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Analysis of pleural amylase levels in a chest disease clinic

Suna Türkeli*, Atilla Güven Atıcı, Servet Kayhan, Yasemin Arı Yılmaz

Department of Chest Disease, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

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*** Correspondence to:**
Suna Türkeli
Department of Chest Disease,
Faculty of Medicine,
Ondokuz Mayıs University,
Samsun, Turkey
e-mail: turkelisuna@gmail.com

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ABSTRACT

The aim of this study was to evaluate whether pleural amylase levels in pleural fluid had a diagnostic value for discriminating the reasons of pleural effusions. Totally 115 patients with pleural effusion were enrolled in this prospective study. Pleural fluids and serum samples were obtained from all of the patients and analyzed for transudate or exudate classification and other biochemical analysis. Amylase levels were measured in vitro by Roche/Hitachi cobas-c systems in biochemical laboratory. Of the patients, 76 (66%) were male and 39 (34%) of them were female. The mean age was 62.2±15.3 and the range of age was between 20 and 94 years. Of the pleural fluids, 26 (22.6%) were determined as transudate and 89 (77.4%) were as exudate. As a common reason of pleural effusions, 16 (61.5%) of the transudates were originated from heart failure and 29 (32.5%) of the exudates were originated from lung cancer. The ratio between the serum amylase level and pleural fluid amylase level was not different statistically in the aspect of all transudates and exudates caused by tumors or any other situations. Seven (6.1%) of pleural effusions were amylase rich and 4 of them were tumoral origin, the other 3 of them caused by extratumoral causes. Amylase rich pleural fluids were determined more frequently in malignant effusions than paramalignant effusions in the present study (p=0.028). As a conclusion, high pleural amylase levels are associated with a variety of benign and malign etiologies and the adenocarcinoma type of lung cancer is predominant reason.

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1. Introduction

Diagnosis of pleural effusion generally needs a systematic evaluation of the patient. Especially exudative effusions have an extensive differential diagnosis. There are many useful tests that have been recommended for routine evaluation of pleural effusions. Measuring of pleural fluid amylase levels was also recommended in exudative effusions previously (Joseph et al., 1992). Elevated pleural fluid amylase levels are potentially helpful in the diagnosis of pancreatitis, esophageal rupture and some of the malignant diseases (Villena et al., 2002). The history, physical examination, and serologic studies associated with pancreatitis usually suggest this diagnosis without further confirmatory studies. Measurement of pleural amylase lacks the sensitivity to serve as a screening study for malignancy. Therefore, it is difficult to justify the routine measurement of pleural fluid amylase levels except suspicion of pancreatic disease or esophageal rupture (Branca et al., 2001). The purpose of this study was to assess the utility of pleural fluid amylase measurement in the evaluation of pleural effusions.

2. Materials and methods

Study population and ethical considerations

Prior to the start of the study, ethical approval was obtained from the ethics committee of Ondokuz Mayıs University with approval number of 2010/96. We enrolled 115 consecutive patients with pleural effusions. They were assessed in our pulmonary disease clinic during the 24-month period from December 2009 through December 2011. All the patients were informed about the study and they gave their consent to this investigation. There were 76 male and 39 female patients. After completion of clinical evaluation, all patients underwent thoracentesis by the guidance of radiology. Pleural effusions were classified into four diagnostic groups as malignant effusion, paramalignant effusion, parapneumonic.

Pleural fluid analysis

A sample of pleural fluid obtained by thoracentesis was collected in a tube and a simultaneous sample of serum were obtained in order to measure the total amylase level. The amylase, protein, and lactate dehyrogenase (LDH) measurements were made using an automated analyzer. α -Amylase levels in pleural fluid or serum were measured in biochemistry laboratory of Ondokuz Mayis University by quantitative Roche/Hitachi cobas c system using *in vitro* tests. The commercial kits of AMYL2 (catalogue no: 3183742, Roche Diagnostics GmbH, Germany) were used for analysis of pleural and serum amylase levels.

