The value of serum tumour markers in the prediction of aetiology and follow up of patients with pericardial effusion

U BILDIRICI, U CELIKYURT, E ACAR, O BULUT, T SAHIN, G KOZDAG, D URAL

Abstract

Background: The aim of this study was to evaluate the value of tumour markers in the differential diagnosis of pericardial effusions and to assess their changing levels during follow up. Methods: Sixty-nine patients who were admitted to hospital with a diagnosis of pericardial effusion were included in the study. Serum tumour markers were measured on admission and after a mean of 18 ± 7 months’ follow up. An aetiological diagnosis was made on clinical evaluation, imaging techniques and biochemical, microbiological and pathological analysis. The patients were divided into five groups according to the aetiology of their pericardial effusions.

Results: Carbohydrate antigen (CA) 12-5 and CA 15-3, and carcinoembryonic antigen (CEA) levels were significantly higher in patients with malignancies than in those with viral/idiopathic pericarditis. With multivariate analysis, CA 15-3 levels were found to be the most significant determinant (p = 0.027). In the ROC curve analysis, CA 15-3 values above 25 U/ml predicted a malignancy with 71% sensitivity and 78% specificity.

Conclusion: Tumour markers, particularly CA 15-3, may be useful in the differential diagnosis and prediction of malignancies in patients with pericardial effusion. In patients with viral/idiopathic aetiology, these serum tumour markers were slightly elevated in the acute phase, but after a mean of one year of follow up, their levels returned to normal, contrary to those with malignancies.

Keywords: pericardial effusion, CA 125, CA 15-3, CEA

Methods

A total of 76 patients with PE who were admitted or referred to our hospital between January 2004 and March 2007 were included in the study. The mean follow-up period was 18 ± 7 months (range 8–27 months). The aetiological evaluation included complete blood count, measurement of troponin I, erythrocyte sedimentation rate, viral disease determination (Epstein Barr, cytomegalovirus, coxsackie A virus, parvovirus, hepatitis A, B, C), thyroid-stimulating hormone, and rheumatological markers [rheumatoid factor (RF), anti-nuclear antibody, anti-smooth muscle antibody, anti-double-stranded DNA].

All patients underwent computerised tomography of the thorax. Patients with heart failure (ejection fraction < 45%) and severe pericardial effusion were excluded (as it could have affected the marker levels). Patients who refused follow-up visits were also excluded. In total, seven patients were excluded from the study.

Echocardiography was performed on all patients and CA markers were checked at the time of hospitalisation and at the end of the follow-up period. Pericardiocentesis was not
performed because the patients had only mild or moderate pericardial effusions and there was no sign of compression of the heart.

CEA, CA 15-3 and CA 19-9 levels were measured in blood samples using an electrochemiluminescence immunoassay on a Roche Modular E170. CA 125 levels were measured with a quantitative immunoassay technique. All results were evaluated by a biochemist who did not know the patients.

Echocardiographic examinations were performed by an experienced cardiologist who was blinded to the tests. They were performed using standard protocol and a standard device (Vivid 7, GE Medical Systems, Horten, Norway). Measurement of the cardiac walls was done according to the American Society of Echocardiography guidelines. Since the number of patients with PE was not large enough to establish quantitative amounts of fluid, these were arbitrarily established by echocardiography using the sum of the epicardial and pericardial separations in the anterior and posterior spaces. The effusions were graded as mild (less than 10 mm), moderate (10–20 mm) and severe (more than 20 mm).

### Statistical analysis

SPSS Inc for Windows, standard version 11.0 was used for statistical analysis. All data are given as mean and standard deviation. Comparison between patients with malignant and other aetiologies was done using the Student’s t-test, and for unequally distributed variables, the Mann-Whitney U-test. Logistic regression analysis adjusting for CA 125, CA 15-3, CA 19-9, alpha-fetoprotein (AFP), prostate membrane antigen (PSA) and CEA was done to evaluate the relationship between malignancies and tumour markers. Threshold values of tumour markers were established by ROC analysis.

### Results

A total of 69 patients (32 women and 37 men with an average age of 58 ± 17 years) were included in the study. Aetiological diagnosis was done on clinical evaluation, imaging techniques and biochemical markers. The patients were grouped into categories depending on the aetiology of the PE (group 1: viral/idiopathic; group 2: bacterial; group 3: tuberculosis; group 4: malignancy; group 5: other).

Twenty-one patients were found to have malignancies and 48 had benign aetiologies after the first examination. During the follow-up period, cancer (three lymphoma, one thymoma, one lung cancer, one gastrointestinal malignancy) developed in six patients who had been considered idiopathic at the first examination. Finally, we had 42 patients with benign and 27 with malignant aetiologies (11 lymphoma, six breast cancer, five lung cancer, three thymoma, one ovarian cancer, one gastrointestinal malignancy). The aetiology in 27 patients could not be identified and they were considered as the viral/idiopathic PE group.

