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Cytology of Pericardial Effusion due to Malignancy

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Background. Malignant pericardial effusion occurs in one tenth of all cancers. It is a very serious disorder that is mainly a secondary process due to metastasis because primary neoplasms of the pericardium such as mesotheliomas, sarcomas being exceedingly rare.

Pericardial effusions with a cardiac tamponade constitute a surgical emergency and the pericardiocentesis represents the first class therapeutic recommendation. Pericardial effusion specimens are uncommon and to the best of our knowledge the current study is the largest systematic evaluation of pericardial fluid cytology performed to date.

Material and Methods. Pericardial effusion specimens from 145 patients collected over a 10 year period were studied by cytology and results were compared with pericardial histology results. The minimum pericardial fluid volume used for adequate cytologic diagnosis in these patients was more than 60 mL.

Results. Cytological diagnosis revealed malignant pericardial exudates in 100% of the studied patients. There was no any false negative result in comparison with histology.

Conclusions. Cytology provides an immediate and accurate means of diagnosis. Immunocytology is very important in the diagnostic evaluation.

Key words: Pericardial effusion, Pericardiocentesis, Cardial tamponade, Pericardial neoplasms, Cytology, Immunocytology.

INTRODUCTION

Normal pericardium is a double-walled sac that contains the heart and the roots of the great vessels. The pericardium is composed of two different layers; an outer fibrous parietal pericardium and an inner visceral pericardium.

The inner visceral pericardium is a serous-type membrane and is located immediately outside of the myocardium. The pericardium prevents sudden dilatation of the heart, especially the right chamber, and displacement of the heart and great vessels, minimizes friction between the heart and surrounding structures, and prevents the spread of infection or cancer from the lung or pleura. The pericardium also contributes to diastolic coupling between the two ventricles.

In between the parietal and visceral pericardium, there is a pericardial cavity filled with 10-50 cc of fluid, an ultrafiltrate of plasma that is produced by the visceral pericardium. Pericardial fluid acts as a lubricant between the heart and the pericardium. Excess fluid or blood accumulation in this cavity is called pericardial effusion.

M-mode and 2-dimensional Doppler echo-cardiography is the most effective technique, and is the gold standard for the diagnosis of pericardial effusion, because it is sensitive, specific, non-invasive, and easily made available at the bedside. Pericardial effusion can be detected as an "echo-free space" on 2-dimensional echocardiography.

Small collections of pericardial fluid, which can be physiologic (25 to 50 mL), may be visible during ventricular systole. When the amount of effusion is more than 50 mL, an echo-free space persists throughout the cardiac cycle.

Malignancy has been noted to be the most common cause of pericardial effusion [1].

Primary neoplasms of the pericardium are 40 times less common than the metastatic ones [2]. The malignant pericardial effusion is mainly a secondary process due to metastasis [3]. Only 12-25% of patients who have metastasis to the pericardium have pericardial effusion. In autopsy series, the prevalence of pericardial involvement varies from 4% in general autopsies to 15-30% in autopsies of cancer patients.

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Approximately 20% of large, symptomatic effusions without an obvious etiology based on routine diagnostic examination constitute the initial presentation of a previously unrecognized cancer [4].

The diagnostic value of the cytological examination in the pericardial liquid is differently presented in the specialty literature [5-7].

The aim of this study is to estimate the diagnostic value of cytological examination in patients with malignant pericardial effusions in establishing the etiological diagnosis and the treatment of patients with cardiac tamponade.

MATERIALS AND METHODS

A total of 145 effusion samples, from 145 patients with cardiac tamponade were received from the University Hospital of Crete, over a 10-year period. Written informed consent was obtained from all participants. The pericardiocentesis was therapeutically performed in all patients.

We analyzed the following tumor markers in the pericardial fluid: carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, carbohydrate antigen (CA) 72-4, squamous cell carcinoma (SCC) antigen and neuron-specific enolase (NSE).

A volume of more than 60 mL was submitted to cytology to ensure adequate diagnosis of pericardial fluids. Appropriate smears (for each patient) were prepared from each effusion sample. One was fixed (95% alcohol) for Papanicolaou stain and the others were air dried for Giemsa stain and immunocytochemistry (ICC). Immunostaining was carried out using the Peroxidase-Antiperoxidase (PAP) protocol. The antibodies used were OPD4, L26 (CD20), CD15, CD30 and PAX5 (for hematopoietic malignancies) involucrin (for squamous cell carcinomas), Chromogranin, Synaptophysin, NSE, S100, CD56 (for small cell lung carcinomas), CK7, CK19, CK20 (for adenocarcinomas) and HMB45, Melan A, Tyrosinase (for melanomas).

RESULTS

ECHOCARDIOGRAPHIC FEATURES

All the patients had a standard echocardiographic examination before pericardiocentesis. Sixty four of patients had a large effusion (circumferential effusions with an arc width of > 1cm) on echocardiography while 34% had a moderate effusion (circumferential effusion with an arc width of < 1 cm at its greatest) and 2% had mild effusion (posteriorly loculated effusions of 1 cm or less in width). Among patients with large effusion 54.5% and 50% had documented evidence of right atrial and right ventricular collapse respectively. On 2D echocardiography 95.5% patients had circumferential and 4.5% had loculated effusion.

