Pulmonary Effusion: Diagnosis and Management of Causative Disorders

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Cover Illustration by Dean Vigyikan
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TRANSUDATIVE AND EXUDATIVE PLEURAL EFFUSIONS

CASE 1 PRESENTATION

A 60-year-old man comes to his physician’s office because of increasing shortness of breath and swelling of the legs that is worse in the right than in the left leg. He reports no chest pain, calf pain, or fever but says that he has gained 3.6 kg (8 lb) in the past 2 weeks and that his stomach appears to be “getting a little larger.” The patient has 1-pillow orthopnea and 2 to 3 episodes of nocturia each night. He has a 20-year history of hypertension and has had 2 myocardial infarctions (MIs) within the past 5 years. Additionally, he sustained a fracture of the right femur 2 years ago in an automobile accident. Before his first MI, he had smoked 2 packs of cigarettes daily for 35 years and drank heavily. Although he subsequently stopped smoking and decreased his alcohol intake slightly, he still drinks despite having been told not to because of cirrhosis.

Although able to walk 1 mile at a normal pace 2 weeks ago, the patient now becomes dyspneic when he walks across the room. Physical examination shows an obese man who looks chronically ill and older than his stated age. Temperature is 98.6°F (37°C), blood pressure is 120/80 mm Hg, pulse is 104 bpm, and respiratory rate is 14 breaths/min. Pulse oximetry reveals an oxygen saturation of 94%. Cardiac examination reveals no cardiomegaly, cardiac murmurs, or gallops. There are signs of a large right-sided pleural effusion, including absent tactile fremitus, dullness to percussion, and absent breath sounds over the entire right hemithorax. Other pertinent physical findings include possible ascites, 2+ pitting edema of the right leg to the midcalf, and 1+ pitting edema of the left leg to the midcalf. Homans’ sign is not present. A chest radiograph shows a massive right-sided pleural effusion and a heart of normal size.

- Does Patient 1 have a transudative or an exudative pleural effusion?
- What diagnoses could account for the large unilateral pleural effusion in this patient?

DIFFERENTIATING TRANSUDATIVE FROM EXUDATIVE PLEURAL EFFUSIONS

Pleural effusions classically have been divided into 2 groups: transudates and exudates. Transudative pleural effusions develop when systemic factors influencing the formation or absorption of pleural fluid are altered so that pleural fluid accumulates. The fluid can originate in the lung, pleura, or peritoneal cavity. The
permeability of the capillaries to proteins is normal in the area in which the fluid is formed. The leading causes of transudative pleural effusions are congestive heart failure, pulmonary embolism, and cirrhosis.

In contrast, exudative pleural effusions develop when the pleural surfaces or the capillaries in the location in which the pleural fluid originates are altered so that fluid accumulates. These types of pleural effusions occur most commonly in patients who have pneumonia with pleural effusion (or parapneumonic effusion), malignant pleural effusion, and pulmonary embolism.

The primary reason to differentiate transudates from exudates is that if the fluid is transudative, no further diagnostic procedures are necessary; therapy should be directed against the underlying cause (eg, congestive heart failure, cirrhosis, nephrosis). In contrast, if the effusion proves to be exudative, a more extensive diagnostic investigation is indicated.

For the past 25 years, the criteria most commonly used to separate transudative from exudative pleural effusions have depended on measurement of lactate dehydrogenase (LDH) and protein in both pleural fluid and serum (Light’s criteria).\(^1\) Pleural fluid is considered exudative if 1 (or more) of the following criteria is met: (1) pleural fluid protein level divided by serum protein level is greater than 0.5; (2) pleural fluid LDH level divided by serum LDH level is greater than 0.6; or (3) pleural fluid LDH level is greater than two thirds of the upper limit of the normal range for serum LDH level. Recently, alternative measurements have been proposed as also being diagnostic of an exudative pleural effusion. These alternatives include a pleural fluid cholesterol level above either 45 or 60 mg/dL, a serum protein level is greater than 0.5; (2) pleural fluid LDH level divided by serum LDH level is greater than the gradient is above 1.2, the patient in all probability has a transudative effusion and the exudative criterion can be ignored.

