Med Clin (Barc). 2015;145(4):171–177

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

Contribution of pleural fluid analysis to the diagnosis of pleural effusion☆

Lucía Ferreiro[a], María Elena Toubes[a], Luis Valdés[a,b,*]

[a] Servicio de Neumología, Complejo Hospitalario Clínico-Universitario de Santiago Santiago de Compostela, Santiago de Compostela, A Coruña, Spain
[b] Grupo Interdisciplinar de Investigación en Neumología, Instituto de Investigaciones Sanitarias de Santiago (IDIS), Santiago de Compostela, A Coruña, Spain

ARTICLE INFO

Article history:
Received 13 July 2014
Accepted 29 August 2014
Available online 11 February 2016

Keywords:
Pleural effusion
Analysis of pleural fluid
Diagnosis of pleural effusion
Parapneumonic pleural effusion
Tuberculous pleural effusion
Malignant pleural effusion

ABSTRACT

Analysis of pleural fluid can have, on its own, a high diagnostic value. In addition to thoracocentesis, a diagnostic hypothesis based on medical history, physical examination, blood analysis and imaging tests, the diagnostic effectiveness will significantly increase in order to establish a definite or high probable diagnosis in a substantial number of patients.

Differentiating transudates from exudates by the classical Light's criteria helps knowing the pathogenic mechanism resulting in pleural effusion, and it is also useful for differential diagnosis purposes. An increased N-terminal pro-brain natriuretic peptide, both in the fluid and in blood, in a due clinical context, is highly suggestive of heart failure.

The presence of an increased inflammatory marker, such as C-reactive protein, together with the presence of over 50% of neutrophils is highly suggestive of parapneumonic pleural effusion. If, in these cases, the pH is <7.20, then the likelihood of complicated pleural effusion is high. There remains to be demonstrated the usefulness of other markers to differentiate complicated from uncomplicated effusions. An adenosine deaminase >45 U/l and >50% lymphocytes is suggestive of tuberculosis.

If a malignant effusion is suspected but the cytological result is negative, increased concentrations of some markers in the pleural fluid can yield high specificity values. Increased levels of mesothelin and fibruline-3 are suggestive of mesothelioma. Immunohistochemical studies can be useful to differentiate reactive mesothelial cells, mesothelioma and metastatic adenocarcinoma.

An inadequate use of the information provided by the analysis of pleural fluid would results in a high rate of undiagnosed effusions, which is unacceptable in current clinical practice.

Contribución del análisis del líquido pleural al diagnóstico de los derrames pleurales

Palabras clave:
Derrame pleural
Análisis del líquido pleural
Diagnóstico del derrame pleural
Derrame pleural paraneumónico
Derrame pleural tuberculoso
Derrame pleural neoplásico

RESUMEN

El análisis del líquido pleural, por sí mismo, puede tener valor diagnóstico. Pero si además de hacer una toracocentesis se establece una hipótesis diagnóstica con base en la historia clínica, la exploración física, el análisis de sangre y las pruebas de imagen, la rentabilidad diagnóstica aumentará de forma relevante y se podrá establecer un diagnóstico definitivo, o de alta probabilidad, en un elevado porcentaje de pacientes.

Diferenciar entre trasudados y exudados, clásicamente a través de los criterios de Light, ayuda a conocer el mecanismo fisiopatológico por el que se produce el derrame pleural, y a estrechar su diagnóstico diferencial. Un valor elevado del fragmento N-terminal del propéptido natriurético cerebral, tanto en líquido como en sangre, en un marco clínico adecuado, es muy indicativo de fallo cardiaco.

Un marcador inflamatorio elevado, por ejemplo la proteína C reactiva, junto con más de un 50% de neutrófilos, revela muy posiblemente un derrame paraneumónico. Si, en estos casos, el pH es < 7,20, existe una alta probabilidad de que el derrame se esté complicando. Está por demostrar la utilidad de otros marcadores para diferenciar entre derrames paraneumónicos complicados y no complicados. Una adenosina desaminasa > 45 U/l y más de un 50% de linfocitos es muy indicativo de tuberculosis.

☆ Please cite this article as: Ferreiro L, Toubes ME, Valdés L. Contribución del análisis del líquido pleural al diagnóstico de los derrames pleurales. Med Clin (Barc). 2015;145:171–177.

* Corresponding author.
E-mail address: luis.valdes.cuadrado@sergas.es (L. Valdés).

2387-0206/

Si se sospecha un derrame neoplásico y la citología es negativa, concentraciones elevadas en el líquido pleural de algunos marcadores son altamente específicas. Altos valores de mesotelina y fibulina-3 evidencian mesotelioma. La inmunohistoquímica puede ayudar a diferenciar entre células mesoteliales reactivas, mesotelioma y metástasis por adenocarcinoma.

Un uso inadecuado de la información que puede proporcionar el análisis del líquido pleural conllevaría un alto porcentaje de derrames no diagnosticados, difícilmente aceptable en la práctica clínica actual.

