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Diagnostic principles in pleural disease

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ABSTRACT: When a patient with an undiagnosed pleural effusion is evaluated, the first question to answer is whether the patient has a transudate or an exudate. This is best done using Light's criteria, but these criteria occasionally misidentify a transudate as an exudate.

If the patient's pleural fluid meets exudative criteria, but the patient appears clinically to have a transudative effusion, then the serum-pleural fluid albumin gradient should be measured. If this is greater than 1.2 g·dL^{-1}, the patient probably does have a transudative effusion. If the patient has an exudative pleural effusion, additional tests are indicated to determine the aetiology of the effusion. The gross appearance and the odour of the pleural fluid should be noted and samples of all exudates should be sent for bacterial cultures. Laboratory tests that are useful in the differential diagnosis of exudative pleural effusions include: differential white cell count of the pleural fluid; cytology of the pleural fluid; and levels of adenosine deaminase, glucose, amylase and lactate dehydrogenase in the pleural fluid.

If pleural tuberculosis is suspected, a needle biopsy of the pleura is indicated. Thoracoscopy is very efficient at diagnosing malignant pleural effusion and tuberculosis pleuritis, but rarely establishes any other diagnosis.
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When a patient is seen with a pleural effusion, there are three questions that should be asked: 1) Should a thoracentesis be performed? 2) If a thoracentesis is performed, is the fluid a transudate or an exudate? 3) If the fluid is an exudate, what is its aetiology? This review will focus on answering these three questions.

Should a thoracentesis be performed?

Most patients who have a pleural effusion should undergo a diagnostic thoracentesis. There are, however, two situations in which a diagnostic thoracentesis is not recommended. Firstly, if the effusion is very small, the risk/benefit ratio of a thoracentesis increases. The amount of pleural fluid can be semiquantitated by obtaining a decubitus chest radiograph with the side of the effusion down, and measuring the distance between the outer border of the lung and the inner border of the chest wall. If this distance is less than 10 mm, a diagnostic thoracentesis is not recommended [1]. The use of ultrasound to facilitate the performance of the thoracentesis is recommended in patients with relatively small effusions (10–15 mm thickness on the decubitus radiograph).

Secondly, if the patient has congestive heart failure, a thoracentesis is recommended only if the patient meets one of the following three conditions: 1) the effusions are not bilateral and comparably sized; 2) the patient has pleuritic chest pain; or 3) the patient is febrile. If none of these three conditions is met, then treatment of the congestive heart failure is initiated. If the pleural effusions do not rapidly disappear, a diagnostic thoracentesis is performed several days later. It should be noted that, with diuresis, the characteristics of the pleural fluid may occasionally change from those of a transudate to those of an exudate [2, 3]. However, in such patients, the serum to pleural fluid albumin gradient usually remains above 1.2 g·dL^{-1}; in this situation, this gradient can be used to assess when the patient has a transudative or an exudative pleural effusion [4].

Is the fluid a transudate or an exudate?

Pleural effusions have classically been divided into transudates and exudates. By definition, a transudative pleural effusion develops when the systemic factors influencing the formation or absorption of pleural fluid are altered, so that pleural fluid accumulates. The fluid may originate in the lung, the pleura, or the peritoneal cavity [5]. The permeability of the capillaries to proteins is normal in the area where the fluid is formed. In contrast, an exudative pleural effusion develops when the pleural surfaces or the capillaries in the location where the fluid originates are altered, such that fluid accumulates. The primary reason to differentiate transudates and exudates is that, if the fluid is a transudate, no further diagnostic procedures are necessary and therapy is directed to the underlying congestive heart failure, cirrhosis, or nephrosis. Alternately, if the effusion proves to be an exudate, a more extensive diagnostic investigation is indicated.

For the past 25 yrs, the criteria most commonly used to separate transudative from exudative pleural effusion

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have been those dependent upon measurement of the pleural fluid and serum lactate dehydrogenase (LDH) and protein (Light's criteria) [6]. With Light's criteria, a pleural fluid is an exudate if one or more of the following criteria are met: 1) pleural fluid protein divided by serum protein greater than 0.5; 2) pleural fluid LDH divided by serum LDH greater than 0.6; 3) pleural fluid LDH greater than two-thirds the upper limit of normal for the serum LDH (usually the cut-off level for pleural fluid is 200 $IU \cdot L^{-1}$).