### Table 1. Characteristics of Patients with PE of Malignant and Benign Aetiologies

| Aetiology          | Malignant PE | Benign PE | p   |
|--------------------|--------------|-----------|-----|
| Patient (M/F)      | 27 (14/13)   | 42 (23/19)| NS  |
| Age (years)        | 57.7 ± 17.8  | 52.1 ± 13.9| NS  |
| Glucose (mg/dl)    | 123 ± 50.2   | 121.7 ± 46.3| NS  |
| Urea (mg/dl)       | 48 ± 22.9    | 39.2 ± 22.9| NS  |
| Creatinine (mg/dl) | 1.1 ± 0.4    | 1.3 ± 0.7  | NS  |
| Sedimentation (mm/h)| 83.2 ± 40.4  | 67.6 ± 37.9| NS  |
| WBC × 1000         | 18.4 ± 19.3  | 20.6 ± 21.9| NS  |
| CRP (mg/dl)        | 14.5 ± 11.2  | 10.5 ± 9.1 | NS  |
| Duration of hospitalisation (days) | 28.3 ± 11.4 | 17.3 ± 9.7 | NS  |

### Table 2. Echocardiographic Parameters of Patients with PE of Malignant and Benign Aetiologies

| Parameter          | Malignant PE (n = 27) | Non-malignant PE (n = 42) | p   |
|--------------------|------------------------|---------------------------|-----|
| LVEDD (cm)         | 48.1 ± 6.1             | 47.4 ± 5.3                | NS  |
| LVESD (cm)         | 12.1 ± 1.7             | 11.6 ± 2.1                | NS  |
| PWD (cm)           | 11.3 ± 2.3             | 11.1 ± 1.5                | NS  |
| EF                 | 64.5 ± 15.6            | 63.1 ± 17.2               | NS  |
| LAD (cm)           | 39.6 ± 5.9             | 36.2 ± 7.3                | NS  |
| E                  | 1.2 ± 0.9              | 1.2 ± 0.7                 | NS  |
| RA                 | 1 ± 0.8                | 1.1 ± 0.6                 | NS  |
| RV                 | 24.7 ± 2.9             | 24.1 ± 4.1                | NS  |

| Parameter          | Malignant PE (n = 27) | Non-malignant PE (n = 42) | p   |
|--------------------|------------------------|---------------------------|-----|
| LVEDD; left ventricular end-diastolic dimension, LVESD; left ventricular end-systolic dimension, PWD; posterior wall dimension, EF; ejection fraction, LAD; left atrial diameter, E; mitral early flow, RA; right atrium, RV; right ventricle; NS; not significant. |
CEA. The only significant relationship was observed with CA 15-3 (0.027). ROC analyses were applied to detect the threshold levels of tumour markers for detecting effusions of malignant origin. In the ROC curve analyses, a CA 15-3 level above 25 U/ml had a sensitivity of 71% and specificity of 78% for predicting pericardial effusions caused by malignancies (AUC = 0.83, SE = 0.05, p = 0.002). Elevated levels of the three markers (cut-off for CA 125 = 66 U/ml; CA 15-3 = 25 U/ml; CEA = 4.2 U/ml) had a sensitivity of 69% and specificity of 88% for the prediction of pericardial effusions caused by malignancies.

In the follow-up period, levels of CA 15-3 and CA 125 decreased significantly in the patients in the idiopathic/viral group. Levels of CA 125 also decreased significantly in any group. Levels of CA 125 were significantly higher at the beginning, but this significance decreased in the follow-up period.

During the follow-up period, malignancy was detected in six patients in the idiopathic group (three lymphoma, one thymoma, one lung cancer, one gastrointestinal malignancy). CA 125 and CA 15-3 levels were high in five and three patients, respectively.

**Discussion**

In this study, we examined the diagnostic value of the CA 19-9, CA 125, CEA, CA 15-3, AFP and PSA for the diagnosis of tumour aetiology in patients with PE. The levels of CA 15-3, CEA and CA 125 were significantly higher in PE patients with malignancies. In the follow-up period, the levels of CA 15-3 and CA 125 decreased in patients in the idiopathic/viral group and remained constant in those with malignancies. The levels of CA 15-3 were more significant in detecting malignancies than those of CA 125.

CEA levels are known to increase in heart failure and this marker has also been used to diagnose pleural effusions with malignant aetiologies. In many studies, a relationship has been found between high levels of CEA and pericardial effusions with malignant aetiologies. Szturmowicz et al. found CEA levels above 5 U/ml had a 90% specificity for the detection of malignancy. Similarly, in our study, the levels of CEA were significantly higher in patients with cancer. In the follow-up period, this significance did not change.

