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Diagnostic Value of Carcinoembryonic Antigen and C-reactive Protein Levels in the Discrimination Between Malignant Pleural Effusion and Parapneumonic Effusion

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ABSTRACT

Introduction: There are problems in the differential diagnosis of malignant pleural effusion (MPE) and parapneumonic effusion (PPE). We investigated the diagnostic value of levels of carcinoembryonic antigen (CEA) and C-reactive protein (CRP) in the discrimination of MPE and PPE.

Materials and Methods: Twenty-eight patients with MPE and 21 patients with PPE were assessed. CEA and CRP levels were measured in the pleural fluids.

Results: CEA levels in the pleural fluid were 55.03±102.96 ng/mL (0.4-387) and 1.11±1.07 ng/mL (0.12-4.30) in patients with MPE and PPE, respectively. The high levels of CEA in patients with MPE were statistically significant (p<0.001). The sensitivity and specificity were 82% and 81%, respectively, when the threshold value for CEA in the pleural fluid was set as 1.45 ng/mL for the discrimination of MPE from PPE. CRP levels in the pleural fluid were 28.75±23.20 mg/L (1.0-84.9) and 53.74±66.39 mg/L (3.10-248) for patients with MPE and PPE, respectively. The level of CRP in patients with PPE was not statistically significant (p=0.24). The sensitivity and specifity were 61% and 58%, respectively, when the threshold value for CRP in the pleural fluid was set as 28.35 mg/L for the discrimination of PPE from MPE.

Conclusion: CEA levels in the pleural fluid were significantly higher in patients with MPE compared to those with PPE. However, the same did not apply for CRP. According to this study, CEA levels in the pleural fluid may be used as an adjunct test for the differential diagnosis of MPE and PPE but CRP is not a good indicator for the discrimination between PPE and MPE.

Key words: malignant pleural effusion, parapneumonic effusion, CEA, CRP

MALİGN VE PARAPNOMONİK EFÜZYON AYRIMINDA PLEVRAL SIVI C-REAKTİF PROTEİN VE KARSİNOEMBRİYONİK ANTİJEN DÜZEYLERİNİN TANISAL DEĞERİ

ÖZET

Amaç: Biz bu çalışmamızda plevral sıvı karsinoembriyonik antijen (CEA) ve C – reaktif protein (CRP) seviyelerinin MPE ve PPE ayrımında ki tanısal değerini araştırdık

Hastalar ve Yöntem:28 MPE ve 21 PPE hastası çalışmaya dahil edildi. Plevral sıvı CEA ve CRP seviyeleri ölçüldü.

Bulgular: MPE ve PPE hastalarında plevral sıvı CEA seviyeleri sırasıyla 55.03±102.96 ng/mL (0.4-387) ve 1.11±1.07 ng/mL (0.12-4.30) ölçüldü. MPE hastalarında yüksek CEA seviyeleri istatistiksel olarak anlamlı idi (p<0.001). MPE ve PPE ayrımında CEA için eşik değer 1.45 ng/mL alındığında duyarlılık 82% ve özgüllük 81% bulundu. MPE ve PPE hastalarında plevral sıvı değerleri sırasıyla 28.75±23.20 mg/L (1.0-84.9) ve 53.74±66.39 mg/L (3.10-248) ölçüldü. PPE için plevral sıvı CRP seviyeleri istatistiksel olarak anlamlı bulunmadı (p=0.24). PPE ve MPE ayrımında CRP için eşik değer 28.35 mg/L alındığında duyarlılık ve özgüllük sırasıyla 61% and 58% olarak ölçüldü.

Sonuç: MPE hastalarında plevral sıvı CEA seviyeleri PPE hastalarına göre istatistiksel olarak anlamlı yüksek bulundu (p<0.001). Çalışmamıza göre MPE ve PPE ayrımında plevral sıvı CEA yardımcı bir test olarak kullanılabilir. Ancak plevral sıvı CRP seviyeleri bu ayrımda yararlı bulunmamıştır.

Anahtar sözcükler: malign plevral efüzyon, parapnömonik effüzyon, CEA, CRP

Introduction

Pleural effusions emerge upon various etiologic reasons. The most frequent reasons of effusion are malignancies, tuberculosis, pneumonia, and congestive heart failure (1). Parapneumonic effusion (PPE) rates in patients with pneumonia may be as high as 57% and majority of them are not infected (2). Gram staining or microbial culture of the pleural fluid can reveal no pathogens in non-complicated PPEs and some complicated PPEs (3). This may lead to some problems in the diagnosis of PPE.

