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Original

Pleural fluid mesothelin for the differential diagnosis of exudative pleural effusions

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ABSTRACT

Background and objective: Malignant mesothelioma (MM) is a highly aggressive tumor that can be difficult to diagnose, resulting in a delayed diagnosis in some cases. Recent studies have reported that determination of soluble mesothelin-related peptides (SMRP) in pleural fluid may be a promising marker for use in the diagnosis of MM.

Patients and methods: Pleural fluid SMRP concentration was measured in 68 patients: 47 had malignant pleural effusions (18 MM and 29 metastatic effusion) and 21 had benign pleural effusion (8 infectious disease and 13 idiopathic effusion). Mann-Whitney analysis was used to compare SMRP values according to the etiology of the effusion.

Results: Pleural fluid SMRP concentration was significantly higher in patients with malignant pleural effusion than in those with benign effusion ($P = 0.02$). When malignant pleural effusions were analyzed separately, MM patients had the highest median pleural fluid SMRP concentration, with significant differences as compared to patients with idiopathic pleural effusion.

Conclusions: Soluble mesothelin-related peptide measurement in pleural fluid may aid in the diagnosis of patients presenting with pleural effusion.

Mesotelina en líquido pleural para el estudio de los exudados

Palabras clave:
Derrame pleural
Mesotelioma
Mesotelina

RESUMEN

Fundamento y objetivo: El mesotelioma es un tumor agresivo y difícil de diagnosticar, lo cual implica que en ocasiones su diagnóstico se produzca de forma tardía. Existen estudios recientes que describen la utilidad de la mesotelina en líquido pleural como marcador precoz para el diagnóstico de los mesoteliomas.

Pacientes y metodo: Se determina mesotelina en líquido pleural de 68 pacientes: 47 pacientes con derrame maligno (18 mesoteliomas y 29 derrames pleurales metástasicos) y 21 derrames pleurales benignos (8 derrames infecciosos y 13 idiopáticos). Se utiliza el test de Mann-Whitney para comparar los niveles de mesotelina según el diagnóstico del derrame pleural.

Resultados: El nivel de mesotelina fue significativamente superior en los pacientes con derrame pleural malignos respecto a los pacientes con derrame pleural benigno ($p = 0.02$). Cuando los derrames pleurales malignos se analizaron de forma separada, los mesoteliomas presentaron las cifras más altas con significación estadística con respecto al resto de etologías.

Conclusiones: La determinación de mesotelina pleural puede ser de utilidad en el estudio de los derrames pleurales exudativos.

Introduction

Malignant mesothelioma (MM) of the pleura is an uncommon, but no longer rare, and highly aggressive tumor that arises from the pleura and frequently extends to adjacent structures.[1]

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The diagnosis of MM is often difficult and can be delayed for several reasons, such as a subacute clinical course, low grade of suspicion in cases unrelated to asbestos exposure, and presence of an exudative pleural fluid with cells that are difficult to distinguish from reactive mesothelial cells or other malignant cells.[1,2]

One of the main problems encountered when establishing the diagnosis in patients with exudative pleural effusion is differentiating between those secondary to neoplastic disease and those with an idiopathic cause, which generally show a favorable evolution.[3,4] In a recent clinical study, we concluded that a range of non-invasive examinations (chest radiographs, biochemical, microbiological and cytological pleural fluid analysis, and chest CT scanning, as well as others) allows accurate differentiation between malignant and idiopathic effusions in most patients. Nevertheless, the study also highlighted the difficulty of diagnosing MM, because 5 of the 13 cases included were not suspected before invasive procedures such as thoracoscopy were performed.[3]

Several studies have analyzed the value of measuring a panel of pleural fluid markers in the assessment of patients with suspected malignant effusion.[5–10] Although several tumor markers are reported to be useful for differentiating between malignant and benign effusions, there is currently no routine standardized test for this purpose.[5–9]

Moreover, there is little available data on pleural fluid tumor markers for the diagnosis of MM. Whereas low levels of carcinoembryonic antigen (CEA) are found in MM, high CEA levels have a strong negative predictive value for this disease, and measurement of cancer antigen (CA) 15.3, cytokine fragment (Cyfra) 21.1 and hyaluronic acid has not been useful for distinguishing between MM and other pleural malignancies.[9,11,12]

Mesothelin-related protein (MRP) is a glycoprotein that is mainly overexpressed in MM, and also in some non-mucinous carcinomas of the ovary and pancreas, and certain squamous carcinomas.[13–17] Most studies on MRPs are immunohistochemical reports assessing frozen tissue.[18–20] At the beginning of 2000, however, the utility of soluble mesothelin-related proteins (SMRPs) was assessed, and a small number of studies showed their potential diagnostic value when measured in serum.[21–28] To date, however, the use of SMRP measurement in pleural fluid for the differential diagnosis of effusions has received little attention.[29–31]

The objective of this study was to evaluate the utility of this new soluble marker measured in pleural fluid for the diagnosis of exudative pleural effusions.