In the last few years, several articles have been published which have proposed other biochemical criteria for the separation of transudates and exudates. The following measurements have been reported to be diagnostic of an exudative pleural effusion: a pleural fluid cholesterol level above 60 $mg \cdot dL^{-1}$ [7, 8] or above 45 $mg \cdot dL^{-1}$ [9], a gradient below 1.2 $g \cdot dL^{-1}$ for the serum albumin minus the pleural fluid albumin [10]; and a value above 0.6 for the pleural fluid bilirubin divided by the serum bilirubin [11].

Two recent papers [4, 12] compared Light's criteria with the other proposed tests and concluded that Light's criteria best separate exudates from transudates. ROMERO *et al*. [12] compared the utility of Light's criteria with cholesterol measurements in 297 patients, including 44 with transudates and 253 with exudates. They reported that Light's criteria had a very high sensitivity (98%) but a lower specificity (77%), and an overall accuracy of 95%. In comparison the cholesterol measurement (>60 $mg \cdot dL^{-1}$) had a lower sensitivity (81%), higher specificity (91%), but an overall accuracy of only 83%. BURGESS *et al*. [4] compared the accuracy of Light's criteria, the cholesterol level, the cholesterol ratio, the bilirubin level and the serum-effusion albumin gradient in 393 patients, including 270 with exudates and 123 with transudates. They found that Light's criteria were most accurate (93%), with a sensitivity of 98% and a specificity of 83%. The next best test was the serum-effusion albumin gradient, which had an accuracy of 89%, a sensitivity of 87% and a specificity of 92%. Of the 19 transudates misclassified by Light's criteria in this study, 13 (68%) were classified correctly by the serum-effusion albumin gradient, and most of these patients were receiving diuretics. No level of pleural fluid cholesterol gave an accuracy above 77%.

In summary, it appears that Light's criteria remain the best means of separating transudates from exudates. The primary problem with Light's criteria is that they label some patients with transudative pleural effusions as having exudative pleural effusions. Most of these patients are receiving diuretics. It is recommended that if a patient is thought to have a transudative effusion by clinical criteria, but the fluid is identified as exudative by Light's criteria, a serum-effusion albumin gradient be obtained. If this is above 1.2 $g \cdot dL^{-1}$, the exudative categorization by Light's criteria can be ignored and the effusion can be considered to be a transudate.

What is the aetiology of this exudative pleural effusion?

When a patient is found to have an exudative pleural effusion, an attempt should be made to determine the aetiology of the effusion. In some instances, the diagnosis is very easy, *e.g*. most cases of parapneumonic effusion. In other cases, the diagnosis is somewhat more difficult, *e.g*. malignant effusions, pulmonary embolization and tuberculosis. In some instances, the diagnosis is very difficult, such as with asbestos pleural effusion or viral pleuritis. The following tests are useful in determining the cause of an exudative pleural effusion: appearance of the pleural fluid; smears and cultures of the pleural fluid; haematocrit and differential cell count of the pleural fluid; cytology of the pleural fluid; levels of adenosine deaminase, glucose, amylase and LDH in the pleural fluid; needle biopsy of the pleura; thoracoscopy; and perfusion lung scans.

Appearance of the pleural fluid

The cheapest test and that which is probably the least frequently performed is to smell the pleural fluid. The odour of the pleural fluid can establish two diagnoses immediately. If the fluid has a putrid or fetid odour, then the patient has an empyema, which is usually anaerobic. If the fluid smells like urine, the patient probably has a urinothorax. This diagnosis can be confirmed by demonstrating that the pleural fluid creatinine is greater than the serum creatinine [13].

The gross appearance of the pleural fluid should always be noted. If the pleural fluid appears bloody, a haematocrit should be obtained on the fluid. The haematocrit on the pleural fluid is frequently much lower than one would expect from the appearance of the pleural fluid. If the haematocrit on the pleural fluid is more than 50% that of the peripheral blood, the patient has a haemothorax. If the haematocrit on the pleural fluid is less than 1%, the blood in the pleural fluid is not significant [14]. Bloody pleural fluid suggests one of three diagnoses: malignancy, pulmonary embolization or trauma [14].

