To cite this article: Utkusavas A, Akkus M, Kolbas I, Ikitimur H. Pathological diagnoses and adenosine deaminase levels in patients undergoing pericardial window operation for large pericardial effusions. Curr Thorac Surg 2023 Nov; 8(3): 143-147. doi: 10.26663/cts.2023.0025. CTSID: 964. Online ahead of print.

Original Article

Pathological diagnoses and adenosine deaminase levels in patients undergoing pericardial window operation for large pericardial effusions

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ABSTRACT

Background: It might be challenging to determine the etiology of pericardial effusions as studies have usually focused on pericardial effusions in patients suspected to have specific underlying clinical conditions. We aimed to evaluate adenosine deaminase (ADA) levels in pericardial fluid samples of patients with large pericardial effusions in whom pericardial window surgeries with biopsy and pathological examinations were carried out.

Materials and Methods: Pericardial fluid ADA levels of 149 consecutive patients having large pericardial effusions were evaluated. Pericardial effusion was detected by transthoracic echocardiography, ADA levels were measured from the fluid taken during pericardial windowing procedure, and pathological examination of the tissue samples were performed.

Results: The median age of selected patients participating in the study was 58.43 ± 14.47 years. All the pericardial fluid samples were found to be exudative and 116 (77.9 %) of the cases had also concomitant pleural effusions. The median ADA level of the cases was calculated to be 19.57 U/L (9.47-38.70), well below the cut-off value (40 U/L). The mean ADA levels value was 9.21 U/L (7.70-9.91) in the nonspecific inflammations group and 38.35 U/L (23.92-48.67) in the lung malignancy group ($p < 0.001$). In the subgroup analysis of lung cancers, ADA levels in pericardial effusions of patients with adenocarcinoma were found to be statistically significantly higher than patients with squamous cell cancer. ($p = 0.007$).

Conclusion: ADA levels in pericardial effusion were found to be significantly higher in lung cancer, especially in cases of lung adenocarcinoma. High levels of ADA may be used as a significative biochemical marker in the diagnosis of lung cancer.

Keywords: pericardial effusion, adenosine deaminase, cancer

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Doi: 10.26663/cts.2023.0025
Received 24.01.2023 accepted 24.04.2023

Introduction

The pericardial cavity normally contains 10 to 50 mL of serous plasma ultrafiltrate. Accumulation of transudative or exudative fluid of more than least >50 mL is considered abnormal and may lead to significant hemodynamic effects which results in cardiac compression and impaired cardiac filling [1]. While some known underlying diseases like acute myocardial infarction, cardiac surgery, end-stage renal disease, or widespread metastatic neoplasm are the common causes for pericardial effusions, sometimes no obvious cause is apparent. [2,3].

Plasma adenosine deaminase (ADA) level is known to increase to a certain level in several disease states associated with lymphocytic pericardial effusions including neoplasms and some acute viral infections, the most widely known increase is observed in tuberculosis [4].

Routine measurements on pericardial fluid should include white blood cell count and differential cellular analysis, hematocrit, and glucose and protein content. Pericardial fluid should be routinely stained and cultured for bacteria, including Mycobacterium tuberculosis and fungi. If there is any suspicion of tuberculous pericarditis, testing for adenosine deaminase and/or polymerase chain reaction should be a routine procedure since waiting for pericardial fluid culture results can markedly delay the diagnosis [3].

Our study aimed to compare the cytological results and pericardial ADA levels of differently diagnosed patient groups, undergoing pericardial fenestration because of consecutive large pericardial effusions that are clinically indicated in a third-level hospital.

Materials and Methods

This study is a retrospective observational study. It was carried out in the chest diseases department of a tertiary teaching and research hospital following the approval of the local ethics committee (No: 2019-36).

149 patients, 60 of whom were women, having large pericardial effusions detected by transthoracic echocardiography, despite empirical treatment, were included in the study. Informed consent forms were obtained from all patients before the intervention. Afterward, a video thoracoscopic pericardial window surgery was performed for diagnosis and treatment. After video thoracoscopic visualization, the pericardium was incised over the phrenic nerve, and pericardial fluid was aspirated with an aspirator. 20 mL of the liquid was taken to evaluate ADA activity. The pericardium was incised, the area was enlarged and an average of 4x4 cm pericardium was resected with ultrasonic scissors and separated as a pathological sample. During the procedure, pericardial fluid was sampled and adenosine deaminase (ADA), albumin and lactate dehydrogenase (LDH) levels were measured. The demographic characteristics of the patients are demonstrated in table 1.