The patient has a transudative pleural effusion because none of Light’s 3 criteria for an exudative pleural effusion are met. Although both hepatic hydrothorax and malignant pleural effusion were initially possible and malignant pleural effusion were initially possible for the past 25 years, the criteria most commonly used to separate transudative from exudative pleural effusions have depended on measurement of lactate dehydrogenase (LDH) and protein in both pleural fluid and serum (Light’s criteria).\(^1\) Pleural fluid is considered exudative if 1 (or more) of the following criteria is met: (1) pleural fluid protein level divided by serum protein level is greater than 0.5; (2) pleural fluid LDH level divided by serum LDH level is greater than 0.6; or (3) pleural fluid LDH level is greater than two thirds of the upper limit of the normal range for serum LDH level. Recently, alternative measurements have been proposed as also being diagnostic of an exudative pleural effusion. These alternatives include a pleural fluid cholesterol level above either 45 or 60 mg/dL, a serum protein level is greater than 0.5; (2) pleural fluid LDH level divided by serum LDH level is greater than the gradient is above 1.2, the patient in all probability has a transudative effusion and the exudative criterion can be ignored.

Differential Diagnosis in Patient 1

Patient 1’s history and chest radiograph suggest several possible causes of his pleural effusion. The patient has a history of 2 MIs, so the possibility of congestive heart failure should immediately come to mind. However, most patients with pleural effusions caused by congestive heart failure have bilateral pleural effusions, which are roughly comparable in size. The occurrence of a massive unilateral pleural effusion secondary to congestive heart failure is extremely unusual.

The patient has a history of trauma to the right leg, and the right leg is more edematous than the left. Accordingly, the possibility of a pulmonary embolus also should be considered. Yet most pleural effusions caused by pulmonary emboli are either small or moderate in size; massive pleural effusions virtually never occur with pulmonary embolism.

Because of the patient’s smoking history, the possibility of a malignant pleural effusion—particularly one associated with lung cancer—should be considered. Pleural malignancy is the leading cause of massive pleural effusions. Pleural fluid in cases of malignant pleural effusion is exudative, and results of cytologic analysis of the fluid are positive for malignant cells in more than 75% of cases when the effusion is massive.\(^4\)

Another possibility that should be considered is hepatic hydrothorax. The patient has a history of heavy alcoholic intake and was told in the past that he had cirrhosis. The pathogenesis of pleural effusion in patients with cirrhosis is thought to be the movement of peritoneal fluid through small holes in the diaphragm into the pleural space.\(^5\) Patient 1 noted that his abdomen seemed to have increased in size. Therefore, hepatic hydrothorax and malignant pleural effusion are the 2 leading diagnostic possibilities. The first step in differentiating these 2 entities is to perform a thoracentesis.

Results of Thoracentesis

A diagnostic thoracentesis yields clear yellow fluid, which is not turbid and has no odor. The pleural fluid protein level is 2.1 g/dL, and the pleural fluid LDH level is 280 U/L. The simultaneously obtained serum protein level is 6.3 g/dL, and the serum LDH level is 560 U/L (normal upper limit for serum LDH level, 630 U/L).

- **What is the most likely diagnosis in Patient 1?**
- **Should further diagnostic tests of the pleural fluid be ordered?**

**Diagnosing Hepatic Hydrothorax**

The patient has a transudative pleural effusion because none of Light’s 3 criteria for an exudative pleural effusion is met. Although both hepatic hydrothorax and malignant pleural effusion were initially possible...
diagnoses, the fact that the fluid is transudative most strongly suggests a hepatic hydrothorax. If a patient has a transudative pleural effusion, there usually is no reason to order laboratory tests on the pleural fluid after measurement of its protein and LDH levels is obtained. However, if a patient has a known malignancy and a transudative pleural effusion, it is worthwhile to order pleural fluid cytology. If pleural fluid cytology is positive for malignancy, it indicates that the patient has a disseminated malignancy.

It is usually easy to establish the diagnosis of hepatic hydrothorax from the clinical findings. Both a paracentesis and thoracentesis should be performed to confirm that the ascites and pleural fluid are both transudative. The protein level in the pleural fluid is usually higher than that in the ascitic fluid but still below 3.0 g/dL.

The predominant mechanism leading to a pleural effusion in a patient with cirrhosis and ascites appears to be the movement of the ascitic fluid from the peritoneal cavity through defects in the diaphragm into the pleural space. The decreased plasma oncotic pressure is only a secondary factor. Signs and symptoms in patients with pleural effusions associated with cirrhosis and ascites usually involve the cirrhosis and ascites. At times, however, the presence of a large pleural effusion can produce severe dyspnea, as is the case in Patient 1. The pleural effusion associated with cirrhosis and ascites is frequently large and can occupy the entire hemithorax. Large effusions occur because the diaphragmatic defect permits fluid to flow from the peritoneal into the pleural cavity until the pleural pressure approaches the peritoneal pressure.