If the pleural fluid is turbid or milky or if it is bloody, the supernatant of the pleural fluid after centrifugation should be examined. If the pleural fluid was turbid when it was originally withdrawn, but the supernatant is clear, then the turbidity was due to cells or debris in the pleural fluid. Alternatively, if the turbidity persists after centrifugation, the turbidity was due to a high lipid content. In this situation, the patient has a chylothorax or a pseudochylothorax. These two entities are usually easily differentiated by their clinical presentation. Pleural fluid lipid analysis can also help in the differentiation, since chylothoraces are characterized by high triglyceride levels (>110 $mg \cdot dL^{-1}$), while pseudochylothoraces are characterized by high cholesterol levels (>200 $mg \cdot dL^{-1}$) [15]. The presence of cholesterol crystals is diagnostic of a pseudochylothorax.

Pleural fluid smears and cultures

Pleural fluid from patients with undiagnosed exudative pleural effusions should be Gram-stained and cultured for bacteria (both aerobically and anaerobically), mycobacteria and fungi. Routine smears for mycobacteria are not indicated because they are almost always negative, unless the patient has a tuberculous empyema

[16]. For bacterial cultures, it is best to inoculate aerobic and anaerobic blood culture media at the bedside. For mycobacterial cultures, use of the BACTEC system with bedside inoculation provides higher yields and quicker results [17].

Differential cell count on the pleural fluid

The differential cell count is useful in determining the aetiology of the pleural fluid. When polymorphonuclear cells predominate, the patient has an acute process affecting the pleural surfaces. If there are concomitant parenchymal infiltrates, then the most likely diagnoses are parapneumonic effusion, pulmonary embolus or bronchogenic carcinoma. If there are no parenchymal infiltrates, the most likely diagnoses are pulmonary embolus, viral infection, gastrointestinal disease, asbestos pleural effusion or acute tuberculous pleuritis [1].

When mononuclear cells predominate in the pleural fluid, the patient has a chronic process involving the pleura. Malignant disease, tuberculosis, pulmonary embolization and a resolving viral pleuritis are the most likely diagnoses. If there are more than a few mesothelial cells in the pleural fluid, it is quite unlikely that the patient has tuberculous pleuritis [18, 19]. If the patient has predominantly small lymphocytes in the pleural fluid, tuberculosis and malignancy are the two most likely diagnoses [14, 18].

When there are more than 10% eosinophils in the pleural fluid, the most likely explanation is the presence of either air or blood in the pleural space [1]. If there is no air or blood in the pleural space, possible diagnoses include asbestos pleural effusion [20], paragonimiasis [21], the Churg-Strauss syndrome [22], or a drug-induced pleuritis [1]. Drugs inducing eosinophilic pleuritis include dantrolene, bromocriptine and nitrofurantoin [1].

Cytology of the pleural fluid

If a patient has malignancy, cytological examination of the pleural fluid is a fast, efficient and noninvasive means by which to establish the diagnosis. The percentage of malignant pleural effusions which are diagnosed with cytology has been reported to be 40–87% [23–25]. There are several factors that influence the diagnostic yield with cytology. If the patient has a malignancy, but the pleural effusion has another aetiology, such as heart failure, pulmonary embolism, pneumonia, lymphatic blockade or hypoproteinaemia, the cytology will be negative. The frequency of positive cytological results also depends upon the tumour type. The yield is less with squamous cell carcinoma, Hodgkin's disease and sarcomas. The yield will be increased if both cell blocks and smears are prepared [25], and if more than one specimen is submitted [14]. Obviously, the yield will also be dependent upon the skill of the cytologist. Overall, if three separate pleural fluid specimens are submitted to an experienced cytologist, one should expect a positive diagnosis in about 70–80% of patients.