Effusions

The nature of the effusions is generally designated as either an exudate or a transudate, based on the concentration of protein and LDH in the pleural fluid. It is classified as an exudate if any of three properties: A ratio of concentration of total protein in pleural fluid to serum (>0.5), an absolute value of LDH (>200 IU) and a ratio of LDH concentrations in pleural fluid to serum (>0.6) (Light, 2007). The normal reference values for serum amylase levels were between 26-100 IU/L. Upper normal limit value of serum amylase level (>100 IU/L) was chosen as the cut-off point for defining amylase rich pleural effusion (ARPE). Existence of cytologic or histologic neoplasm within the pleural space are classified as malignant effusions. Paramalignant effusions are benign effusions accompanying with histologic diagnosis of a tumor in any other organs in the absence of any other reason for collecting effusion in the pleural space. Pleural effusions coexisting with cough, fever, and a radiographic pulmonary infiltrate that disappeared with antibiotic treatment are called as parapneumonic effusions. Unknown effusion etiology or several potential causes of pleural effusion are classifed as undetermined causes.

Table 1. Analysis of pleural and serum amylase levels according to etiologies in transudates (n:26)

Diagnosis	No	%	SA (U/L)*	PA (U/L)*	PA/SA*
Heart failure	16	61.5	54 (17-94)	26 (6-82)	0.51(0.2-1.4)
Atelectasis	2	7.7	86 (80-93)	40 (28-52)	0.47(0.3-0.7)
Urinothorax	2	7.7	73 (51-95)	31 (16-46)	0.40(0.3-0.7)
Hipoalbuminemia	2	7.7	67 (58-76)	31 (31-32)	0.47(0.4-0.5)
Lung cancer and heart failure	1	3.8	86 (80-93)	30	0.4
FMF	1	3.8	115	25	0.2
Nephrotic syndrome	1	3.8	45	29	0.7
Venous thromboembolism	1	3.8	93	109	1.2
Total	26	100	58(17-115)	29 (6-109)	0.48(0.2-1.4)

*Median (minimum-maximum) levels, **PA:** Pleural amylase; **SA:** Serum amylase; **FMF:** Familial mediterranean fever

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normal distribution of the data. Mann-Whitney U test and Kruskall-

Table 2. Analysis of pleural and serum amylase levels of pleural fluids according to reasons in exudates (n:89)

Types	No	%	SA (U/L)*	PA (U/L)*	PA/SA*
Malignant effusions					
Lung cancers	29	32.5	49 (52-147)	33 (8-830)	0.6 (0.1-13.8)
Adenocarcinoma	8		58 (48-128)	46 (22-830)	0.6 (0.4-13.8)
Epidermoid cell carcinoma	9		31 (5-125)	33 (15-44)	0.6 (0.1-13.8)
Undifferentiated carcinoma	4		48 (33-74)	19 (8-669)	0.54 (0.1-1.2)
Small cell carcinoma	8		47 (31-147)	33 (10-65)	0.58 (0.2-1.2)
Mesothelioma	2	2.2	32 (30-35)	21 (16-26)	0.31 (0.2-0.5)
Pleural metastasis	1	1.1	633	496	0,8
Extrathoracic cancer	13	14.6	32 (16-83)	21 (9.6-33)	0.6 (0.3-1.0)
Gasrtric	4		30 (16-44)	17 (9-28)	0.59 (0.5-0.6)
Mammary	3		30 (28-43)	25 (16-26)	0.6 (0.6-0.8)
Urinary bladder	2		55 (28-83)	29 (28-31)	0.66 (0.4-1.0)
Ovary	1		39	33	0.8
Endometrium	1		33	18	0.5
Pancreas	1		83	31	0.4
Lymphoma	1		32	10	0.3
Benign effusions					
Parapneumonic	14	15.7	55 (22-508)	35 (14-122)	0.68 (0.1-3.6)
Empeyema	6	6.7	50 (17-77)	26 (8.5-90)	0.65 (0.1-2.3)
Tuberculosis	8	9	59 (52-80)	59 (37-112)	0.95 (0.7-1.6)
Thromboembolism	5	5.6	53 (40-67)	28 (7.7-40)	0.60 (0.1-1.0)
Intraabdominal abscess	4	4.5	85 (22-228)	58 (12-78)	0.60 (0.3-0.7)
Other benign causes	5	5.6	40 (34-95)	32 (4-56)	0.58 (0.1-1.3)
Unknown reason	2	2.2	61 (45-75)	26 (15-34)	0.34 (0.3-0.5)
Total	89	100	49 (5,2-633)	32 (4-830)	0.61 (0.1-13.8)

*Median (minimum-maximum) levels, **PA:** Plevral amylase, **SA:** Serum amylase.

Vallis tests were used for analysis of difference between groups. Correlations were studied using the Spearman correlation coefficient. P values less than 0.05 were considered as statistically significant. The variable was categorized into groups based on the distribution percentiles and compared using the log-rank test. Datas were analyzed using SPSS 15.0 statistical software.