Managing Hepatic Hydrothorax

The initial management of pleural effusion associated with cirrhosis and ascites should be directed toward treatment of the ascites. Patient 1 should be put on a low-salt diet and given diuretics. If diet and diuretics do not control the effusion, the optimal treatment most likely is liver transplantation; unfortunately, this option is not feasible in the majority of patients. The next best approach involves implantation of a transjugular intrahepatic portosystemic shunt (TIPS). TIPS is effective in the management of hepatic hydrothorax because, when it operates successfully, it decreases the rate at which ascitic fluid forms. If neither TIPS nor liver transplantation is feasible, the best alternative treatment is videothoracoscopy with closure of the diaphragmatic defects and pleural abrasion.

PLEURAL EFFUSION IN PATIENTS WITH PNEUMONIA

CASE 2 PRESENTATION

A 45-year-old woman from a rural area comes to the emergency department reporting a 5-day history of fever, right-sided chest pain, and malaise; she says symptoms began after she plowed a field on her farm. The patient also has had a cough productive of thick green sputum for the past 4 days. Because she “does not like doctors,” she initially self-medicated her symptoms with whiskey, which effected no improvement. She says that she has been in good health her entire life and had not seen a physician since her last child was born 11 years ago. The patient has smoked 2 packs of cigarettes daily for 25 years and drinks 2 to 4 oz of whiskey each evening.

On examination, the patient looks acutely ill and has splinting on the right side because of pleuritic chest pain. Coughing is productive of thick yellowish-green sputum. Vital signs include a temperature of 103.2°F (39.6°C), a blood pressure of 120/80 mm Hg, a pulse of 128 bpm, a respiratory rate of 24 breaths/min (breathing is shallow), and an oxygen saturation (while the patient breathes room air) of 92%. Chest examination suggests the presence of a right-sided pleural effusion. The remainder of the physical examination is noncontributory.

Posteroanterior and lateral chest radiographs (Figure 1) reveal an increased density that occupies the majority of the right lower lung field and obliterates the diaphragm. The homogeneity of the density suggests that it is pleural fluid; the lateral radiograph shows an anterior density that is thought to be loculated pleural fluid. A computed tomography (CT) scan of the chest (with contrast) is then obtained (Figure 2).

Leukocyte count is $32 \times 10^3$/mm$^3$ with 96% neutrophils. Sputum and blood cultures are obtained, and the patient is admitted to the hospital and started on daily levofloxacin 500 mg, intravenously.

- What is the most likely diagnosis in Patient 2?
- What further treatment is most appropriate at this time?

NATURAL HISTORY OF A PARAPNEUMONIC EFFUSION

The evolution of a parapneumonic effusion can be divided into 3 stages. The first is the exudative stage, in which a focus of parenchymal infection leads to increased pulmonary interstitial fluid that traverses the
visceral pleura and results in the accumulation of pleural fluid. In this stage, the pleural fluid is characterized by a relatively low LDH level, a normal pH, and a normal glucose level.

The second stage is the fibropurulent stage, which is characterized by the invasion of the pleural fluid by bacteria. As this stage progresses, the pleural fluid becomes increasingly cloudy and viscous because it contains large amounts of fibrin, cellular debris, and leukocytes. In this stage, there is a progressive tendency toward loculation of the fluid and the formation of limiting membranes. Although loculation prevents extension of the pleural infection, it makes drainage of the pleural space difficult. Results of bacterial culture of the pleural fluid are positive for organisms in the fibropurulent stage and, as this stage progresses, the pleural fluid pH and glucose level become progressively lower, and the pleural fluid LDH level becomes progressively higher.

The third stage is the organization stage, in which fibroblasts grow into the exudate from both the visceral and parietal pleural surfaces to produce an inelastic membrane called the pleural peel; the peel encases the lung and renders it virtually functionless. At this stage, the exudate is very thick and, if the patient has remained untreated, the fluid can drain spontaneously through the chest wall (empyema necessitatis) or into the lung, in which case a bronchopleural fistula is produced.

**FURTHER DISCUSSION OF PATIENT 2**

Patient 2 has a parapneumonic effusion. By definition, a parapneumonic effusion is any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis. The CT scan of the chest shows that Patient 2 has infiltrates in the right lung. The presence of high fever and cough productive of green sputum in conjunction with pulmonary infiltrates is, essentially, diagnostic of pneumonia. The CT scan more specifically shows an infiltrate in the right lower lobe and pleural fluid in the right pleural space, which appears to be loculated.