Pericardial fluid was hemorrhagic in 68%, serous in 14%, serosanguinous in 11% and purulent in 7%.

Of the tumor markers tested the mean concentrations of the CEA, CA 72-4 and CA 19-9 were significantly high: (CEA = 350.46 ± 1420.18 μg/L, CA 19-9 = 1119.31 ± 2120.37 kU/L, CA 72–4 = 538.90 ± 1164.33 kU/L).

The pericardial neoplastic samples comprised 145 cases. The hematopoietic (HL and NHL) malignancies were the most frequent (50 cases) cause of malignant effusion (34.5%) (Figure 1). Forty six (46) cases were due to squamous lung carcinoma (31.7%), thirty two (32) cases were due to small cell lung carcinoma (22%), eleven (11) cases were due to lung and breast adenocarcinoma (Figure 2) (7.6%), while six (6) cases to malignant melanoma (4.2%) (Table 1). The above diagnoses were confirmed histologically.

Table 1
Distribution of malignancies in 145 Pericardial Effusion specimens

No. of cases 145		
50	Hematopoietic neoplasia	34.5%
46	Squamous carcinomas	31.7%
32	Small cell lung carcinomas	22%
11	Adenocarcinomas	7.6%
6	Melanomas	4.2%

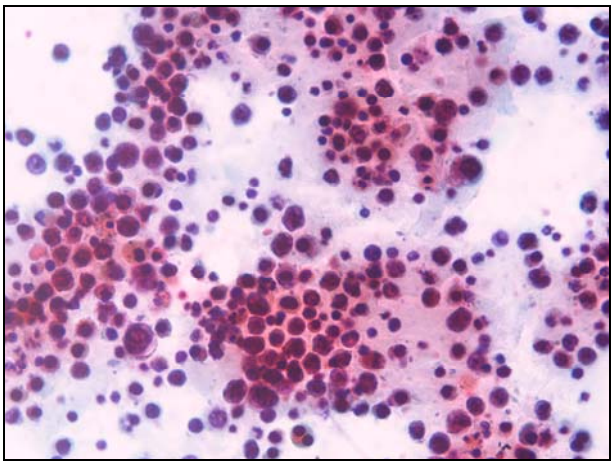

Figure 1. Pericardial Effusion. Direct smear: Non Hodgkin's lymphoma. Numerous neoplastic lymphoid cells with variability in shape and size. Papanicolaou stain × 200.

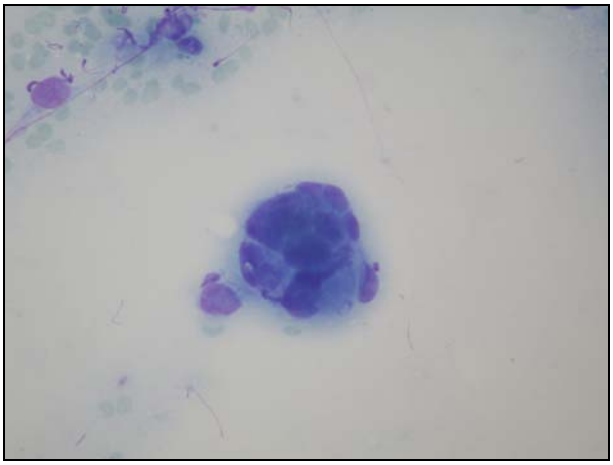

Figure 2. Pericardial Effusion. Direct smear. Metastatic breast adenocarcinoma. Papillary formation of tumor cells. Giemsa stain × 200.

DISCUSSION

The aim of our study is important for emphasizing the role of cytological examination in malignant pericardial fluids. Small-volume pericardiocentesis specimens detect fewer malignancies and have inferior sensitivity compared with pericardial biopsy. A minimum volume of more than 60 mL was necessary for adequate cytologic diagnosis of malignant pericardial effusions in our settings.

Echocardiography is the most useful diagnostic tool for evaluating patients with cardiac tamponade, and it should be performed without delay in patients if suspected.

Cardiac tamponade is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots, or gas as a result of effusion, trauma, or rupture of the heart

Although cardiac tamponade is considered a clinical diagnosis, clinical findings like dyspnea, hypotension, tachycardia, elevated jugular venous pressure, and pulsus paradoxus, are known to have limited sensitivity and specificity.

The most common cause of cardiac tamponade reported is malignancy, which is involved in > 50% of all tamponade cases. Especially lung cancer was involved in > 70% of cardiac tamponade of malignant origin.

When a pericardial effusion is detected by echocardiography, the next step is to assess the size of the effusion, its location, hemodynamic importance, and associated diseases.

The cytological diagnosis revealed malignant pericardial exudates in 100% of the studied patients (diagnostic accuracy 100%).

The diagnosis in all cases of our study required a constellation of cytology- immunocytology and a correlation with the clinical history of the patient.