3. Results

We assesed 115 consecutive patients with pleural effusions in our clinic during two years. Seventysix (66%) of the patients were male and 39 (34%) of them were female. The mean age was 62.2±15.3 ranged between 20 and 94 year. According to smoking beheaviour of the study group; 18.2% of the participants were current smokers, 32.3% of them were ex-smokers and 49.5% were non-smokers. Of the pleural fluids, 26 (22.6%) were determined as transudate and 89 (77.4%) were as exudate. The most common reasons for pleural effusions, heart failure (n=16, 22.6%) for transudates and lung cancer (n=29, 32.5%) for exudates. The serum amylase levels and pleural fluid amylase levels were not found to be different in the aspect of smoking behaviour and being transudate or exudate statistically (p>0.05). There were 8 patients with adenocarcinoma in the study group high plasma amylase (PA) level than serum amylase (SA) and only one case of adenocarcinoma had PA/SA < 1 rate. Among 19 patients with a rate of PA/SA>1, it was found 5 pleural effusions with PA > 100U/L level. ARPE was determined more frequently and a significant differential factor in malignant effusions (p=0.028). Serum and pleural amylase levels and the rate between tumoral or extratumoral disorders were not different (p>0.05). Table 1 and Table 2 show the results of serum and pleural amylase levels found in this study according to etiologic factors and characteristics of transudate and exudate.

Table 3. Analysis of pleural and serum amylase levels in exudates and transudates

Parameter	Transudates	Exudates	P
PA (U/L)*	29 (6.8-109)	32 (4-830)	0.346
SA (U/L)*	58 (17-115)	49 (5.2-633)	0.306
PA/SA*	0.48 (0.2-1.4)	0.61 (0.1-13.8)	0.075

*Median (minimum-maximum) levels, **PA:** Plevral amylase, **SA:** Serum amylase.

Pleural and serum amylase levels and PA/SA rates between transudates and exudates were similar by Mann-Whitney U test (p > 0.05) (Table 3). Pleural and serum amylase levels and PA/SA rates also were not different between tumoral and extratumoral disorders by Kruskall-Vallis test (p>0.05) (Table 4). Seven (6.1%) of the pleural effusions were found as ARPE consisting of 4 tumoral and 3 extratumoral, these were cases with pleural tuberculosis, parapneumonic effusion and pulmonary thromboembolism (Table 5). Amylase rich effusions were found higher in malignant effusions than paramalignant effusions by independent two sample test (p=0.028).

Table 5. Diagnosis and amylase results of the cases with amylase rich pleural effusion

No	Diagnosis	PA (IU)	SA (IU)	PA/SA
1	Lung cancer (adenocarcinoma)	830	67	12.3
2	Lung cancer (adenocarcinoma)	111	100	1.1
3	Lung cancer (adenocarcinoma)	675	49	13.8
4	Metastatic pleural adenocarsinoma	496	633	0.8
5	Tuberculosis	112	69	1.6
6	Parapneumonic effusion	122	104	1.2
7	Pulmonary thromboembolism	109	93	1.2

PA: Pleural amylase, **SA:** Serum amylase

4. Discussion

In healthy individuals, the rates of fluid entry and efflux are about equal and pleural fluid volume remains virtually constant. The equilibrium of pleural effusion is accounted for primarily by the forces employed in Starling's equation for transmicrocirculatory exchange, which is formulated as: $F=k\,[(P_{capillary}-P_{pleural})-q(\pi_{capillary}-\pi_{pleura})]$, where F: The rate of the fluid movement, P and π: The hydrostatic and oncotic pressures respectively, k: The filtration coefficient, q: The osmotic reflection coefficient for protein (Kinasewitz, 1998).

According to this equation, net filtration or reabsorption of water and its solutes across a semipermeable membrane is determined by hydrostatic and oncotic pressure balances on the two sides of the membrane. Pleural surfaces are covered by porous mesothelium, so the endothelium of the pleural capillaries is the principal barrier to pleural fluid filtration and reabsorption (McKenna et al., 1977). Many different disorders may cause accumulation of fluid in pleural space. We found that the most common reason in transudative pleural effusions was heart failure (22.6%) and it was lung cancers (32.5%) in exudative effusions in our study. We have also found a higher PA/SA rate (0.61) in exudates than that rate of transudate (0.48) but this difference was not significant statistically.