**Initial Evaluation**

When a patient with acute bacterial pneumonia is evaluated initially, the physician should determine whether or not a parapneumonic effusion is present. If the posterior costophrenic angles are not blunted on the lateral chest radiograph, one can assume that there is not a clinically significant pleural effusion, unless the chest radiograph reveals loculated fluid elsewhere in the chest. If the posterior costophrenic angles are blunted or if the diaphragm is obscured by an infiltrate, as was the case with Patient 2, then a lateral decubitus chest radiograph normally should be obtained, with the suspicious side down. However, a decubitus radiograph was not obtained in Patient 2 because the CT scan demonstrated the presence of the pleural effusion.
The amount of pleural fluid can be semiquantitated on the decubitus film by measuring the distance between the inside of the chest wall and the bottom of the lung. If this measurement is less than 10 mm, it can be assumed that the effusion is not clinically significant and that thoracentesis is not necessary. If the thickness of the fluid is greater than 10 mm on the decubitus radiograph, a therapeutic thoracentesis should be performed, with removal of all pleural fluid. At the time of the thoracentesis, pleural fluid should be cultured and analyzed to determine its leukocyte count, pH, and LDH and glucose levels; Gram stain should be performed. Results that indicate a poor prognosis are listed in Table 1.

If the pleural fluid does not reaccumulate after it is removed by therapeutic thoracentesis, no additional treatment of the effusion is necessary. If the pleural fluid recurs, however, the next step is guided by the initial pleural fluid findings. If none of the poor prognostic indicators listed in Table 1 are present, no invasive procedures are indicated as long as the patient is doing well clinically. If any of the poor prognostic indicators are present at the initial thoracentesis, however, another therapeutic thoracentesis should be performed and the pleural fluid reanalyzed. If the pleural fluid accumulates a third time, a small (8 to 13 French) chest tube should be inserted into the pleural space unless none of the poor prognostic factors listed in Table 1 was present at the time of the second thoracentesis.

Management of Complicated Parapneumonic Effusion

If the pleural fluid cannot be removed completely with a therapeutic thoracentesis or with a small chest tube, it is probably loculated. A therapeutic thoracentesis was attempted in Patient 2, but only a small amount of foul-smelling pleural fluid was obtained. Analysis of the pleural fluid revealed a glucose level of 27 mg/dL, a pH of 6.87, and an LDH level of 27,000 U/L; Gram stain revealed gram-positive cocci.

Loculation indicates a high level of inflammation in the pleural space. The majority of loculated pleural effusions require drainage. If the pleural fluid is loculated and if any of the poor prognostic factors in Table 1 is present, efforts should be made to break down the loculations in order to obtain complete drainage of the pleural space. There are 2 primary means by which the loculations can be broken down: (1) fibrinolytic therapy via chest tubes, or (2) thoracoscopy with the breakdown of adhesions.

Recent randomized controlled studies have shown that fibrinolytic agents are superior to tube thoracostomy alone in breaking down adhesions. One study used streptokinase 250,000 U, and the other study used 100,000 U urokinase. Because the availability of urokinase is limited at the present time, streptokinase is presently the preferred fibrinolytic agent.

Regarding the alternative approach to patients with loculated pleural effusions (ie, thoracoscopy with the breakdown of adhesions), one study concluded that proceeding directly to thoracoscopy was more cost-effective than was using an intermediate step with fibrinolytic agents. Because the fluid could not be removed completely by therapeutic thoracentesis in Patient 2, a thoracoscopy with breakdown of adhesions was performed. The patient rapidly became afebrile and was discharged from the hospital after 5 days. One advantage of thoracoscopy is that the chest tube can be positioned in the most dependent part of the empyema cavity. Before thoracoscopy is performed, a CT scan should be obtained to provide information about the size and extent of the empyema cavity and to help guide the planned procedure. A thickened visceral pleural peel without septations suggests that the empyema may be chronic and probably will not be amenable to thoracoscopic débridement alone.

It is recommended that patients with loculated parapneumonic effusions who have any of the poor prognostic indicators listed in Table 1 on analysis of their pleural fluid be treated initially with thoracoscopy; if the expertise for this procedure is available locally. If it is not, then a trial of fibrinolytic agents is warranted. If there is not substantial improvement within a few days, more invasive procedures are necessary.

Thoracotomy with decortication is the most invasive procedure for the treatment of parapneumonic effusions...
and empyema. With decortication, all fibrous tissue is removed from the visceral pleura, and all purulent material is evacuated from the pleural space. The primary indication for decortication is a trapped lung; loculations are better treated with thoracoscopy. Decortication allows the underlying lung to reexpand and obliterate the pleural space. Some thoracic surgeons recommend this procedure in all cases in which a thick pleural peel remains after closed or open drainage of a pleural infection. However, since the pleural peel frequently improves substantially in the months after drainage, decortication should be delayed for at least 6 months if the infection has been controlled and the lung reexpanded. After this time, decortication should be performed only if the patient has limited exercise capacity and if close evaluation of the patient’s pulmonary status suggests that the procedure will improve pulmonary function.