Methods

Soluble mesothelin-related proteins were measured in pleural fluid from 68 patients admitted for pleural effusion.

From November 1992 to September 2006, 1184 consecutive pleural effusions were prospectively recorded at Vall d'Hebron Hospittal and classified on the basis of clinical symptoms, pleural fluid characteristics, and additional examinations.[3] From this series we selected a minimum number of consecutive patients according to the final diagnosis to include all the diagnostic categories. Furthermore we included the 5 patients with demonstrated MM identified at the Arnau de Vilanova University Hospital in Lleida from 1995 to 2006. These included: 1) 18 patients with MM on histological examination of the pleura; 2) 29 patients with metastatic malignant pleural effusion diagnosed by malignant findings on pleural cytologic or histologic examination, including 9 patients with lung cancer (5 adenocarcinoma and 4 oat cell), 5 with breast cancer, 5 with pancreas cancer, 5 with ovarian cancer and 5 with hematological malignancy; 3) 4 uncomplicated parapneumonic effusions defined by pneumonia and pleural fluid with a non-purulent appearance, negative on gram stain and culture, and pH >7.2 and/or glucose >40 mg/dL; 4) 4 tuberculous effusions defined by positive pleural fluid on Ziehl-Nielsen stain or Löwenstein-Jensen culture, or pleural biopsy specimen showing granulomas or positive Ziehl-Neelsen stain or positive Löwenstein-Jensen culture, or pleural fluid adenosine deaminase (ADA) levels >43 IU/L with consistent clinical signs and symptoms, pleural fluid lymphocyte predominance and good response to antituberculosis treatment; and 5) 13 idiopathic pleural effusions, defined as undiagnosed pleural effusion after complementary examinations were performed and a minimum follow-up of two years.[3]

Soluble mesothelin-related protein levels were determined in the Department of Biochemistry of the Vall d'Hebron Hospital using sandwich ELISA (Mesomark; CIS Bio International, Gif/Yvette, France; Fujirebio Diagnostics, Inc., Malvern, PA) according to the manufacturers' instructions; results are expressed in nmol/L. Laboratory research investigator did not know the diagnosis of pleural effusion.

Statistical analysis

All data are expressed as median and interquartile range. Due to the presence of extreme values, Mann–Whitney analysis was used to compare the distribution of SMRP levels between patients with malignant pleural effusion and those with benign effusion, and subsequently, between patients with MM and those with other malignancies or idiopathic pleural effusion. Area and standard errors of receiving operating curves (ROC) were calculated using standard techniques. Area under ROC curves (AUC) are reported with their 95% confidence intervals (95%CI). Sensitivity and specificity for different cut-off were calculated. [32]

Results

Pleural fluid SMRP levels according to the etiology of the effusion are shown in Table 1.

As is seen in Fig. 1, SMRP values were significantly higher in patients with MM (median 33.4 nmol/L) than in those with metastatic pleural effusion (median 8.8 nmol/L; $P = 0.002$) or benign effusion (median 4 nmol/L; $P = 0.002$), which included infectious (median 6.2 nmol/L) and idiopathic pleural effusion (median 3.7 nmol/L). Significant differences were found between patients with pleural effusion due to MM and metastatic effusion ($P = 0.002$) or benign effusion ($P = 0.002$). There were also significant differences between those with metastatic effusion and benign effusion ($P = 0.002$). There were no differences in SMRP levels between patients with idiopathic pleural effusion and infectious effusion.

Soluble mesothelin-related proteins were significantly higher ($P = 0.02$) in patients with malignant disease (MM and metastatic pleural effusions) (median 9.8 nmol/L) than in patients with benign disease (infectious and idiopathic pleural effusions).

Since the differential diagnosis of idiopathic effusions mainly includes malignant disease, we performed a separate analysis of the differences with MM and metastatic pleural effusions. SMRP levels were significantly higher in pleural fluid of patients with MM and metastatic pleural effusion than in patients with idiopathic pleural effusion ($P = 0.01$ and $P = 0.009$ respectively).

When MM were compared to the rest of etiologies AUC was 0.7050 (95%CI, 0.5224–0.8875). Sensitivity and specificity for different cut-off are reported in Table 2.