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Malignant pleural effusion (MPE) develops due to pulmonary and non-pulmonary malignancies. Cytological examination of the pleural fluid demonstrates a specificity of 100% in the diagnosis of MPE, while giving a false-negative result rate of 30-50% (4,5).

Rapid and valid tests are needed for the diagnoses of both PPE and MPE. Pleuritis due to pneumonia may develop in patients with risk of malignancy as well as pneumonia or pleural effusion associated with pneumonia or pleural effusion due to malignancy in patients with pulmonary or non-pulmonary malignancies. In these cases, the clinical findings become complicated and we are faced with the problem of whether the effusion is associated with the malignancy or pneumonia or not (4,6,7).

CEA is a member of the immunoglobulin superfamily. Although CEA or molecules like CEA are found in some of the healthy tissues, their concentrations in malignant tissues are found to be 60-fold higher compared to non-malignant tissues (8). CRP is an acute phase protein synthesized in the hepatocytes. Its levels in the serum increase within 6-9 hours following an infection or tissue damage (9,10).

The objective of this study was to investigate the values of carcinoembryonic antigen (CEA) and C-reactive protein (CRP) levels in the discrimination of malignant pleural effusion (MPE) and parapneumonic effusion (PPE).

Materials and methods

Patients who were admitted to the Department of Chest Diseases in our hospital and diagnosed with MPE and PPE following the detection of pleural effusion were included in this prospective study which was carried out between July 2008 and June 2010. The study was approved by the hospital ethics committee.

MPE diagnosis was established by the detection of malignant cells in the pleural fluid by cytological examination or pleural biopsy. PPE was defined as newly developed pleural effusion with fever, purulent phlegm, leukocytosis and new infiltrations in the chest X-ray. Patients with complicated parapneumonic effusion and empyema were not included in the study.

Pleural fluids of the patients with MPE and PPE were collected in this study. The pleural fluids were centrifuged at 1500 g for 15 min. Free cell supernatants were stored at –80°C for CEA and CRP testing.

Pleural fluid concentrations of CEA were measured using the electrochemiluminescence (Roche Cobas, Germany) method. CRP levels in pleural fluid were measured by nephelometric method (Beckman Coulter Immage 800 Immunochemistry System, USA).

Statistical analysis

The data were expressed as mean ± SD and frequency. Non-parametric tests were used for group comparisons. Differences between two independent groups were determined by Man Whitney U test. The diagnostic value of the CEA and CRP for discriminating between patients with MPE and patients with PPE was expressed as sensitivity, specificity, and area under curve (AUC), the receiver operating characteristics (ROC) curve, and accuracy with a cut-off level obtained from optimal value of the ROC curves. P values smaller than 0.05 were considered as statistically significant. Analyses were carried out using the SPSS 15.0 package program (SPSS inc. USA).

Results

Forty-nine patients diagnosed with MPE and PPE were included in the study following the examinations. Among these patients, 28 had MPE and 21 had PPE. Mean age of the patients with MPE and PPE were 65.46 ± 12.29 and 52.14 ± 23.44, respectively. Sixteen of the patients with MPE were male and 12 were female, and 17 of the patients with PPE were male and 4 were female. There were no statistically significant differences between the two groups in terms of age and gender (p = 0.38 and 0.082, respectively).

The most frequent histological type of the patients with MPE was lung cancer, followed by breast cancer and mesothelioma (Table 1).

Table 1. Etiologies for patients with malignant pleural effusion

Etiology	*Number of Cases*	%
Malignancy		
Lung	15	53.5
Breast	4	14.2
Mesothelioma	3	10.7
*Other	6	21.4
Total	28	100

**2 Gastrointestinal tumor, 1 Thyroid tumor, 1 Malignant melanoma, 1 Atypical carcinoid tumor, 1 Germ cell tumor*

Table 2. Operating characteristics for the discrimination of malignant pleural effusion and parapneumonic effusion

	Mean ± SD	*Cut-off*	*Sensitivity*	*Specifity*	*PPV*	*NPV*	*AUC (95%CI)*
CEA	MPE:55.03±2.9 PPE:1.11±1.07	1.45ng/mL	82%	85%	85%	77%	0.914 (0.884-0.995)
CRP	MPE:28.75±23.2 PPE:53.74±66.39	28.35 mg/L	61%	57%	52%	66%	0.599 (0.436-0.761)

*__MPE:__ Malignant pleural effusion, __PPE:__ Parapneumonic effusion, __PPV:__ Positive predictive value, __NPV:__ Negative predictive value, __AUC:__ Area under curve, __CI:__ Confidence interval.