**MALIGNANT PLEURAL EFFUSION**

**CASE 3 PRESENTATION**

A 55-year-old woman comes to her physician reporting increasing dyspnea on exertion and a dull aching pain over the posterior part of her right chest. The patient had been in good health throughout her life but during the past 2 months has noted decreased appetite and a 5.4-kg (12-lb) weight loss. Physical examination shows normal vital signs but signs of a moderately large right pleural effusion. Abdominal examination reveals no masses. There were no breast masses and no lymphadenopathy. A chest radiograph reveals a moderately sized right pleural effusion without any evidence of a lung mass.

- What are the possible diagnoses in Patient 3?
- What laboratory tests should be ordered on the pleural fluid?

**ETIOLOGY OF MALIGNANT PLEURAL EFFUSIONS**

There are many different causes of pleural effusions, the 4 most common being congestive heart failure, pneumonia, malignancy, and pulmonary embolism. The diagnosis of congestive heart failure is unlikely in Patient 3 because she lacks other symptoms suggesting heart failure, has a unilateral pleural effusion, and has right-sided chest pain. The observation that Patient 3 might have a chronic illness makes the diagnosis of pneumonia unlikely. Malignancy seems to be a very likely diagnosis. Pulmonary embolism is still a diagnostic possibility, and this diagnosis should be pursued if a diagnosis is not established after the initial thoracentesis and examination of the pleural fluid.

Of course, another diagnosis that should be considered in a patient with chronic symptoms and a pleural effusion is tuberculosis. A pleural effusion resulting from tuberculosis has been compared to a chancre caused by syphilis—both the effusion and the chancre will resolve spontaneously without therapy. Nevertheless, in most cases the patient will go on to develop significant complications of the primary disease. In the case of a tuberculous pleural effusion, the patient usually develops pulmonary or extrapulmonary tuberculosis.

**DIAGNOSIS IN PATIENT 3**

**Laboratory Evaluation**

In patients with pleural effusions, pleural fluid protein and LDH levels should be measured to determine if the pleural fluid is transudative or exudative, as previously discussed. A differential cell count also should be obtained because this will provide evidence about whether the pleural process is acute (predominantly neutrophils) or chronic (predominantly mononuclear cells). The pleural fluid should be cultured for bacteria (including mycobacteria) and fungi. The glucose level of the pleural fluid also should be determined.

Initial pleural fluid analysis in Patient 3 shows an odorless clear yellow fluid with a protein level of 3.8 g/dL (serum level, 5.9 g/dL), LDH level of 570 U/L (serum level, 560 U/L [normal upper limit, 630 U/L]), and leukocyte count of 14 × 10³/mm³; differential reveals 5% neutrophils, 80% lymphocytes, and 15% other mononuclear cells. Pleural fluid glucose level is 82 mg/dL, and adenosine deaminase (ADA) level is 22 U/L. Cytologic analysis of the pleural fluid shows no malignant cells. A spiral CT scan shows a pleural effusion with no filling defects in the pulmonary

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**Table 1. Indicators* of a Poor Prognosis in Patients with Bacterial Pneumonia**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Details</th>
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<tbody>
<tr>
<td>Presence of purulence</td>
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<tr>
<td>Gram stain of pleural fluid that is positive for bacteria</td>
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</tr>
<tr>
<td>Pleural fluid glucose level &lt; 40 mg/dL</td>
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<tr>
<td>Pleural fluid pH &lt; 7.00</td>
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<tr>
<td>Pleural fluid culture that is positive for bacteria</td>
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<tr>
<td>Loculated pleural fluid</td>
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<tr>
<td>Pleural fluid LDH level that is more than 3 times the upper limit of the normal range</td>
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*Arranged in order of increasing severity.
arteries and no parenchymal infiltrates. The effusion recurs within 4 days, and the patient continues to have chest pain.

• **How can a diagnosis be established in Patient 3?**

**Establishing the Diagnosis of Pleural Malignancy**

**Pleural fluid cytology.** Cytologic examination of the pleural fluid is a fast, efficient, and minimally invasive means by which to establish the diagnosis of pleural malignancy in patients. The percentage of malignant pleural effusions diagnosed with cytology has been reported to be anywhere between 40% and 87%.4 There are several factors that influence the diagnostic yield with cytology. For example, most adenocarcinomas can be diagnosed with cytology, but the yield is less in patients with squamous cell carcinoma, Hodgkin’s disease, mesothelioma, and sarcoma. Moreover, the yield is also dependent on the skill of the cytologist. Overall, if 3 separate pleural fluid specimens are submitted to an experienced cytologist, a positive diagnosis can be expected in approximately 70% to 80% of patients with pleural malignancy.1 However, this cytologic methodology was not diagnostic in Patient 3.