Lindgren et al. showed a relationship between CA 125 levels and ovarian cancer. More recently it was realised that CA 125 levels can also increase in benign serious effusions.

| TABLE 3. TUMOUR MARKER LEVELS OF THE PATIENTS WITH AND WITHOUT CANCER |
|--------------------------|--------------------------|--------------------------|--------------------------|
| **Malignant PE** | **Non-malignant PE** | **P** |
| (n = 42) | (n = 27) | |
| CA 125 (U/ml) | 90.3 ± 88.6 | 55.2 ± 67.8 | 0.03 |
| CA 15-3 (U/ml) | 32.3 ± 14.6 | 17.0 ± 8.9 | 0.002 |
| CA 19-9 (U/ml) | 18.9 ± 20.2 | 18.7 ± 19.4 | NS |
| CEA (ng/ml) | 4.5 ± 5.2 | 2.0 ± 1.2 | 0.04 |
| AFP (U/ml) | 1.9 ± 1.7 | 1.7 ± 0.8 | NS |
| PSA (mg/ml) | 2.1 ± 2.5 | 3.1 ± 4.1 | NS |

Unlike CEA and CA 15-3, CA 125 is secreted from mesothelial cells in patients with PE of benign aetiology. For this reason, it can be used to determine the existence of fluid but it does not inform on the aetiology.

Two other studies revealed that CA 125 and CEA levels increased in heart failure, and that these levels could be related to the amount of pericardial fluid present. In our study, the levels of these markers were significantly higher in the PE patients with malignancies and remained high during the follow-up period.

High levels of CA 15-3 were first detected in breast cancer patients and this was used to evaluate recurrence in the follow-up period. In later studies, high levels of CA 15-3 were also found in effusion patients with malignancies. Romero et al. reported that CA 15-3 markers could be used to detect the underlying aetiology of the effusion.

In our study, in patients with no malignancies, CA 15-3 and CA 125 levels decreased significantly in the follow-up period. The levels of CA 15-3 were significantly higher in patients with malignancies and this increase remained significant in the follow-up period. CA 15-3 was found to be a valuable marker in the multi-analysis. In ROC curve analysis, CA 15-3 levels above 25 U/ml had a 71% sensitivity and 55% specificity for the prediction of malignancies underlying the pericardial effusions.

Malignancy was developed during the follow-up period in six of our patients whose initial diagnosis was idiopathic. At least one marker was high in five of these patients and CA 15-3 levels were high in three patients. These results indicate that if the underlying aetiology of the PE is unknown but there are high levels of CEA, CA 125 and CA 15-3, one should investigate for malignancy. Use of all three markers had a low sensitivity (29%) but a high specificity (97%) for detecting malignancy. Therefore determination of levels of these markers is very useful in the early diagnosis of malignancies.

Pericardiocentesis and pericardial biopsy are the best diagnostic tests for detecting malignant aetiologies of PE. However, where pericardiocentesis is not indicated, there are a limited number of other tests available. This study indicates that CA 125, CA 15-3, CEA are useful markers for detecting malignant aetiologies of PE. High levels of all three markers or increased levels of only CA 15-3 appeared to be predictive of effusions caused by malignancy. High levels of CA 15-3 in the follow-up period supported our hypothesis. Effusions categorised as idiopathic with high levels of these markers must be followed up closely or re-examined for possible malignancies.

There were some limitations to our study. The patient numbers in the groups according to the aetiology of PE were not equal. The number of patients was limited and they were heterogeneous in aetiology.

**Conclusion**

CA 125, CA 15-3 and CEA markers can be used in the differential diagnosis of benign and malignant aetiologies in patients with chronic pericardial effusions. Combined use of these three markers improves their prognostic value. Importantly, we must suspect malignancy in patients with PE whose aetiology cannot be determined.

**References**

1. Golland S, Caspi A, Malnick SD. Idiopathic chronic pericardial effusion. *N Engl J Med* 2000; 342(19): 1449–1450.
2. Sagristà-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med* 1999; 341(27): 2054–2059.

3. Sochocky S. Chronic pericardial effusion. *S D J Med* 1970; 23(3): 9–14.

4. García-Riego A, Cuiñas C, Vilanova JJ. Malignant pericardial effusion. *Acta Cytol* 2001; 45(4): 561–566.

5. Szturmowicz M, Tomkowski W, Fijalkowska A, Burakowski J, Szturmowicz A, Filipecki S. The role of carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) evaluation in pericardial fluid for the recognition of malignant pericarditis. *Int J Biol Markers* 1997; 12(3): 96–101.

6. Szturmowicz M, Tomkowski W, Fijalkowska A, Kupis W, Cieślik A, et al. Diagnostic utility of CYFRA 21-1 and CEA assays in pericardial fluid for the recognition of neoplastic pericarditis. *Int J Biol Markers* 2005; 20(1): 43–49.