There is an association between amylase rich pleural effusions and pancreatitis and neoplastic diseases (McKenna et al., 1977; Villena et al., 2002). The mechanism of ARPE seems to be associated with an increase in microvascular

Table 4. Analysis of pleural and serum amylase levels according to etiologies

Etiology of effusions	No (%)	SA (U/L)	PA (U/L)	PA/SA	P
Tumoral reasons	47 (41)	44 (5-633)	29 (8-830)	0.6 (0.1-13)	>.05
Malignant	23	47 (28-633)	31 (111-830)	0.6 (0.2-13)	
Paramalignant	22	43 (5-128)	29 (8-52)	0.55 (0.1-7.5)	
Undetermined	2	76 (28-125)	33 (28-37)	0.6 (0.3-1)	
Extratumoral reasons	68 (59)	56 (17-508)	32 (4-122)	0.6 (0,1-3.6)	>.05
Total	115 (100)	52 (5-633)	31 (4-830)	0.6 (1-13.8)	

*Median (minimum-maximum) levels, **PA:** Pleural amylase, **SA:** Serum amylase, **NS:** Not significant

permeability. There are two isoenzymes of amylase that separate with electrophoresis. Pancreatic-type amylase originates in the pancreas, and its elevation in serum or in other body fluids is specific for pancreatic inflammation. Salivary-type amylase is produced in the salivary glands, lungs, and fallopian tubes and may be secreted ectopically by a variety of tumors. In a prospective study, Joseph et al (1992) performed an isoenzyme analysis in 200 patients with pleural effusions, they found primarily salivary-type amylase in 18 of 25 amylase-rich effusions confirming previous studies and reports of the cases with nonpancreatic effusions (Shapiro et al., 1981; Kramer et al., 1989; Devuyst et al., 1990). It is reported that nearly half of the patients with ARPE have also increased level of serum amylase produced by ectopic tumor cells (Salt and Schenker, 1976; Devuyst et al., 1990; Branca et al., 2001; Light, 2007; Hooper et al., 2010). On the other hand PA may accumulate in pleural space due to tumoral obstruction of lymphatics (Branca et al., 2001).

Pleural amylase levels were investigated by many studies and some of them reported a significant correlation between PA and lung cancers particularly adenocarcinoma (Foresti et al., 1994; Gupta et al., 2001; Villena et al., 2002;)Villena et al. (2002) reported a positive correlation between increased levels of amylase in ARPE and malignancy and the average expectancy of life also decreased by high PA levels. Foresti et al. (1994) found higher levels (106.3±101 IU/L) of PA in malign effusions and PA/SA rates (1.02±0.9) than the other benign effusions and transudates in their study including 167 patients with pleural effusion. Branca et al. (2001) investigated 379 patients with pleural effusions and the authors concluded that routine measurement of amylase level in pleural fluids is not recommended. Gupta et al. (2001) reported that salivary type isoenzyme of amylase increases in malign effusions and there is a specific correlation between PA levels and cytologic type of adenocarcinoma in malign effusions. Viellena et al. (2002) determined ARPE 13% in tumors, 14% in malign effusions and 12% in paramalign effusions. They reported a rate of 18% in 98 patients with adenocarcinoma leading to malign effusions. In this study, there were 8 patients with adenocarcinoma with high PA/SA (>1) rate and four of these cases with ARPE (> 100 IU/L) in this study. In this study we determined that ARPE is a significant differential factor in malignant effusions (p0.028).

We have collected the pleural fluid samples only from a group of the patients who admitted to a chest disease clinic for 1 year. But pleural effusions may also show a significant high amylase levels and be found in different clinical conditions, like ovarian tumor with metastasis In cases of effusion with unexplained amylase elevations, the possibility of ovarian cancers also should be thought, even in the absence of metastasis (Cramer and Bruns, 1979). Moreover amylase isotyping is not done at all which is very important in seperating malignant pleural effusions. Previously it has been reported that salivary isoamylase and pleural fluid/serum ratio more than 1, should alert the physician about the possibility of malignancy, particularly lung cancer (Gupta et al., 2001).

5. Limitations

The study was performed in a chest disease clinic and this is the reason why our study population included limited number of different organ pathologies of pleural effusions such as pancreatic diseases and ovarian tumors.

6. Conclusion

This study describes a consecutive unselected series of 115 patients in whom levels of PA were measured. As a result, high pleural amylase levels are associated with a variety of benign and malign etiologies and adenocarcinoma is more commonly associated with ARPE than the other histologic types of lung cancers.

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