**Flow cytometry.** Flow cytometry can provide a rapid quantification of nuclear DNA. Most malignancies are aneuploid and, consequently, have abnormal DNA levels. In contrast, the majority of benign effusions are diploid with normal DNA levels. Nevertheless, because some benign effusions have abnormal DNA levels and some malignant effusions have normal DNA levels, the diagnosis of malignancy cannot be ruled in or out with this test.15 The routine use of flow cytometry thus is not recommended; however, flow cytometry is quite useful for demonstrating the homogeneity of a population of cells in the pleural fluid of patients with lymphoma.14

**Tumor markers in the pleural fluid.** There have been many publications evaluating the utility of tumor markers (such as carcinoembryonic antigen, alphafetoprotein, CA 15-3, CA 19-9, enolase) in the pleural fluid in the diagnosis of pleural malignancy.3,5,13 In general, the results of studies involving pleural fluid tumor markers have been disappointing. If the cutoff level for malignancy is set high enough for false positives to be unlikely, then the tests are very insensitive.

**Establishing the Diagnosis of Tuberculous Pleuritis**

Tuberculous pleuritis is one of the more difficult diagnoses to make, but the diagnosis can be established with a high degree of certainty by analysis of the pleural fluid. In the past 15 years, 3 tests of pleural fluid have been developed which have made the diagnosis of tuberculous pleuritis easier: (1) measurement of ADA level, (2) measurement of interferon gamma (IFN-γ) level, and (3) performance of polymerase chain reaction (PCR) to detect mycobacterial DNA.

**Pleural fluid adenosine deaminase 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.17,18 Almost all patients with tuberculous pleuritis will have ADA levels above 40 U/L.19 (Recall that Patient 3’s pleural fluid ADA level was only 22 U/L.) The 2 other disease entities that tend to have a high pleural fluid ADA level are empyema and rheumatoid pleuritis, both of which are easily distinguished from pleural tuberculosis by clinical findings. The only other 2 diseases associated with a lymphocytic pleural effusion and a high pleural fluid ADA level are Q fever and lymphoma.

**Pleural fluid interferon-γ level.** Pleural fluid IFN-γ levels are elevated as well in cases of tuberculous pleuritis. Pleural fluid IFN-γ level is very efficient in separating tuberculous from nontuberculous pleural effusions.20

**Polymerase chain reaction.** PCR can detect the presence of DNA from *Mycobacterium tuberculosis* in the pleural fluid, which generally is diagnostic of tuberculous pleuritis. Although it has been evaluated less extensively than has determination of the pleural fluid ADA level, performance of PCR on pleural fluid does appear to be useful in diagnosing of tuberculous pleuritis.21

**Options When No Diagnosis Is Reached After Initial Thoracentesis**

When no diagnosis has been reached after an initial thoracentesis (which includes cytologic analysis of the pleural fluid and assessment of a pleural fluid marker for tuberculous pleuritis), there are several diagnostic options available. The first procedure that should be performed is spiral CT scanning. With a spiral CT scan, the likelihood of a pulmonary embolus can be evaluated and the presence of pulmonary infiltrates or mediastinal lymphadenopathy determined.22 If the spiral CT scan does not demonstrate a pulmonary embolus, there are 5 options available to the physician: (1) observation, (2) needle biopsy of the pleura, (3) bronchoscopy, (4) thoracoscopy, or (5) thoracotomy with open biopsy.

**Observation.** This option is generally best if the patient is improving and there are no parenchymal infiltrates. In this regard, it is important to remember that no diagnosis is ever established in approximately 15% of patients who have exudative pleural effusions. If the patient has malignancy, spontaneous improvement
is unlikely to occur. If the patient has pulmonary embolism, the diagnosis should have been made on the basis of a previous spiral CT scan; if the patient has tuberculous pleuritis, results of assessment of one of the pleural fluid markers for tuberculosis should have been positive.

**Bronchoscopy.** Bronchoscopy is useful in the diagnosis of pleural effusion only if 1 (or more) of the following 3 conditions is present: (1) there is a pulmonary infiltrate on the chest radiograph or CT scan (in this situation, particular attention should be paid to the area that contains the infiltrate); (2) hemoptysis occurs (because hemoptysis in the presence of a pleural effusion is very suggestive of an endobronchial lesion); and (3) the pleural effusion is massive (ie, occupying more than three fourths of the hemithorax). In patients with pleural effusions in whom cytologic analysis is positive for malignancy but who have no hemoptysis or parenchymal infiltrates, bronchoscopy will not identify the primary tumor.