7. Pawlak-Cieślik A, Szturmowicz M, Fijalkowska A, Tomkowski W, Kupis W, et al. Neoplastic pericarditis—the role of different diagnostic procedures. *Pol Arch Med Wewn* 2006; 115(1): 37–44.

8. Terracciano D, Di Carlo A, Papa P, Cicalese M, Maietta P, et al. New approaches in the diagnostic procedure of malignant pleural effusions. *Oncol Rep* 2004; 12(1): 79–83.

9. Svenberg T. Carcinoembryonic antigen-like substances of human bile. Isolation and partial characterization. *Int J Cancer* 1976; 17(5): 588–596.

10. Shiriti D, Zingerman B, Shiriti AB, Shlomi D, Kramer MR. Diagnostic value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125 assays in pleural effusions: analysis of 116 cases and review of the literature. *Oncologist* 2005; 10(7): 501–507.

11. Ohuchi N, Sato S, Akimoto M, Taia Y, Matoba N, et al. The correlation between the immunohistochemical expression of DF3 antigen and serum CA15-3 in breast cancer patients. *Jpn J Surg* 1991; 21(2): 129–137.

12. Nicolini A, Anselmi L, Michelassi C, Carpi A. Prolonged survival by ‘early’ salvage treatment of breast cancer patients: a retrospective 6-year study. *Br J Cancer* 1997; 76(8): 1106–1111.

13. Porcel JM, Vives M, Esquerda A, Salud A, Pérez B, Rodríguez-Panadero F. Use of a panel of tumor markers (carcinoembryonic antigen, cancer antigen 125, carcinoembryonic antigen 15-3, and cytokeratin 19 fragments) in pleural fluid for the differential diagnosis of benign and malignant effusions. *Ches* 2004; 126(6): 1757–1763.

14. Romero S, Fernández C, Arriero JM, Espasa A, Candela A, et al. CEA, CA 15-3 and CYFRA 21-1 in serum and pleural fluid of patients with pleural effusions. *Eur Respir J* 1996; 9(1): 17–23.

15. Shimokata K, Totani Y, Nakashiki K, Yamamoto M, Hasegawa Y, et al. Diagnostic value of cancer antigen 15-3 (CA15-3) detected by monoclonal antibodies (115D8 and DF3) in exudative pleural effusions. *Eur Respir J* 1988; 1(4): 341–344.

16. Mezger J, Permanetter W, Gerbes AL, Wilmanns W, Lamerz R. Tumor associated antigens in diagnosis of serous effusions. *J Clin Pathol* 1988; 41(6): 633–643.

17. Kandyilos K, Vassiliomanolakis M, Baziotes N, Papadimitriou A, et al. Diagnostic significance of the tumor markers CEA, CA 15-3 and CA 125 in malignant effusions in breast cancer. *Ann Oncol* 1990; 1(6): 435–438.

18. Ammon A, Eiffert H, Reil S, Beyer JH, Droese M, Hiddemann W. Tumor-associated antigens in effusions of malignant and benign origin. *Clin Invest* 1993; 71(6): 437–444.

19. Galve E, Garcia-Del-Castillo H, Evangelista A, Batlle J, Permanyer-Miralda G, Soler-Soler J. Pericardial effusion in the course of myocardial infarction: incidence, natural history, and clinical relevance. *Circulation* 1986; 73(2): 294–299.

20. Tatsuta M, Yamamura H, Yamamoto R, Ichii M, Ishi H, Noguchi S. Carcinoembryonic antigens in the pericardial fluid of patients with malignant pericarditis. *Tumor Markers* 1984; 21: 328–330.

21. Koh KK, In HH, Lee KH, Kim EL, Cho CH, et al. New scoring system using tumor markers in diagnosing patients with moderate pericardial effusions. *Int J Cardiol* 1997; 61(1): 5–13.

22. Lindgren J, Kuusela P, Hellström PE, Pettersson T, Klockars M. The ovarian cancer associated antigen CA 125 in patients with pleural effusions. *Eur J Cancer* 1991; 27: 737–739.

23. Faggiano P, D’Alloia A, Brentana L, Bignotti T, Fiorina C, et al. Serum levels of different tumor markers in patients with chronic heart failure. *Eur J Heart Fail* 2005; 7(1): 57–61.

24. Whiteside TL, Dekker A. Diagnostic significance of carcinoembryonic antigen levels in serous effusions. Correlation with cytology. *Acta Cytol* 1979; 23(6): 443–448.

25. Seo T, Ikeda Y, Onaka H, Hayashi T, Kawaguchi K, Kotake C, Toda T, Kobayashi K. Usefulness of serum CA125 measurement for monitoring pericardial effusion. *Jpn Circ J* 1993; 57(6): 489–494.