Introduction

Pleural effusion (PE) is a common condition with a prevalence over 400 cases/100,000 inhabitants.[1] Despite the diagnostic tests available, in 20% PE diagnosis will not be possible,[2] which is a clinical problem. In the past it was estimated that thoracentesis provided a confirmatory diagnosis in 18% of cases and possible diagnosis in 55% of cases.[3] In the remaining 27%, pleural fluid analysis (PFA) was not useful because there were several presumptive diagnoses, but it excluded other diagnoses, such as infection. With the current level of knowledge on PFA, the clinician should be able, after initial thoracocentesis and with the support of the clinical history, to yield a confirmatory or presumptive diagnosis in about 95% cases.[4] This article is aimed at reviewing the contribution of PFA to the diagnosis of PE.

Observation

The color and smell of pleural fluid (PF) are important. A clear or straw-colored PF evidence a transudate, but a paucicellular exudate should not be excluded. If PE is haematic and there is no history of trauma, we should think of a tumor, a benign asbestosis, Dressler syndrome or pulmonary infarction. A hemothorax is usually caused by a penetrating trauma, an invasive procedure, anticoagulation with hemorrhagic pulmonary infarction or catamenial hemothorax.[5] A milky PF may be due to a chylothorax a pseudochylothorax or an empyema. Upon centrifugation, the supernatant is clear in the latter (empyema) and remains milky in the former (chylo and pseudochylothorax). A yellow-green PF indicates a rheumatoid PE, and if greenish, a biliopleural fistula.[6] If a central venous catheter migrates extravascularly to the mediastinum (MECVC) and breaks the parietal pleura, the PE will look like the infused fluid. If the PF is pus, the diagnosis is empyema, and if the smell is putrid, it is likely that the infection is due to anaerobic organisms. The cause of a PF with debris is possibly rheumatoid PE. If PF smells ammonia, urinothorax should be dismissed.[7]

Differentiation between transudates and exudates

In case of a PE the first step is to differentiate between transudates and exudates (Table 1). In transudates, PE is caused by increased hydrostatic pressure or decreased oncotic pressure in the pleural capillaries, or by decreased negative pressure in the pleural space. In exudates, the cause for PE is the increased permeability of the pleural capillaries or obstruction of lymphatic drainage.[8] Exudate contains high concentrations of high molecular weight proteins, absent in transudates, and diagnosis often requires additional diagnostic tests. For this differentiation various biochemical parameters are used in both PF and blood. The most used parameters are the Light's criteria (PF/serum protein ratio > 0.5; lactate dehydrogenase ratio [LDH] PF/serum > 0.6; LDH PF > 2/3 ULN in serum). A single criterion is sufficient to consider PF an exudate,[9] therefore up to 25% of transudates might be erroneously classified as exudates.[10] Furthermore, as taking diuretics may alter results[11] it has been proposed to use alternative markers such as PF-serum albumin gradient[12] or pleural cholesterol.[13] A formal meta-analysis did not demonstrate superiority of any of the parameters.[14]

Table 1
Causes of pleural effusion.

Transudates	Exudates
Frequent	
Heart failure	Neoplastic
Hepatic Cirrhosis	Tuberculous
	Parapneumonic
Less frequent	
Nephrotic syndrome	Chylothorax/pseudochylothorax
Urinothorax	Vascular effusions
Peritoneal dialysis	Systemic diseases
Lung trapped	Benign asbestosis
	PE after revascularization surgery by coronary artery bypass
	Gastrointestinal disorders
Infrequent	
Cerebrospinal fluid leakage into the pleura	Gynecological effusions
Extravascular migration of a central venous catheter	Lymphatic system disorders
Glycinothorax	Uremia
Ventriculoperitoneal and ventriculopleural fistulas	Drugs

PE, pleural effusion.

Nucleated cells

The count of PF nucleated cells usually provides useful information. Most transudates have below 1000 cells/μl and are usually lymphocyte predominat. A count >10,000 cells/μl is usually parapneumonic PE (PPE), acute pancreatitis, hepatic or splenic abscess, pulmonary infarction, Dressler syndrome or systemic lupus erythematosus (SLE, whereas >50,000/μl have only been observed in complicated PPE (CPPE) and empyema, and very rarely in acute pancreatitis and pulmonary infarction.

One factor influencing the type of cell population is the evolution time of the effusion. Thus, neutrophilic PE (>50%) are usually observed in acute responses, whereas lymphocytic PE are more frequent in PE of over two weeks of evolution[4,15] (Table 2). In PE in tuberculosis (TBPE) a predominance of polymorphonuclear leukocytes can be observed within the 2 first weeks.[16] The clinical significance of eosinophil PE (eosinophil count > 10%) is more controversial. They were considered to be associated with a lower risk of malignancy,[17] but have been shown not to be an indicator of benignity and that their study should be the same as for any PE.[18,19] Mesothelial cells are rarely found in the TBPE and other inflammatory processes, and a high number of plasma cells may indicate the presence of multiple myeloma.

Natriuretic peptides

In response to acute distension and increased pressure in the heart ventricles, the cardiomyocytes secrete natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal pro-brain