UPDATE IN PLEURAL EFFUSIONS 2009

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The current update in Pleural Effusions reviews the past year's most influential articles relevant to pulmonologists. They present possible new diagnostic approaches for pleural effusions secondary to heart failure (HF), infections or malignancies by the application of certain biomarkers and imaging techniques. A summary of changes that clinicians can implement on the basis of this research is provided in the Table 1.

Detection of pleural effusions by physical examination

The bedside determination of the presence of pleural effusions may identify patients who require diagnostic imaging. A metaanalysis addressed the diagnostic accuracy of the physical examination for pleural effusion using chest radiograph or computed tomography (CT) scan as the reference standard (1). To achieve this objective, the authors identified 310 potential studies, of which only 5, totaling 934 patients, met the inclusion criteria. Of the 8 physical examination maneuvers evaluated in the included studies, the presence of dullness to conventional percussion (summary positive likelihood ratio-LR-8.7) and asymmetric chest expansion (positive LR 8.1) argued convincingly for the diagnosis of pleural effusion. In contrast, the absence of reduce tactile vocal fremitus reduced the probability of pleural effusion (negative LR 0.21). These signs should guide clinical teaching and performance of the clinical examination for detecting pleural effusion.

Pleural effusions secondary to diseases of the heart

The diagnosis of pleural effusions resulting from HF is usually made clinically and supported by finding a transudate, according to Light's criteria, when pleural fluid is examined. However, the pleural fluid from approximately 20%of patients with HF may fulfill Light's criteria for an exudate. Mislabeled transudates are particularly likely in patients receiving diuretics or in those whose pleural fluid red blood cell count is greater than 10,000/mm^3. Traditionally, it has been proposed that an albumin gradient (serum albumin-pleural fluid albumin) >1.2 g/dL or a protein gradient > 3.1 g/dL be used to identify these misclassified transudates. In the last few years, it has become apparent that the measurement of natriuretic peptides, either NT-proBNP or BNP, help to diagnose HF. One study has recently evaluated whether the pleural fluid levels of BNP or NT-proBNP can be used to make the diagnosis of HF. And, if these natriuretic peptides allow better categorization of cardiac effusions misclassified by Light's criteria than do the albumin or protein gradients (2). NT-proBNP > 1300 pg/mL performed better than BNP > 115 pg/mL for discriminating 90 cardiac effusions from 91 non-cardiac effusions (AUC 0.96 vs 0.90, respectively). In addition, NT-proBNP correctly classified 90% of mislabeled cardiac effusions, as compared with BNP (70%) or the protein (50%) or albumin (75%) gradients. Therefore, NT-proBNP should be measured whenever a suspected cardiac effusion meets the exudative criteria.

Tablo 1. Changes to clinical practice emerging from articles important to pulmonologists in 2009

Change to practice	Reference
Start	
Carefully assessing dullness to percussion and tactile fremitus in all patients with suspected pleural effusion	1
Implementing the measurement of pleural fluid mesothelin in patients with suspected mesothelioma, particularly in areas with high tumor prevalence	8
Consider	
Isolated right heart failure in the differential diagnosis of transudative effusions	3
Using small bore catheters (< 14F) for the drainage of complicated parapneumonic effusions, including empyemas	5
The diagnosis of parapneumonic effusion if the concentration of CRP in the pleural fluid is greater than 80 mg/L	4
Monitoring patients treated for malignant mesothelioma through the serial measurement of serum mesothelin	9
Performing a PET-CT scan in selected patients with undiagnosed exudative effusions	7
Analyzing pleural fluid NT-proBNP if a pleural effusion meets exudative criteria, but it is thought to be due to HF	2
Assessing the presence of pleural nodular thickening by US to help distinguish between benign and malignant effusions	6
Stop	
Considering pleural fluid eosinophilia as a clue to the origin of a pleural effusion	11
Limiting the diagnosis of chylothorax to pleural fluids with milky appearance	12
Encouraging the use of IGRAs for diagnosing pleural tuberculosis	10

It has traditionally been taught that left HF, but not isolated right HF, leads to the occurrence of pleural effusions. However, a recent retrospective study of 147 patients with idiopathic or familial pulmonary arterial hypertension does not support this dogma (3). Thirty-one (21%) of these patients had pleural effusions, although there were explanations other than right HF in 10 of them and the cause of the effusion was elusive in two additional cases. Of the 19 patients with isolated right HF and pleural effusions, 16 had an additional serosal involvement, either ascites or pericardial effusion. Most of the pleural effusions were trace to small (63%) in size and right-sided (58%) or bilateral (26%) in distribution. Four of the 5 patients who underwent thoracentesis had transudates according to Light's criteria. In conclusion, pleural effusions are not rare in patients with isolated right HF.