Transthoracic echocardiography

2-D transthoracic echocardiography (TTE) is the imaging modality of choice for the evaluation of pericardial effusion as well as tamponade physiology. TTE should also be used to guide pericardiocentesis. Pericardial effusions appear as an echolucent space between the parietal and visceral pericardium. Pericardial effusions are graded as small (echo-free space in diastole <10 mm), moderate (10–20 mm space), and large (more than 20 mm space) [5].

Exudative-transudative effusions

Useful criteria in favor of exudative pericardial effusions include a pericardial fluid to serum protein ratio greater than or equal to 0.5 and/or pericardial fluid to serum LDH ratio greater than or equal to 0.6 and/or pericardial fluid lactate dehydrogenase value greater than or equal to 200 U/L [6].

ADA analyses

The Giusti technique for measuring ADA activity through calorimetry was uniformly used in all the selected studies. ADA was determined in the same samples following Giusti's method [7] by simultaneously taking blood and pericardial fluid samples, centrifuging them for 3 h, and freezing the remainder at –20°C. For each patient ADA levels (U/L) were determined in the pericardial fluid (the cut-off value for increased ADA level was 40 U/L) [8].

Statistical Analysis

SPSS 26 (IBM Corp, 2019, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY) was used to process the data obtained in the study. The conformity of the data to the normal distribution was evaluated with histograms, Q-Q plots, and the Shapiro-Wilk test. Continuous data conforming to the normal distribution is expressed as the mean and standard deviation, non-conforming data is expressed as the median and percentiles of 25% - 75%, and nominal variables are expressed as frequency and percentage. An intergroup comparison T-test or Mann-Whitney U test was performed according to the normal distribution The Chi-square and, where necessary, Fisher's Exact tests were used to compare

nominal variables. The statistical significance level was accepted as $p < 0.05$ for all calculations.

Results

The median age of patients participating in the study was 58.43 ± 14.47 years (Table 1). All the pericardial fluid samples were found to be exudative and 116 (77.9 %) of the cases had also concomitant pleural effusions.

Pathological diagnoses were as follows: 60 nonspecific inflammations, 59 lung cancer metastasis, 14 pericarditis, 7 granulomatous inflammations, 4 breast cancer metastasis, 3 renal cell cancer metastasis and 2 mesotheliomas (Table 2). The median ADA levels of the cases was calculated to be 19.57 U/L (9.47 - 38.70), well below the cut-off value (40 U/L) (Table 3).

As the number of patients was low in the pathological diagnosis subtitles except lung cancer metastasis and nonspecific inflammation group, a statistical study was performed between these two groups (Table 4). The mean ADA level was 9.21 U/L (7.70 - 9.91) in the nonspecific inflammations group and 38.35 U/L (23.92 - 48.67) in the lung malignancy group ($p < 0.001$). In the subgroup analysis of lung cancers, ADA levels in pericardial effusions of patients with adenocarcinoma were found to be statistically significantly higher than in patients with squamous cell cancer. ($p = 0.007$) (Table 5).

Table 1. Demographic characteristics of the patients with pericardial effusion.

(n=149)	N(%) Mean±SD Median (%25-75)
Age	58.43±14.47
Female	60(40.3)
Male	89(59.7)

Table 2. Pathological diagnoses of the patients with pericardial effusion

Nonspecific inflammations	60(40.3)
Lung malignancy	59(39.6)
Pericarditis	14(9.4)
Granulomatosis inflammations	7(4.7)
Brest cancer	4(2.7)
Renal cell cancer	3(2)
Mesothelioma	2(1.3)

Table 3. Laboratory results of the patients with pericardial effusion.

ADA	19.57 (9.47-38.70)
Total Protein	4.84 (4.11-5.44)
Albumin	2.913±0.657
LDH	532 (305-740)

Discussion

Pericardial effusion is a common cardiovascular disease that occurs due to benign or malignant causes [9]. Pericardial effusion with a transudate nature is mainly caused by systemic diseases such as cardiac, kidney and liver disease, or endocrine disorders such as hypothyroidism. Pericardial effusions of an exudate nature are usually because of malignancy or tuberculosis [9]. Treatment strategies for pericardial effusion depend on etiology and prognosis. Therefore, the diagnosis should be made quickly and accurately.

Survival in patients with malignant pericardial effusion is usually less than 12 months, and hemodynamic instability and death due to pericardial tamponade develop in 1/3 of malignant patients [10].

The clinical manifestations of patients with malign pericardial effusion are not specific, and it can be quite difficult to distinguish malignant pericardial effusion from benign pericardial effusion. Though exfoliative cytology and diagnostic pericardial biopsy of pericardial effusion are of decisive importance in the diagnosis of malignant pericardial effusion, the sensitivity of these methods is relatively low [10]. The accuracy of cytological fluid analysis is 67-92% and negative reporting of cytology does not exclude malignancy [10-12].

