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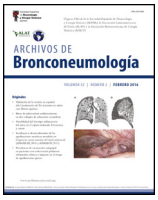

Original Article

Detection of Pleural Fluid Biochemistry Changes in Two Consecutive Thoracenteses for Differentiating Malignant From Benign Effusions☆

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ABSTRACT

Objective: To assess whether changes in pleural fluid (PF) biochemistries between two consecutive thoracenteses enable clinicians to predict malignant or benign pleural effusions (PE).
Methods: Retrospective study of patients with lymphocytic exudates and negative PF cytology, who underwent a second thoracentesis in our center in the last 15 years in whom a final diagnosis was reached (derivation sample). Absolute (Δa) and percentage differences (Δp) in PF biochemistries which predicted a malignant or benign PE in the derivation sample were evaluated in an independent population (validation sample).
Results: The derivation sample included 214 PE patients (70 malignant and 144 benign PE). Δp lactate dehydrogenase (LDH)>0%, Δp neutrophils>−10% (any increase or less than 10% decrease) and Δa protein <0.1 g/dL (any increase or less than 0.1 g/dL decrease) between the second and the first thoracentesis had an odds ratio of 6.4, 3.9 and 2.1, respectively, to discriminate malignant from benign PE. The presence of the three conditions together had a positive likelihood ratio of 5.6, whereas the absence of any of the three parameters had a likelihood ratio of 0.04 for predicting malignancy. These results were reproduced in the validation sample.
Conclusion: An increase in LDH and neutrophils along with a decrease in protein in a second thoracentesis increase the probability of malignant PE, while the opposite reduces it significantly.

Cambios en los parámetros bioquímicos del líquido pleural entre 2 toracocentesis consecutivas para diferenciar derrames malignos de benignos

Palabras clave:
Derrame pleural maligno
Toracocentesis
Líquido pleural
Lactato deshidrogenasa

RESUMEN

Objetivo: Evaluar si los cambios en los parámetros bioquímicos del líquido pleural (LP) entre 2 toracocentesis sucesivas permiten predecir derrames pleurales (DP) malignos o benignos.
Métodos: Estudio retrospectivo de los pacientes con exudado linfocitario y citología negativa para malignidad que se sometieron a una segunda toracocentesis en nuestro centro durante los últimos 15 años (muestra de derivación), y en los que se alcanzó un diagnóstico final. Las diferencias absolutas (Δa) o porcentuales (Δp) de diferentes parámetros bioquímicos del LP capaces de predecir la naturaleza maligna o benigna del DP en la muestra de derivación se evaluaron en una población independiente.

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Resultados: Se incluyeron 214 pacientes con DP (70 malignos y 144 benignos) en la muestra de derivación. Las Δp LDH (lactato deshidrogenasa) > 0%, Δp neutrófilos > −10% (cualquier aumento o bien un descenso inferior al 10%), y Δa proteínas < 0,1 g/dL (cualquier descenso o bien un aumento inferior a 0,1 g/dL) entre la segunda y primera toracocentesis mostraron unas *odds ratio* de 6,4, 3,9 y 2,1 para discriminar DP maligno de benigno, respectivamente. La presencia de las 3 condiciones conjuntamente se asoció con una *likelihood ratio* positiva de 5,6, mientras que la ausencia de cualquiera ellas se asoció con una *likelihood ratio* negativa de 0,04 para predecir malignidad. Los resultados se reprodujeron en la población de validación.

Conclusión: El aumento de LDH y neutrófilos, junto con el descenso de proteínas en una segunda toracocentesis, aumenta la probabilidad de que el origen del DP sea neoplásico, mientras que lo contrario la reduce significativamente.