In the past decade, several different tests have been proposed, which could increase the diagnostic accuracy of cytology. These include: flow cytometry with deoxyribonucleic acid (DNA) analysis [26–28] or immunocytometry [29]; electron microscopic examination [30, 31]; and immunohistochemical studies [32–34]. The theory behind DNA analysis is that malignant cells will have abnormal numbers of chromosomes and, therefore, an abnormal amount of DNA. However, studies have shown that DNA analysis *via* flow cytometry is less sensitive than cytology [26, 27], and also has more false positives than cytology [28]. Flow cytometry using immunocytometry can identify the cell lineage (T- or B-cells) and the clonality of a population of lymphocytes [29]. Therefore, this is a useful test when pleural lymphoma is suspected. Examination of pleural fluid cells *via* electron microscopy is useful for distinguishing adenocarcinomas from mesotheliomas; mesotheliomas have microvilli which are numerous and long, whilst adenocarcinomas have microvilli which are sparse and short [30, 31]. Immunohistochemical staining, using the monoclonal antibodies carcinoembryonic antigen (CEA), B72.3 and Leu-M1, is also useful for distinguishing adenocarcinoma from mesothelioma. If the specimen stains positive for at least two of these antibodies, the patient probably has adenocarcinoma. Alternatively, if the specimen does not stain for any of the antibodies, the patient probably has mesothelioma [34].

Pleural fluid adenosine deaminase (ADA) level

Measurement of the ADA level in pleural fluid is diagnostically useful because ADA levels tend to be higher in tuberculous pleural effusions than in other exudates. In one early report, all 48 patients with tuberculous pleuritis had pleural fluid ADA levels above 45 $U \cdot mL^{-1}$ whilst only 5 of 173 patients (3%) with pleural effusions due to other aetiologies had ADA levels that exceeded 45 $U \cdot mL^{-1}$ [35]. A more recent report on 405 pleural fluids, including 91 due to tuberculosis, confirmed these results [36]. The two other disease entities that tend to have a high pleural fluid ADA level are empyema and rheumatoid pleuritis and both of these are easily distinguished from pleural tuberculosis by the clinical picture.

If the patient has a lymphocytic pleural effusion and an ADA that exceeds 45 $U \cdot mL^{-1}$, the likelihood is very high that the pleural effusion is due to tuberculous pleuritis. It has been suggested that pleural biopsy in such patients is not necessary to confirm the diagnosis of tuberculous pleuritis [37]. It appears that the pleural fluid ADA level is less useful in Asians [1], and there was one report that suggested that acquired immune deficiency syndrome (AIDS) patients with tuberculous pleuritis frequently had a pleural fluid ADA level below 40 $U \cdot mL^{-1}$ [38].

Pleural fluid gamma-interferon levels are also elevated with pleural tuberculosis [36]. Since this measurement is much more expensive than the pleural fluid ADA measurement and does not provide additional diagnostic information, it is not recommended. To my knowledge, commercial laboratories in the United States do not perform either ADA or gamma-interferon measurements.

Pleural fluid glucose level

Measurement of the pleural fluid glucose level is useful because a low pleural fluid glucose level (<60 $mg \cdot dL^{-1}$) indicates that the patient probably has one of four disorders, namely; tuberculosis; malignant disease; rheumatoid disease; or a complicated parapneumonic effusion. Other rare causes of a low glucose pleural effusion include: paragonimiasis; haemothorax; the Churg-Strauss syndrome; and, occasionally, lupus pleuritis [1].

Pleural fluid amylase level

Measurement of the pleural fluid amylase level is useful because elevated pleural fluid amylase indicates that the pleural effusion is due to pancreatic disease, metastatic adenocarcinoma or oesophageal rupture. The pleural fluid amylase level is elevated in approximately 10% of patients with pleural malignancy, and the primary tumour is usually not in the pancreas [14]. Since the pleural fluid amylase with pleural malignancy is the salivary type, determination of the pleural fluid amylase isoenzyme pattern can differentiate malignancy from pancreatic disease [39]. Patients with both acute pancreatitis and chronic pancreatic disease may have pleural effusions. The effusion with acute pancreatitis is probably due to pleural inflammation. The effusion with chronic pancreatic diseases arises when a sinus tract is formed and leads from the pancreas through the diaphragm into the mediastinum and then into the pleural space. This sinus tract conveys pancreatic fluid from the pancreas to the pleural space. In this instance, thoracic rather than pancreatic symptoms may predominate [40]. The elevated amylase with oesophageal rupture is due to saliva, with its high amylase content, entering the pleural space [41].

