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ORIGINAL ARTICLE

Value of plasma and pleural effusion fibulin-3 levels in the diagnosis of malignant pleural mesothelioma effusions

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KEYWORDS

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Abstract *Background:* Malignant pleural mesothelioma (MPM) is a highly aggressive tumor that arises from the surface cells of the pleura with a poor survival rate. Fibulin-3 is a protein biomarker found in blood and pleural fluid of patients with mesothelioma and can reliably predict the presence, or absence, of mesothelioma cancer cells. The possible role of fibulin-3 in diagnosis of MPM was studied.

Patients and methods: Sixty patients were included in the study, 30 with pleural effusions due to MPM and another 30 with non mesothelioma malignant pleural effusion (MPE). Plasma and pleural effusion fibulin-3 levels were estimated for all patients using an enzyme-linked immunosorbent assay (ELIZA).

Results: Plasma and pleural effusion fibulin-3 levels were significantly higher in patients with MPM (113 ± 3.7 ng/ml and 594.2 ± 65.7 ng/ml, respectively) compared to those with non mesothelioma MPE (44.4 ± 7.1 ng/ml and 187.3 ± 14.5 ng/ml, respectively) ($P < 0.001$). Plasma and effusion fibulin-3 levels discriminated significantly between patients with MPM and those with non mesothelioma MPE, with area under receiver operating characteristic (ROC) curves of 0.98 and 0.94, respectively, at cut-off values of 54.3 ng/ml for plasma fibulin-3 and 520 ng/ml for effusion fibulin-3, with sensitivity of 100% and 90%, specificity of 96.7% for both, positive predictive value (PPV) of 96.8% and 96.4% and negative predictive value (NPV) of 100% and 90.6%, respectively.

Conclusion: Plasma and effusion fibulin-3 levels can differentiate mesothelioma effusions from other malignant effusions.

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Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor that arises from the surface cells of the pleura with a poor survival rate. Previously it was considered as a rare tumor, MPM has become a common public health problem, and its incidence is expected to continue to increase in the next 10 years [1].

Diagnosis of MPM is a challenging issue. Potential markers in mesothelioma diagnosis include soluble mesothelin-related peptides (SMRPs) and osteopontin, but no subsequent validation has been published yet [2]. Soluble mesothelin related protein, the most extensively studied blood based mesothelioma biomarker, is limited by an overall sensitivity of 47% and 96% specificity [3]. Another finding is that a significantly elevated level of SMRPs was found only in epithelioid mesothelioma but not in sarcomatoid type, as already suggested by *Robinson and his colleagues* [4]. Interestingly, *Ordonez* has reported that only epithelioid mesothelioma cells are positive for mesothelin staining, some patients with mixed-type MPM also had elevated values of serum SMRPs. It can be speculated that the level of serum SMRPs is correlated to the percentage of the epithelioid component in the tumor [5].

Recently it was found that fibulin-3 is a new protein biomarker found in blood and pleural fluid of patients with mesothelioma and can reliably predict the presence, or absence, of mesothelioma cancer cells. This finding could open the way for a long sought-after screening tool for anyone exposed to asbestos [3].

Patients and methods

The current prospective study was conducted at Pulmonary Medicine and Cardiothoracic Surgery Departments, Zagazig University Hospitals, during the period from July 2010 to November 2013. Patients suspected of, or recently diagnosed with malignant pleural effusions [6] were recruited in the study. Pathologic diagnosis by trained pathologists was done on pleural biopsies obtained by thoracoscopy, thoracotomy, or by CT or ultrasound-guided biopsy.

Exclusion criteria were:

1. The presence or suspicion of any concomitant infectious disease.
2. Patients with transudative pleural effusions.
3. Previous thoracic surgery, radiotherapy, or chemotherapy for the MPM.
4. Patient refusal to participate in the study.

After final diagnosis was confirmed pathologically, patients were divided into 2 groups: 30 cases with confirmed MPM and 30 cases with non mesothelioma malignant pleural effusion (MPE). After inclusion: blood and pleural fluid samples were collected from each patient where; total protein levels, lactate dehydrogenase (LDH) levels, pleural fluid glucose levels, total and differential cell counts, in addition to levels of fibulin-3 (FBLN3) were estimated. Clinical data and outcome of the patients were also collected.

Fibulin-3 enzyme-linked immunosorbent assay

Levels of fibulin-3 in plasma and pleural effusions were measured in duplicate wells and quantified in nanograms per milliliter with the use of the human fibulin-3 enzyme-linked immunosorbent assay. Assay was done according to the manufacturer instructions; the kit is a sandwich enzyme immunoassay for in vitro quantitative measurement of fibulin-3 in human serum, plasma, urine and other biological fluids. (USCN Life Science Inc. www.uscnk.us; www.uscnk.com).

Statistical analysis

Statistical analysis was performed with Epi Info™ version 7 and the SPSS version 19 statistical software package (SPSS Inc., Chicago, IL, USA). *P*–value <0.05 was considered significant.

Results

Table 1 shows the socio- demographic data of all studied patients. Patients with MPM were more significantly exposed to asbestos than those with non mesothelioma MPE with no significant difference regarding age and sex.

Tables 2 and 3 show no significant differences between both studied groups as regards pleural fluid characteristics and diagnostic procedures used to reach the final diagnosis. Most of the patients in both groups were finally diagnosed through tissue biopsy obtained by thoracoscopy (66.7% vs. 70% in MPM vs. non mesothelioma MPE).

Table 4 shows that epithelioid type (73.3%) was the most prevalent histopathological type among patients with MPM followed by mixed (16.7%) then sarcomatoid (10%) types.

Table 5 shows sites of primary tumor in patients with non mesothelioma MPE. Of these patients, 12 patients (40%) had lung adenocarcinoma, 4 patients (13.3%) had lung squamous cell carcinoma, 5 patients (16.7%) had breast adenocarcinoma, 3 patients (10%) had ovarian carcinoma, 2 patients (6.7%) had gastrointestinal adenocarcinoma, 1 patient (3.3%) had lymphoma and 3 patients (10%) had cancer of unknown primary site.

Table 6 shows that plasma and effusion fibulin-3 levels were significantly higher in patients with MPM when compared with those with non mesothelioma MPE ($P < 0.001$).

Table 1 Demographic data of the studied patients.

Parameter	Mesothelioma (no = 30)	Non mesothelioma MPE (no = 30)	*P*-value
Age in years	64.4 ± 7.6	62.2 ± 5.9	0.22
Sex: M/F	19/11	16/14	0.60
Hx. of asbestos exposure, no. (%)	23 (76.7%)	8 (26.7%)	<0.001

MPE; malignant pleural effusion. Hx; History. M; Male. F; Female.