**Thoracoscopy.** In the diagnosis of pleural disease, thorascoscopic procedures should be used only when less invasive diagnostic methods have not yielded a diagnosis. Fewer than 10% of patients who have exudative pleural effusions will require a thoracoscopy for diagnosis. If a patient does have malignancy, thoracoscopy will establish the diagnosis more than 90% of the time; in fact the diagnosis of mesothelioma is probably best made with thoracoscopy. An advantage to thoracoscopy in the diagnosis of pleural disease is that pleural abrasion also can be performed at the time of the procedure, and that should produce a pleurodesis. It should be emphasized, however, that thoracoscopy rarely establishes the diagnosis of benign diseases other than tuberculosis.

**Needle biopsy of the pleura.** Over the past 40 years, needle biopsy of the pleura has been primarily used to diagnose tuberculous pleuritis. However, as mentioned previously, markers for tuberculous pleuritis obtained from the pleural fluid are very efficient at establishing that diagnosis. Needle biopsy of the pleura also can establish the diagnosis of malignant pleural disease, although in most patients, cytologic analysis of the pleural fluid is much more sensitive in establishing this diagnosis; if analysis of the fluid is negative for malignancy, a needle biopsy is unlikely to be diagnostic. In 1 study, needle biopsy of pleural fluid was positive for malignancy in only 20 of 118 (17%) patients with pleural malignancy in whom cytologic analysis was not diagnostic. In contrast, thoracoscopy is diagnostic in more than 90% of patients with malignant pleural effusions in whom cytologic analysis is not; consequently, it is the preferred diagnostic procedure in patients with pleural effusions suspected of being malignant in whom results of cytologic analysis are not diagnostic.

**FURTHER DISCUSSION OF PATIENT 3**

Patient 3 undergoes thoracoscopy, which shows scattered nodules over the visceral pleura; pleural abrasion is performed during the procedure. Biopsy of the nodules confirms adenocarcinoma. Subsequent mammography reveals a breast mass, which also proves to be adenocarcinoma. There has been no recurrence of the pleural effusion.

**SUMMARY**

When a patient with a pleural effusion is initially evaluated, the first question that needs to be answered is whether the patient has a transudative or an exudative pleural effusion. This is best determined by examining the levels of protein and LDH in the pleural fluid. If any of the following 3 criteria are met, the patient most likely has an exudative pleural effusion: (1) pleural fluid protein/serum protein ratio is greater than 0.5; (2) pleural fluid LDH/serum LDH ratio is greater than 0.6; or (3) pleural fluid LDH level is greater than two thirds of the upper limit of normal for the serum level. If the patient has a condition such as congestive heart failure or cirrhosis, in which one would expect to find a transudative effusion, and meets the criteria for an exudative effusion, the difference between the serum and pleural fluid albumin levels should be measured. If this difference exceeds 1.2 g/dL, the patient has a transudative pleural effusion.

In patients with cirrhosis of the liver and ascites, pleural effusions sometimes occur because the ascitic fluid passes through defects in the diaphragm into the pleural space. The pleural effusion (ie, a hepatic hydrothorax) tends to be on the right side and to occupy the entire hemithorax because the fluid is drawn from the peritoneal cavity into the pleural cavity as a result of negative pleural pressure. The management of hepatic hydrothorax is difficult. If the ascitic fluid cannot be controlled by medical therapy, the best therapy is liver transplantation. If this is not feasible, consideration should be given to performing a TIPS procedure.

Patients with pneumonia frequently have an accompanying pleural effusion (ie, a parapneumonic effusion). When such patients are initially evaluated, they should undergo therapeutic thoracentesis if there is a significant amount of fluid present. The fluid should be evaluated for poor prognostic factors, which include the...
presence of purulent material, a Gram stain or culture that is positive for bacteria, a pleural fluid glucose level that is less than 40 mg/dL, a pleural fluid pH that is less than 7.00, or a pleural fluid LDH level that is more than 3 times the upper limit of normal for the serum level. If the fluid recurs, a repeat therapeutic thoracentesis should be performed if any of the poor prognostic factors were present originally. If the fluid is loculated and cannot be removed with a therapeutic thoracentesis, consideration should be given to either tube thoracoscopy, including administration of fibrinolytic agents, or thoracoscopy, involving the breakdown of fibrin membranes. If tube thoracoscopy with fibrinolytic therapy is ineffective, then thoracoscopy should be performed. If thoracoscopy is unavailable or ineffective, thoracotomy should be performed. However, a definitive procedure for parapneumonic effusions should be performed within 10 days of the patient’s initial presentation.