Because of pericardial fluid sampling is a difficult procedure, there are limited resources and studies on this tissue [10]. In this context, proof can be obtained by using biochemical biomarkers that can give results faster than the pathological examination [13-15].

Imazio et al reported that pericardial effusions are found to be idiopathic in many cases in developed countries whereas tuberculosis is the leading cause of pericardial effusions in developing countries where it is endemic [16].

Porte et al studied 114 patients with a recent or remote history of cancer and pericardial effusion of unknown origin for which drainage was required for diagnostic or therapeutic purposes [17]. The malignant pericardial disease was found in 44 (38%) patients, while 70 (61%) patients had non-malignant pericardial effusions (idiopathic in 33 patients, radiation-induced in 20 patients, infectious effusion in 10 patients, and hemopericardium as a result of coagulation disorders in 8 patients) [17].

Table 4. The analysis of primary outcome.

(n=119)	Inflammation n (%) 60 (50.4)	Malignancy n (%) 59 (49.6)	OR (%95 GA)	p
Age Mean±SD	59.2±14.9	60.8±13.1	-	0.525
Sex (female) n (%)	25(41.7)	22(37.3)	-	0.625
ADA	9.21(7.70-9.91)	38.35(23.92-48.67)	-	<0.001
Total Protein	5.14(4.17-5.53)	4.61(3.99-5.09)	-	0.01
Albumin	2.99±0.66	2.71±0.64	-	0.022
LDH	581(303-872)	639(305-762)	-	0.722
Pleural effusion n (%)	43(71.7)	50(84.7)	-	0.084

Table 5. The analysis of secondary outcome.

(n=59)	Squamous cell ca n (%) 27 (45.8)	Adenocarcinoma n (%) 32 (54.2)	OR (%95 GA)	P
Age. Mean ± SD	60.2±13	61.4±13.5	-	0.719
Sex (Female). n (%)	7 (25.9)	15 (46.9)		0.097
Laboratory results Mean ± SD / Median (%25 - %75)				
ADA	29.97 (20.18-44.49)	44.63 (35.98-50.83)	-	0.007
Total Protein	4.55±0.94	4.41±1.12	-	0.633
Albumin	2.64±0.65	2.76±0.64	-	0.476
LDH	646 (392-782)	567 (235-709)	-	0.267
Pleural effusion* n (%)	22 (81.5)	28 (87.5)	-	0.719

** The p value was found by Fisher's exact test.*

The study by Sagristà- Sauleda et al [3], included 322 patients, 132 with moderate and 190 with severe pericardial effusion. In this series, the most common diagnosis was acute idiopathic pericarditis which accounted for 20% of patients. The next most prevalent diagnoses were iatrogenic effusion (16%), neoplastic effusion (13%), and chronic idiopathic pericardial effusion (9%) [3]. Lui et al, in their study including 110 cases, showed that there was no significant difference in ADA levels as 37.63 ±31.98, 38.21 ± 94.45 of patients having a diagnosis of tuberculosis and malignant pericardial effusion.

Malignant pericardial effusion is the most common presentation of tumoral infiltration of the pericardium and may sometimes be the first symptom of a malignant disease which is detected in approximately 40-50% of patients with severe pericardial effusion [18,19].

ADA is an enzyme required for the conversion of adenosine to inosine. ADA can be found in all tissues, but the largest concentration is in the lymphoid tissue, mainly in T-lymphocytes [20].

As in line with the literature, in our study, the mean pericardial fluid ADA levels were not found to be increased in patients having large pericardial effusions caused by malignancy and non-specific inflammation. Aggeli et al reported that ADA levels were found to be high in the group consisting of 2 lung and 2 breast cancer patients. In the same literature, ADA levels were found to be low in 10 cases with pericardial effusion due to idiopathic causes [21].

Increased ADA levels due to malignant effusions have been reported in clinical studies [2,22]. When the cause of ADA increase in malignant pleural etiologies was evaluated, it was shown that it was associated with the increase in cytokines related to inflammation (due to increased levels of interleukin 8) and permeability (vascular endothelial growth factor, transforming growth factor B) [22]. In these studies, the cause of malignant pleural effusions was lung cancer but the pathological subtype was not determined. In our study, we found that the ADA levels in pericardial effusions caused by lung cancer is significantly higher in the adenocarcinoma subtype.

In conclusion, ADA levels in pericardial effusion were found to be significantly higher in lung cancer, especially in cases of lung adenocarcinoma. High levels of ADA may be used as a significative biochemical marker in the diagnosis of lung cancer.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study was approved by the Local Ethics Committee of University of Health Sciences, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. The committee's reference number is a (2019/36).

Authors' contributions

AU; conceptualized and drafted the article, wrote the paper MA,IK; drafted the article, collected and analyzed data, HI; collected data.

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