Parapneumonic effusions

The clinical diagnosis of infectious pleural effusions, either parapneumonic or tuberculosis, is sometimes elusive. One study investigated the pleural fluid concentrations of four potential biomarkers of infection, namely triggering receptor expressed on myeloid cell (sTREM-1), procalcitonin (PCT), lipopolysaccharide-binding protein (LBP) and C-reactive protein (CRP), in 308 patients with different causes of pleural effusion (4). An sTREM-1 ≥80 pg/mL argued for the presence of an infectious effusion (LR positive=6.4), while pleural fluid values of CRP <20 mg/L or LBP <7 µg/mL argued against it (LR negative=0.22). Moreover, the two individual biomarkers that increased the probability of parapneumonic effusion were CRP ≥80 mg/L (LR positive=7.4) and LBP ≥17 µg/mL (LR positive=4.7). On the other hand, it is paramount to determine whether a complicated parapneumonic effusion (CPPE) is present because a delay in instituting pleural drainage in such patients substantially increases morbidity. However, in this study none of the new biomarkers demonstrated to be more effective than pleural fluid pH, glucose or LDH in predicting which parapneumonic effusions were complicated. Overall, pleural fluid PCT had no value for the differential diagnosis of pleural effusions.

The optimal size of chest tubes that should be used to treat CPPEs is a matter of debate. In a recent sub-group analysis from the MIST trial (5), there was no significant difference in the frequency with which 266 patients with CPPE who were treated with small chest tubes (<14F) either died or required thoracic surgery as compared with 139 patients

who received larger chest tubes (36% vs 42%). However, the latter experienced significantly higher pain scores than the former, particularly if a blunt dissection technique rather than a Seldinger insertion technique was used. In conclusion, the clinical outcome of patients treated with different chest tube sizes for CPPE is similar. The advantage of the smaller tube is that it is easier to insert and less painful to the patient.

Malignant effusions

Ultrasonography (US) is a long-established imaging procedure for detecting pleural fluid and guiding thoracentesis and chest tube placement. One study assessed the diagnostic accuracy of US in differentiating between malignant and benign pleural effusions (6). Fifty-two consecutive patients with pleural effusion of unknown etiology were recruited. The final diagnoses, based on accepted reference standards, were malignancy in 33 patients (including 14 mesotheliomas) and benign effusions in the remaining 19. US morphological criteria for malignancy included any one of the following: diaphragmatic or parietal pleural nodule(s), pleural thickening >1 cm or the presence of hepatic metastases. US yielded a sensitivity of 78%, a specificity of 94%, a LR positive of 15 and a LR negative of 0.22 for diagnosing malignancy. Thus, US may become a valuable adjunct in the diagnosis of malignant pleural effusion. Few studies have examined the role of positron-emission tomography (using 18-fluorodeoxyglucose) combined with CT (PET-CT) in the investigation of pleural diseases. In one series, 83 patients with undiagnosed effusions and/or pleural thickening after routine clinical investigations (including blind pleural biopsy) underwent a PET-CT scan before a thoracoscopic or open surgical biopsy (7). The final histopathological diagnoses were malignant disease in 44 patients (including 25 mesotheliomas) and benign pleural conditions in the remaining 39 patients (30 chronic pleuritis and 9 tuberculosis). The operating characteristics of PET-CT for identifying malignant pleurisy were: sensitivity 100%, specificity 94%, positive LR 19.5 and negative LR 0.01. Notably, PET-CT scans detected extra-thoracic metastases in one third of patients with pleural metastatic tumors. This technique could facilitate decision making as to when to proceed with invasive procedures. A positive PET-CT should always lead to a tissue diagnosis.

In the past several years, there has been great enthusiasm in the search for a reliable biomarker for mesothelioma, as this malignancy is difficult to diagnose. The marker that has received the most attention is soluble mesothelin. Davies et al measured pleural fluid mesothelin concentrations in 24 patients with mesothelioma, in 67 with pleural metastases and in 75 with benign pleural conditions, using a commercially available ELISA (8). Values exceeding 20 nM detected mesothelioma with a positive LR of 7.1 and a negative LR of 0.32. Mesothelin measurement was superior to cytological examination in the diagnosis of mesothelioma (71% vs 35%). All 8 cases of mesothelioma with positive pleural fluid cytology exhibited mesothelin levels above the established threshold. In 105 patients with cytology-negative effusions, pleural fluid mesothelin levels < 20 nM offered support for the exclusion of an underlying mesothelioma (negative predictive value of 94%). These results demonstrate that pleural fluid mesothelin provides valuable additional information in addition to pleural fluid cytology. Clinicians should consider its measurement in all patients with an undiagnosed pleural effusion.