All patients with undiagnosed pleural effusions should have specimens of their pleural fluid submitted for both cytologic examination for malignant cells and assessment for a pleural fluid marker for tuberculous pleuritis. The best pleural fluid markers for tuberculous pleuritis are an elevated ADA level or an elevated IFN-γ level. If no etiology of the pleural effusion is present after the initial thoracentesis, a spiral CT scan should be obtained. Not only can the diagnosis of pulmonary embolism be established with a spiral CT scan, but the presence of parenchymal abnormalities or abnormalities in the mediastinum can also be evaluated.

If no diagnosis is apparent after a spiral CT scan, the alternatives are observation, bronchoscopy, or thoracoscopy. Observation is indicated if the patient is improving. Bronchoscopy is indicated if the patient has a parenchymal abnormality or hemoptysis. Thoracoscopy is indicated if there is a suspicion of malignancy. Needle biopsy of the pleura is rarely indicated because the diagnosis of tuberculous pleuritis can be made with markers of tuberculosis in the pleural fluid, and needle biopsy is positive in fewer than 20% of cases of malignant disease of the pleura when the pleural fluid cytology does not demonstrate malignancy.

**BOARD REVIEW QUESTIONS**

Choose the single best answer for each question.

1. A 72-year-old man reports increasing dyspnea on exertion, pedal edema, and orthopnea. The chest radiograph reveals a large heart and bilateral pleural effusions. Thoracentesis and analysis of the pleural fluid yields the following results: leukocyte count, \(12 \times 10^3/\text{mm}^3\); protein level, 2.9 g/dL (simultaneous serum protein level, 5.6 g/dL); lactate dehydrogenase (LDH) level, 214 U/L (simultaneous serum LDH level, 400 U/L [upper normal limit, 632 U/L]); and glucose level, 82 mg/dL. Which of these findings indicates that the patient has an exudative pleural effusion?
   A) Leukocyte count
   B) Pleural fluid glucose level
   C) Pleural fluid LDH/serum LDH ratio
   D) Pleural fluid protein/serum protein ratio
   E) None of the above

2. Which of the following is the predominant mechanism by which pleural fluid is formed in patients with hepatic hydrothorax?
   A) Hypoalbuminemia
   B) Inflammation of the diaphragm
   C) Leakage of fluid from the thoracic duct
   D) Movement of fluid from the peritoneal cavity to the pleural cavity by way of the diaphragmatic lymph nodes
   E) Movement of fluid from the peritoneal cavity to the pleural cavity through holes in the diaphragm

3. Which of the following pleural fluid findings does NOT indicate a poor prognosis in patients with a parapneumonic effusion?
   A) Glucose level of 32 mg/dL
   B) Gram stain that is positive for organisms
   C) Leukocyte count of \(37.5 \times 10^3/\text{mm}^3\)
   D) pH of 6.96
   E) Thick pleural fluid, which appears to be pus

4. A 44-year-old woman has symptoms and signs of acute bacterial pneumonia. A chest radiograph shows an extensive infiltrate in the right lung field; the right hemithorax is approximately 40% full of fluid. It does not appear that the fluid is loculated. Which of the following is the most appropriate initial step in management?
   A) Administer antibiotics and monitor the patient using serial chest radiographs to determine if the amount of the fluid is decreasing
   B) Perform diagnostic thoracentesis with analysis of pleural fluid
   C) Perform therapeutic thoracentesis with analysis of pleural fluid
   D) Perform thoracotomy with decortication
   E) Perform tube thoracostomy and administer fibrinolytic agents intrapleurally
5. Which of the following best describes the natural history of an untreated tuberculous pleural effusion?
   
   A) The effusion will gradually continue to enlarge until it either breaks through the pleura, producing a bronchopleural fistula, or breaks through the chest wall, leading to a pleurocutaneous fistula
   
   B) The effusion will resolve completely over several weeks, but the patient is likely to develop pulmonary or extrapulmonary tuberculosis within the next few years
   
   C) The number of mycobacteria in the pleural fluid will gradually increase, and the bacteria will eventually invade the lung, producing pulmonary tuberculosis
   
   D) The patient will develop miliary tuberculosis
   
   E) The pleural fluid will become loculated, the visceral pleural will become markedly thickened, and the patient will require decortication

6. Which of the following statements concerning malignant pleural effusions is true?
   
   A) Demonstration of abnormal amounts of DNA in cells from pleural fluid is diagnostic of pleural malignancy
   
   B) Pleural fluid adenosine deaminase levels are frequently elevated in malignant pleural effusions that are lymphocytic
   
   C) Pleural fluid cytology is more sensitive than is thoracoscopy in establishing the diagnosis of pleural malignancy
   
   D) Tumor markers are a sensitive test by which the diagnosis of malignant pleural effusions can be made
   
   E) None of the above

ANSWERS


REFERENCES


SUGGESTED READINGS

