finding is consistent with previous studies in the literature.

Mesothelioma is a malignancy originating from the epithelial cells of the mesothelium. Primary malignant pericardial mesotheliomas are very rare, and their incidence is 0.0022% [28]. It commonly affects men and develops in the fifth and seventh decades of life [29]. Primary malignant pericardial mesotheliomas make up 0.7% of all mesotheliomas, and primary malignant pericardial mesothelioma is the most common cause of primary pericardial tumors, accounting for nearly half of them [30]. Four patients were found to have mesothelioma in our study. This higher rate compared with the literature can be attributed to asbestos, which is still widely used in our country.

Patients with hemorrhagic PE are more likely to have malignancy as the etiologic cause compared with those with serous PE. In a study conducted by Meyers et al. of 175 patients, it was found that PE was hemorrhagic in 80% of patients with malignancy and this was statistically significant [31]. In another study by Colombo et al., it was found that neoplasia (36%), idiopathic pericarditis (32%), and uremia (20%) were the most frequent etiologic causes in 25 patients with severe PE, and all cases of PE in the neoplastic group were hemorrhagic [32]. In a study conducted by Zayas et al. of 100 patients with acute pericarditis, 27 patients underwent pericardiocentesis, and benign causes were significantly higher in the serous pericardial fluid group [33]. In line with the literature, we also found that the malignancy rate was significantly higher in the hemorrhagic group than in the serous group.

### Limitations

The main limitation of our study is that it is single-center study and was not carried out as a randomized and prospective study. The absence of clinical characteristics and follow-up data of the patients are other limiting factors.

### Conclusion

**In our study, benign PE was the most frequent cytological diagnosis of PE. Chronic nonspecific pericarditis was detected as the most frequent type of pericarditis in the benign group. Lung adenocarcinoma was the most frequently detected malignancy in the malignant PE group. The rate of malignancy was significantly higher in the hemorrhagic group than in the serous**

**group. Cytological investigation cannot alone determine the primary origin of a tumor in patients with malignant PE. In the setting of malignant PE, a multidisciplinary team involving cardiologists, oncologists, radiologists, and possibly gynecologists is essential for an early diagnosis and for appropriate management.**

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### Compliance with ethical guidelines

**Conflict of interest.** C. Gecmen, G.G. Gecmen, D. Ece, M. Kahyaoğlu, A. Kalayci, C.Y. Karabay, O. Candan, M.E. Isik, F. Yilmaz, O. Akgun, M. Celik, I.A. Izgi, C. Kirma, S. Keser declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

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## Wieder mehr Infektionen mit dem Hantavirus

Bundesweit haben die Erkrankungen mit dem Hantavirus im Vergleich zum Vorjahr zugenommen. Das geht aus Zahlen des Robert Koch-Instituts (RKI) hervor. Demnach sind bis Mitte März 136 Fälle gemeldet worden – deutlich mehr als im vergangenen Jahr mit 38 Fällen. Allerdings schwankten die Zahlen von Jahr zu Jahr erheblich, sagte eine Sprecherin des RKI. 2016 sei ein Jahr mit sehr geringen Fallzahlen gewesen. Nur 282 Menschen seien damals erkrankt, 2012 seien es beispielsweise 2.825 gewesen.

### Spitzenreiter Baden-Württemberg

In einigen Teilen Deutschlands ist das Hantavirus derzeit besonders aktiv. So wurden dem Landesgesundheitsamt in Baden-Württemberg seit Jahresbeginn bereits 108 Fälle gemeldet. 2016 habe es dort insgesamt nur 84 Erkrankungen gegeben. Für Baden-Württemberg rechnen Experten derzeit mit mehr als 2.440 Erkrankungen im Jahr 2017.

### Nagetiere übertagen das Hantavirus

Grund für die hohen Zahlen sei der gute Ertrag der Buchen in den Wäldern im vergangenen Jahr. Dadurch habe es viele Bucheckern gegeben, die vor allem der Rötelmaus als Nahrung dienten. Die Rötelmäuse und andere Nagetiere übertragen das Hantavirus. Um sich zu schützen, sollten Menschen nach Expertenangaben vor allem in Gebieten mit viel Buchenwald den Kontakt mit Ausscheidungen von Nagern vermeiden – etwa bei Holzarbeiten in Wald und Garten und bei der Reinigung von Kellern, Schuppen, Scheunen und Ställen. Hantaviren sind nach Angaben des RKI weltweit verbreitet. Übertragen wird es durch Speichel, Kot oder Urin von infizierten Nagetieren wie der Rötelmaus. Atmet der Mensch die Erreger ein – etwa wenn kontaminierter Staub aufgewirbelt wird – kann er sich infizieren. Die Symptome ähneln denen einer Grippe mit Fieber, Kopf-, Bauch- und Rückenschmerzen. Blutdruckabfall und Nierenfunktionsstörungen bis hin zum -versagen können folgen.

Quelle: Deutsches Ärzteblatt  
www.aerzteblatt.de