Mesothelin has also been proposed as a test for monitoring patients with malignant mesothelioma under treatment. In a retrospective study, serial measurements of serum mesothelin were determined in 19 patients with mesothelioma subjected to chemotherapy, 16 treated with gene-therapy and 5 receiving the best supportive care (9). Thirty-five (87.5%) mesotheliomas had an epithelial histology. The criteria for assessment of response relied on CT scan and are internationally known as RECIST (Response Evaluation Criteria in Solid Tumors). More than 75% of patients who experienced disease progression after therapy exhibited a significant increase of serum mesothelin over time (i.e., >10% of baseline value), whether they had initial normal or high levels of the latter. In contrast, patients having an objective response after treatment showed decreased or stable mesothelin levels. Additionally, the survival of 7 patients with stable or decreasing serum mesothelin at the end of the treatment was significantly higher than in 10 patients with increasing values (27.7 vs 4.4 months respectively). If substantiated in further prospective investigations, serum mesothelin could be considered as a predictive marker to monitor the response of mesothelioma to treatment.

Miscellaneous effusions

T-cell interferon-gamma release assays (IGRAs) have emerged as attractive alternatives to the tuberculin skin test for the diagnosis of latent tuberculosis, although their contribution to the diagnosis of tuberculous pleurisy is less clear. One prospective study has recently compared the diagnostic performance of four different IGRAs using pleural fluid mononuclear cells with that of unstimulated IFN-γ concentrations in pleural fluid, in 63 patients from a high TB/HIV burden setting (10). All IGRAs, which included the commercially available QuantiFERON-TB Gold in-tube

and T-SPOT-TB, performed poorly because, at best, they missed 15% of TB cases and incorrectly diagnosed a further 20%. In contrast, unstimulated IFN-γ levels >0.31 IU/mL had 97% sensitivity and 100% specificity for identifying TB pleuritis. Currently, there is little convincing evidence to support the use of IGRAs against other available markers of TB such as IFN-γ or adenosine deaminase.

Pleural fluid eosinophilia is defined as a pleural fluid eosinophil count of greater than 10% of the total nucleated cells. A retrospective study of 1868 consecutive patients with pleural effusion identified 135 (7.2%) with eosinophilic pleural effusion (EPE) (11). The underlying conditions associated with EPE were malignancy (35%), infections (19%), unknown causes (14%), trauma (9%) and miscellaneous (23%). Therefore, the finding of a significant number of eosinophils in the pleural fluid does not appear to have diagnostic significance. Thirty percent of patients had an associated peripheral blood eosinophilia. The higher the percentage of pleural eosinophils (e.g. >40%), the less likely that there is a malignancy and the more likely an unknown etiology exists. Traditionally, it has been thought that many patients have pleural fluid eosinophilia due to the introduction of air into the pleural space during a prior thoracentesis. However, in this study repeated thoracentesis did not significantly increase the proportion of patients with EPE and the incidence of new EPEs in those undergoing a second pleural aspiration was only about 5%.

Chylothorax is most commonly associated with surgery, trauma or malignancy (particularly non-Hodgkin lymphoma). Chylous pleural effusions are typically described as lymphocytic exudates with a white or milky appearance. A triglyceride level in the pleural fluid >110 mg/dL is currently being used to establish the diagnosis. Maldonado et al retrospectively reviewed the pleural fluid characteristics of 74 patients with chylothorax (defined by the presence of chylomicrons) caused by surgical (51%) or medical conditions (12). In this series, the pleural fluid associated with a chylothorax lacked the classic milky appearance in more than half of the patients. Fourteen percent of chylothoraces were transudates, with the most common cause being cirrhosis. The authors reported 10 (14%) pleural effusions with a triglyceride level <110 mg/dL, of which 2 exhibited values lower than 50 mg/dL. It should be noted that the lipid content of these effusions varies according to the nutritional status of the patient. Thus, nonmilky fluids may be particularly prevalent during periods of fasting.

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