The cytological evaluation might be false negative in patients with lymphoma or mesothelioma, with 100% specificity but a variable sensitivity.

In this study the use of immunocytology was very important, and thus we had no any false negative diagnosis. Many times it was useful to perform cell blocks too.

Sometimes the cytology examination cannot differentiate the reactive mesothelial cells from the malignant mesothelial or metastatic cells. The differential diagnosis often includes a primary tumor such as mesothelioma [8] or a tumor arising in the pericardium (rhabdomyosarcomas, angiosarcomas, myxosarcomas, fibrosarcomas, leiomyosarcomas, reticulum cell sarcomas, desmoplastic small round cell tumor, and liposarcomas, primary carcinomas) [9], or a mediastinal tumor (lymphoma, thymoma, seminoma or malignant teratoma) [10], a metastasized tumor or a chronic inflammatory lesion like rheumatoid or TBC pericarditis [11, 12].

The literature data shows that pericardial effusions might appear in 20-21% of the patients with cancer [13, 14]. 50% of these patients may have cardiac tamponade and in another 50% of patients. cardiac tamponade is the first manifestation of cancer. These data are in agreement with ours.

In a previous analysis conducted by Dragoescu and Liu [15], authors claim that the performance of pericardial fluid cytology in detecting malignancy is better than that of pericardial biopsy, with a sensitivity of 71%, and a specificity of 100%, compared with 64% sensitivity and 85% specificity for the pericardial biopsy.

Several grading systems have been developed, based on the size of the pericardial effusion. However, a generally accepted system is the effusion graded as minimal (scanty), small, moderate, or large. For circumferential pericardial effusions, any pericardial effusion with less than 5 mm of pericardial separation in diastole (corresponding to a fluid volume of 50 to 100 mL) is defined as minimal; 5 to 10 mm of separation as small (corresponding to a fluid volume of 100 to 250 mL); 10 to 20 mm of separation as moderate (corresponding to a fluid volume of 250 to 500 mL); and greater than 20 mm separation as large (corresponding to a fluid volume greater than 500 mL) [16].

This classification may be useful in daily clinical practice. However, even the diffused and circumferential effusion dimensions of the echo-free space may be different in the views examined; therefore, it is more correct and easier to measure and annotate the dimension of the effusion and to report where it has been evaluated (e.g., 12 mm in the left ventricular lateral wall in the apical four-chamber view; 10 mm along the right atrium in the subcostal view). This methodology not only facilitates the definition of effusion size, but also allows follow-up studies by detecting changes in the amount of pericardial fluid after therapy [16].

Except for the epicardial fat, the abnormal masses attached on the epicardial surface or floating in the pericardial space must also be reported. It may be an infiltrative metastatic mass, inflammatory fibrin strands, pus, or a blood clot [16].

Other imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), may be used to identify the characteristics of pericardial effusion and tamponade in the presence of a technically-limited echocardiographic study.

Currently, these modalities have adjunctive roles to echocardiography, especially in situations that show atypical hemodynamics, presence and severity of tamponade are doubtful, or when there are other unexplained conditions. For instance, in the case of pericardial effusion associated with intrathoracic malignancies, such as lung, breast, or esophageal cancer, chest CT might be useful for understanding the disease progression [16].

The definitive diagnosis of malignant pericardial effusion is established by a positive cytological examination of the pericardial fluid. However, pericardial fluid cytology, although specific, has variable sensitivity. Tumor markers are often investigated after pericardiocentesis but their utility as an aid for the diagnosis of malignant pericardial effusion is not well established [17].

In our settings malignant pericardial effusions were associated with significantly high pericardial concentrations of the tumor markers CEA, CA 72-4, and CA 19-9.

In conclusion, th2e cytological analysis of pericardial fluid has increased the certainty of the etiological diagnosis in patients with no antecedents or clinical data of neoplasia. The use of immunocytochemistry and cell blocks increases the diagnostic value of cytology.

Introducere. *Epanşamentele pericardice maligne apar într-o zecime din toate cancerele. Este o afecțiune foarte gravă şi apare datorită metastazelor sau datorită neoplasmelor pericardului cum sunt mezotelioamele, sarcoamele fiind extrem de rare. Epanşamentele pericardice reprezintă o urgență chirurgicală, iar pericardiocenteza este prima opțiune terapeutică. Epanşamentele pericardice sunt rare şi din cunoştiințele noastre acesta este primul studiu care analizează citologia epanşamentelor pericardice neoplazie într-un număr mare.*

Materiale şi metode. *Lichid pericardic a fost prelevat de la 145 de pacienți cu epanşament pericardic. Pacienții au fost recrutați timp de 10 ani. Citologia a fost comparată cu rezultatul histopatologic. Lichidul minim extras pentru analiză a fost de 60 de mL.*

Rezultate. *În toate cazurile citologia pericardică a evidențiat originea neoplazică a epanşamentului. Nu au fost rezultate fals negative.*

Concluzii. *Citologia lichidului pericardic reprezintă o investigație imediată şi precisă pentru diagnosticul originilor epanşamentelor pericardice, fiind o etapă importantă pentru diagnostic.*

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