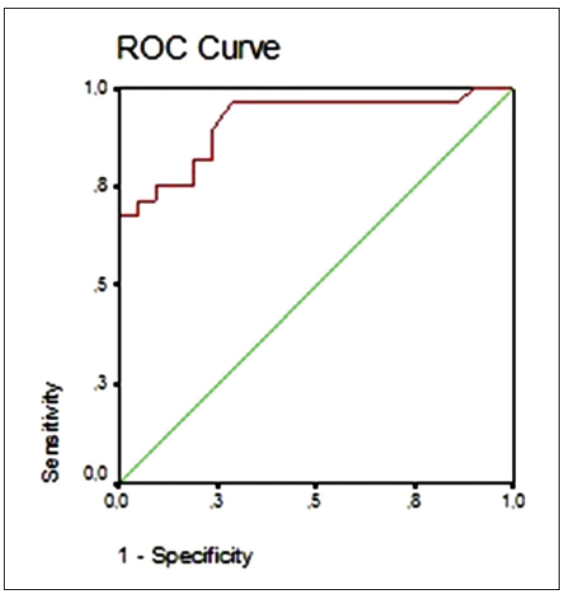

Figure 1. Receiver operating curve for CEA levels in pleural fluids in discrimination between MPE and PPE.

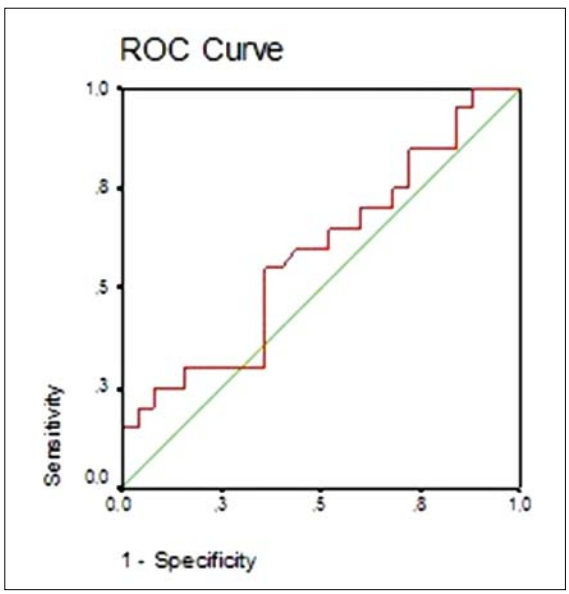

Figure 2. Receiver operating curve for CRP levels in pleural fluids in discrimination between MPE and PPE.

CEA levels in the pleural fluid were 55.03 ± 102.96 ng/mL (0,4-387) and 1.11 ± 1.07 ng/mL (0,12-4,30) in patients with MPE and PPE, respectively. The high levels of CEA in patients with MPE were statistically significant (p < 0,001). The area under the curve was found to be 0,901 (CI 95%: 0,810-0,992) when operating characteristics curve is analyzed for CEA levels in the pleural fluid for the discrimination of PPE from MPE (Figure 1). The sensitivity, specificity and positive and negative predictive values were 82%, 81%, 85%, and 77%, respectively, when the threshold value for CEA in the pleural fluid was set as 1.45 ng/mL for the discrimination of PPE from MPE (Table 2). Positive/negative likelihood ratios by the operating characteristics curve were found to be 4.31 and 0.21, respectively.

CRP levels in the pleural fluid were 28,75 ± 23,20 ng/mL (1,0-84,9) and 53,74 ± 66,39 mg/L (3,10-248) in patients with MPE and PPE, respectively. The CRP levels for the discrimination between patients with MPE and PPE were not statistically significant (p = 0,24). The area under the curve was found to be 0.599 (CI 95%: 0.436-0.761) when operating characteristics curve is analyzed for CRP levels in the pleural fluid for the discrimination of PPE from MPE (Figure 2). The sensitivity, specificity and positive and negative predictive values were 61%, 58%, 52%, and 66%, respectively, when the threshold value for CRP in the pleural fluid was set as 28.35 ng/mL for the discrimination of PPE from MPE (Table 2). The operating characteristics curve and positive/negative likelihood ratios were found to be 1.45 and 0.56, respectively.

