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Diagnostic and prognostic significance of survivin levels in malignant pleural effusion

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Summary
We aimed to evaluate the diagnostic and prognostic value of measuring survivin levels, which is an inhibitor of apoptosis in pleural effusions. *Methods:* Group I, malignant (MPE) ($n = 51$); Group II, tuberculosis (TPE) ($n = 18$); Group III transudative (TE) ($n = 9$) effusions were enrolled prospectively. We used ELISA to analyze 78 effusions. The value for the differential diagnosis and the correlation between survivin and survival in MPE were analyzed. *Results:* Survivin level was 41.75 ± 76.20 in MPE, 15.83 ± 10.92 in TPE and 8.33 ± 8.67 in TE. When the patients divided two groups as malignant and non-malignant pleural effusion (non-MPE), survivin level was significantly higher in MPE (41.75 ± 76.20) than in non-MPE (13.33±2.05) ($p = 0.012$). The cutoff value for survivin levels detected by ROC curve analysis was 7.5 pg/ml, with sensitivity and specificity values of 72%, 44%, respectively. Survivin had no discriminative power in differentiating exudative effusions of MPE from TPE ($p = 0.405$). There was no correlation between survivin level and age, sex, location, fluid pH, glucose, protein, albumine and ADA level while there was significant moderate correlation with fluid LDH ($r = 0.49$; $p < 0.001$). Survivin levels can distinguish patients who had poor prognosis (median survival 75 days, $n = 24$) and those who had good prognosis (median survival 219 days, $n = 27$, $p = 0.03$) in MPE.

In conclusion, survivin expression levels detected with ELISA had no discriminative power in differentiating exudative effusions included MPE and TPE. Elevated survivin levels are associated with poor survival in MPE. Our results suggest that survivin may be a potential prognostic marker in MPE.
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Introduction

Malignant pleural effusion (MPE) is a common and important cause of cancer-related mortality and morbidity. [1,2] Prompt diagnosis using minimally invasive test is important because the median survival after diagnosis is only 4—9 months. The sensitivity of cytologic examination of pleural effusion is variable with limited sensitivity and not predictive of prognosis.[3,4] Consequently, many patients need to undergo invasive diagnostic tests such as thoracoscopic pleural biopsy. Besides, none of the prognostic marker has been validated until now for MPE.

Survivin is an inhibitor of apoptosis that may be a novel diagnostic and prognostic marker of cancer. It is selectively upregulated in many human tumors, where its overexpression correlates with poor outcome.[5—9] Tissue expression of survivin has a critical role for diagnosis, prognosis and the prediction of response to therapy.[5,7,8] But, there are limited data on the expression and prognostic role of survivin in malignant pleural effusion.[10—13] So, its value in the analysis of biological fluids such as pleural effusion is not known.

We aimed to determine the discriminative power of survivin in proven cases of MPE and non-MPEs diagnosed by conventional cytopathologic and histopathologic methods, and testing the prognostic value of survivin levels in MPE.

Materials and methods

Subjects

Between October 2009 and July 2010, a total of 78 patients [51 with malignant, 18 with tuberculosis and 9 with congestive heart failure (CHF)] with pleural effusion admitted to our clinic were included in the study. All patients consecutively diagnosed with MPE, tuberculous pleurisy (TPE) and CHF were included. All patients were diagnosed according to criteria cited below which was considered as a reasonable standard for diagnosis. Distribution of patients according to the primary etiology has been shown in Table 1.

Medical history was taken from all patients included in the study. Physical examination was made, and posteroanterior chest X-ray ordered. Thoracentesis was carried out in all patients. Total protein, albumin, LDH, glucose and pH were measured in the pleural fluid and blood sample, and ADA levels also were studied in pleural fluid. In addition, fluid cell formula and acid-fast bacilli were analyzed in effusions in the microbiology laboratory.

The diagnosis of TPE was done according to the following criteria; (1) Pathological demonstration of a necrotizing granulomatous inflammation in the pleural tissue sample taken with closed biopsy or Video Assisted Thoracoscopic Surgery (VATS) (17 patients); or (2) microbiologic isolation of *Mycobacterium tuberculosis* in the pleural fluid (2 patients); plus exclusion of other possible diagnosis by clinical and radiological examination.

The diagnosis of MPE was done according to the following criteria; malignant cells in the cytology of the pleural fluid (27 patients) and/or on histopathologic examination of the pleural tissue obtained by VATS (6 patients) or pleural blind biopsy (18 patients).

The diagnosis of CHF is based on medical history, physical examination and detection of cardiomegaly in chest X-ray. Left ventricular systolic dysfunction on echocardiography and response to diuretic therapy was also used in the confirmation of the diagnosis.

Methods

Study has been approved by the ethical committee and informed consents were obtained from all participants. From each patient 5 ml aliquots of pleural fluid were

Table 1 Distribution of patients according to primary etiology.

	N (%)	Survivin levels (pg/ml)	Survival, median ± SE (95% CI)
Malignant pleural effusion	51 (65)	41.75 ± 76.20	
Primary lung carcinoma	24	52 ± 95[a]	75 ± 4 (67—82)
Adeno	22		
Squamous	1		
Small cell carcinoma	1		
Metastatic other than lung	14	25 ± 20	45 ± 67 (0—177)
Breast	6		
Pancreas	2		
Colon	1		
Gastrointestinal system	1		
Prostate	1		
Adenoid cystic carcinoma	1		
Cervix	1		
Unknown primary	1		
Mesothelioma	8	18 ± 22	181 ± 29 (122—239)
Lymphoma	5	86 ± 124	215 ± 119 (0—449)
Tuberculosis (TPE)	18 (23)	15.83 ± 10.92	
Congestive Heart Failure (CHF)	9 (12)	8.33 ± 8.67	

[a] No statistically significant difference was found between the tumor groups according to survivin level ($p = 0.22$).