Introduction

Pleural effusion (PE) is a common medical problem that has more than 60 recognized causes.[1] Cancer is the most common reason for PE studied by thoracentesis, accounting for around 30% of cases.[2] The diagnosis of malignant PE is definitive when cancer cells are detected in a cytological study of the pleural fluid (PF). However, only 51% of tests are positive in the first analysis.[2] Analysis of new PF samples can increase the diagnostic yield to around 60%, so the percentage of false negatives on cytology is significant.[3] Moreover, only 34% of malignant PEs are associated with a history of cancer that could orient the clinician toward the potentially cancerous nature of the specimen.[4]

The biochemical parameters of PF offer more immediate information on this type of specimen. Malignant PE is typically an exudate with a predominance of lymphocytes.[5] A second diagnostic thoracentesis is often performed while awaiting results from the first cell block or when the cytology results from the first sample are negative. If two cytological studies of PF that include a cytology smear and a cell block are negative, yet malignancy is suspected, a diagnostic thoracoscopy is recommended.[5] However, this technique is invasive, so it should be reserved for patients who might benefit from the procedure.[6]

Some experts suggest that the serial measurement of lactate dehydrogenase (LDH) in PF may help guide diagnosis in patients with PE of uncertain etiology, since this enzyme is a reliable indicator of the degree of pleural inflammation.[7] A progressive increase in LDH levels observed on a repeat thoracentesis indicates increased inflammation in the pleural space, and the search for an accurate diagnosis should continue. However, if LDH levels fall, the process is probably resolving, and invasive diagnostic procedures can be avoided. This theory, however, is based purely on expert opinion, and has not been corroborated in any study.

The aim of this study was to evaluate and validate changes in LDH and other biochemical variables in PF in successive thoracentesis as predictors of malignant or benign PE. This may help to select patients who would require more intensive investigation for a definitive diagnosis with the use of procedures such as thoracoscopy.

Materials and Methods

Patient Selection

This was a retrospective study that included all consecutive patients with PE seen in the Hospital Universitario Arnau de Vilanova de Lleida between January 2001 and December 2016 who met the following criteria (derivation sample): (a) at least two diagnostic thoracenteses with available biochemical data on PF (if three or more thoracenteses were performed, only the first two were considered); (b) PF in the first thoracentesis was an exudate (according to Light's criteria[8]) with >50% lymphocytes in the leukocyte count and a negative cytology for malignancy; and (c) a definitive diagnosis for PE etiology or else PE determined to be idiopathic (see definition below). The Hospital Universitario Arnau de Vilanova de Lleida is a 440-bed reference hospital with a catchment population of 450 000 inhabitants, and carries out around 400 diagnostic thoracenteses per year.

Patients were divided into two groups according to the final diagnosis: malignant PE and benign PE. The benign PE group was then subdivided into idiopathic and other etiologies. Absolute and relative changes in the PF biochemical variables between two successive thoracentesis considered significant in the derivation sample were validated in a population with the same inclusion criteria, seen in the Hospital de Mendaro between January 1995 and August 2015 (validation sample). Hospital de Mendaro is a 125-bed county hospital with a catchment population of 80 000, and performs 50 diagnostic thoracenteses every year.

The following variables were recorded: demographic data (sex and age); date of both thoracenteses; protein and LDH serum concentrations; and red blood cell and white blood cell counts, neutrophil and lymphocyte percentages, glucose, LDH, proteins, adenosine deaminase (ADA), pH, and C-reactive protein (CRP) in PF. The local ethics committee approved the study protocol (CEIC-1592).

Diagnostic Criteria

PE was defined as malignant if malignant cells were found in PF or pleural biopsy. PE due to heart failure was diagnosed from the clinical history, physical examination, chest X-ray, electrocardiogram, echocardiogram (if available), and good response to diuretics. Confirmation of a diagnosis of pleural tuberculosis required tuberculosis bacillus to be isolated from sputum samples, PF or pleural biopsy, or granulomas observed in the latter. Pleural tuberculosis was considered likely in patients with lymphocytic exudate and ADA≥35 U/L in PF, whose PE resolved with antituberculosis treatment. Parapneumonic PEs were those associated with pneumonia, bronchiectasis, or pulmonary abscess. Finally, PE was classified as idiopathic when it resolved with no specific treatment and its etiology could not be determined despite an in-depth study that included PF analysis (biochemistry, cytology), chest and abdominal computed tomography (CT), and, in selected cases, pleural biopsy. Other diagnoses were established according to widely accepted clinical criteria.[2] All patients with benign pleural diseases were followed up clinically until complete resolution of the PE, which, in the case of idiopathic PE, was at least a year.

Pleural Fluid Analysis

PF was collected from the derivation population in 5 mL heparinized tubes, and biochemical analysis was performed