Discussion

Our findings demonstrated that CEA was statistically significantly higher in patients with MPE compared to those with PPE. CRP was higher in patients with PPE, though this level was not statistically significant. Findings of this study suggest that CEA is useful as an adjunct test in the discrimination of MPE and PPE where CRP does not provide a satisfying benefit for this discrimination.

Therapy after the diagnosis of MPE requires a palliative approach (including chest tube thoracostomy, chemical pleurodesis with thoracoscopy procedure for pleural abrasion or talc poudrage) which minimizes the physical and mental damage to the patient. Indications for appropriate antibiotherapy, tube thoracostomy in complicated cases, fibrinolytic treatment, thoracoscopy in progressed cases, open surgical drainage or decortication may be possible after the diagnosis of PPE. Discrimination between MPE and PPE is therefore of vital importance (2,3,11,12).

At present, the definitive diagnosis for etiology of pleural effusions is established only by histological or cytological examination. The rate of diagnosis can be up to 80% with repeated pleural puncture and pleural biopsy. Though invasive and not practicable for every patient and every site, the rate of diagnosis can be up to 90% in the remaining patients with the aid of thoracoscopy (13,14).

CEA levels in the pleural fluid were determined as the best tumor marker in patients with MPE in the previous studies (4,13-16). In our study, CEA levels were significantly higher in patients with MPE compared to those with PPE (approximately 50-fold). However, the levels of specificity and sensitivity were not adequate but acceptable for clinic discrimination. The operating characteristics curve and positive/negative likelihood ratios were found to be 4.31 and 0.21, respectively. These ratios suggest that the CEA levels in the pleural fluid alone are not sufficient to differentiate between MPE and PPE, while a conclusion is achieved that it can be used as an adjunct tool together with other diagnostic methods. However, sensitivity and specificity were found to be 67% and 100%, respectively, when the cut-off value was set at 5.15 ng/mL (~5 ng/mL). Therefore, CEA levels in the pleural fluid over this value may be considered as a strong indicator for MPE.

CRP is increased as an acute phase inflammatory reactive in the serum and non-serum fluids including pleural fluid in infections, tissue injuries and immunomodulator stimuli (9,17-19). CRP was previously investigated for use in the diagnosis and follow-up of cancer, pleural effusion and pneumonia associated with cancer, and pleural effusions associated with pneumonia, as well as in the differential diagnosis of pleural effusions (6,7,9,10,17-22). We explored in this study whether CRP can be used in the in the differential diagnosis of MPE and PPE or not.

CRP levels in our study were higher in patients with MPE compared to those with PPE though statistical significance was not achieved. In a study by Porcel et al, CRP levels in the pleural fluid higher than 80 mg/L were strongly indicative of PPE and levels under 20 mg/L were associated with a very low possibility for PPE (10). However, we observed no significant power for discrimination between the two groups for the cut-off value of 20 and 80 mg/L. Garcia-Pachon et al considered a level of CRP under 20 mg/L in all the exudative fluids in favour of malignancy, where a level higher than 45 mg/L is detected to rule out this possibility (23). However, sensitivity is quite low (0.50) and specificity is at acceptable levels (0.89) in this study. Yılmaz Turay et al found a high sensitivity (93.7%) and specificity (76.5%) for the cut-off value of 30 mg/L for CRP in the pleural fluid for distinguishing PPE from other pleural fluids (24) in their study. In our study, sensitivity was found to be 0.61 and specificity 0.58 for a cut-off value of 28.35 and LR+ and LR- were 1.45 and 0.56, respectively. Therefore, our opinion is that CRP is not a sufficient indicator for the discrimination between PPE and MPE.

Conclusion

CEA levels in the pleural fluid were significantly higher in patients with MPE compared to those with PPE. However, the same did not apply for CRP. According to this study, CEA levels in the pleural fluid may be used as an adjunct test for the differential diagnosis of MPE and PPE but CRP doesn't show good abilities to separate PPE from MPE.

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