Pleural fluid LDH level

Although the pleural fluid LDH level is used to distinguish transudative and exudative pleural effusions, it is not useful in separating different exudative pleural effusions [6]. Nevertheless, it is recommended that the pleural fluid LDH level be measured each time a thoracentesis is performed, since the level of pleural fluid LDH is a reliable indicator of the degree of pleural inflammation. If with repeated thoracentesis, the pleural fluid LDH level increases, the degree of inflammation in the pleural space is becoming progressively worse and one should be aggressive in pursuing a diagnosis. Alternatively, if the pleural fluid LDH level decreases with repeated thoracentesis, the degree of inflammation in the pleural space is becoming progressively less and one need not be as aggressive in the approach to the patient [1].

Needle biopsy of the pleura

The primary two diagnoses that can be established with needle biopsy of the pleura are tuberculosis and malignancy. Over the past 40 yrs, the diagnosis of tuberculous pleuritis has usually been made by needle biopsy of the pleura. With tuberculous pleuritis, the initial needle biopsy is positive for granulomas in 50–80% of patients [42–44]. A specimen of the pleural biopsy should also be cultured for mycobacteria, since the cultures may be positive when microscopy of the biopsy is negative [45]. The combination of microscopy and culture of the pleural biopsy should provide a positive diagnosis in more than 80% of patients with tuberculous pleuritis. If the initial biopsy is nondiagnostic and the patient has tuberculous pleuritis, a second biopsy will be positive 10–40% of the time [43]. As mentioned above, the diagnosis of tuberculous pleuritis can be made noninvasively by demonstrating a high (>45 $U \cdot L^{-1}$) level of ADA in the pleural fluid [37].

Cytological examination of the pleural fluid establishes the diagnosis of pleural malignancy more frequently than does needle biopsy of the pleura. The reported incidence of positive pleural biopsies ranges 39–75% [16, 43, 46], and probably averages about 45%. The explanation for the relatively lower yield with pleural biopsy than with cytology is that the parietal pleural is involved later in the course of the disease than is the visceral pleura, and the involvement of the parietal pleura is frequently patchy [47]. Therefore, one would anticipate that the cytology would be positive more frequently than would a blind needle biopsy of the parietal pleura.

Thoracoscopy

Thoracoscopy has been used extensively in Europe for the diagnosis of pleural malignancy and pleural tuberculosis. With the advent of video-assisted thoracic surgery (VATS), there has been renewed interest in the use of thoracoscopy for the diagnosis of pleural disease in the United States. The view of the pleural space with VATS compares favourably with that obtained by direct view through a limited axillary, infra-mammary, or lateral thoracotomy [48]. Most reports on the usefulness of thoracoscopy for the diagnosis of pleural effusion have been glowing. For example, HARRIS *et al*. [49] reported that thoracoscopy had a diagnostic sensitivity of 95% for malignancy and 100% for benign disease, in a series of 182 effusions. However, when one examines this series closely, one finds that no definite diagnosis was established at thoracoscopy in the benign effusions. Fifty eight of the patients had benign effusions, such as empyema, haemothorax, parapneumonic effusions for which the diagnosis should have been established by noninvasive means. In addition, 26 additional patients were labelled as having "idiopathic" pleural effusions.

In summary, thoracoscopy is very efficient in establishing the diagnosis of malignant disease. However, as demonstrated above, the combination of pleural fluid cytology and needle biopsy should establish the diagnosis of malignant disease in more than 80% of patients with malignant disease. For the diagnosis of pleural disease, thoracoscopy should only be used when the less invasive methods of diagnosis, such as pleural fluid cytology and needle biopsy of the pleura, have not yielded a diagnosis. In one series of 620 patients, only 48 (8%) remained without a diagnosis after these less invasive

procedures [50]. When these 48 patients were subjected to thoracoscopy, a diagnosis of malignancy was established in 24 (50%). When one performs thoracoscopy for diagnostic purposes, it is important to be prepared to perform a procedure to create a pleurodesis at the time of surgery. Our preferred method is the insufflation of 2–5 g of talc. If a patient has a recurrent benign effusion, consideration should also be given to creating a pleurodesis with the insufflation of talc.

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