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# The Undiagnosed Pleural Effusion

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Frequently, the etiology of a pleural effusion is in question after the initial thoracentesis. In this article, I assume that the pleural effusion persists after the initial diagnostic workup, which includes measurement of a pleural fluid marker for tuberculosis, such as adenosine deaminase (ADA) or $\gamma$-interferon.

## Diseases that cause undiagnosed persistent pleural effusions

When a patient with a persistent undiagnosed pleural effusion is encountered, the first step to be considered is the list of the diseases most likely to be associated with a persistent undiagnosed pleural effusion (Box 1). The first question to answer in a patient with a persistent undiagnosed pleural effusion is whether the effusion is a transudate or an exudate. For the past several decades, this differentiation has been made by measuring the levels of protein and lactate dehydrogenase (LDH) in the pleural fluid and in the serum (Light's criteria). If one or more of the following criteria are met, the patient has an exudative pleural effusion [1]:

1. Pleural fluid protein or serum protein > 0.5
2. Pleural fluid LDH or serum LDH > 0.6
3. Pleural fluid LDH > 0.67 the normal upper limit for serum

Light's criteria are sensitive at identifying exudates, but they also identify up to 25% of transudative pleural effusions as being exudative pleural effusions [2–4]. Usually, the transudates that are misclassified only minimally meet the exudative criteria (eg, the protein ratio is 0.52 or the LDH ratio is 0.63). Moreover, the patients with transudates who are misclassified are usually receiving diuretics [4]. If the pleural fluid LDH is more than the upper limit for the serum LDH or if the protein level is more than 4.0 g/dL, the patient does not have a transudate. These transudates that are misclassified as exudates can be classified correctly if the difference or gradient between the protein levels in the serum and the pleural fluid is measured. If this gradient is greater than 3.1 g/dL, the exudative classification by Light's criteria can be ignored, because almost all such patients have a transudative pleural effusion [5,6]. The protein gradient alone should not be used to separate transudates from exudates because, by itself, it misidentifies approximately 13% of exudates as transudates [4,6].

## Transudative pleural effusions

### *Congestive heart failure*

Congestive heart failure is the most common cause of pleural effusion [7]. At times in patients with persistent pleural effusion, it is not obvious that the heart failure is the cause of the effusion. Certainly, symptoms of congestive heart failure, such as dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and nocturia, should be sought when the history is taken. In addition, signs of congestive heart failure, such as basilar rales, $S_3$ gallop, distended neck veins, and pedal edema, should be sought during the physical examination. If the patient clinically has congestive heart failure but the initial pleural fluid analysis reveals an exudate that just

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**Box 1. List of diseases most likely to produce a persistent undiagnosed pleural effusion**

*Transudative pleural effusions*

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Urinothorax
- Myxedema
- Cerebrospinal fluid leaks to the pleura

*Exudative pleural effusions*

- Malignancy
- Pneumonia (especially anaerobic)
- Tuberculosis
- Pulmonary embolism
- Fungal infection
- Pancreatic pseudocyst
- Intra-abdominal abscess
- After coronary artery bypass graft surgery
- Postcardiac injury syndrome
- Pericardial disease
- Meigs' syndrome
- Ovarian hyperstimulation syndrome
- Rheumatoid pleuritis
- Lupus erythematosus
- Drug-induced pleural disease
- Asbestos pleural effusion
- Yellow nail syndrome
- Uremia
- Trapped lung
- Chylothorax
- Pseudochylothorax

barely meets Light's criteria, the difference between the pleural fluid and serum protein should be measured as detailed previously. If this gradient is greater than 3.1 g/dL, the effusion can be attributed to the congestive heart failure. If the patient has a transudative effusion but does not have obvious heart failure, further investigations of cardiac function, such as echocardiography, are indicated. It has recently been shown that measurement of the levels of pro-brain natriuretic peptide (BNP) in pleural fluid is useful in establishing the diagnosis of congestive heart failure. Patients with congestive heart failure have pleural fluid N terminal pro-BNP levels greater than 1500 pg/mL, whereas almost all other patients have pleural fluid N terminal pro-BNP levels less than 1000 pg/mL [8,9].

*Cirrhosis with hepatic hydrothorax*

If the patient has overt cirrhosis and massive ascites, the diagnosis of hepatic hydrothorax is easy. If the patient does not have ascites, however, the diagnosis of hepatic hydrothorax may be difficult to establish. In 1998, Kakizaki and colleagues [10] reviewed the literature and were able to find 28 cases of hepatic hydrothorax without ascites. Of these 28 cases, 27 were on the right side. The only left-sided effusion occurred in a patient who had a tear in the left diaphragm as a result of a splenectomy. The mean serum albumin in these 28 cases was 2.7 g/dL, with a range of 1.9 to 3.6 g/dL [10]. The explanation for the pleural effusion in the absence of overt ascites is that the patients have defects in their diaphragm. When fluid is present in the peritoneal space, it flows immediately into the pleural space, because the pleural pressure is negative compared with the peritoneal pressure. This diagnosis can be established by demonstrating radioactivity in the thorax after the intraperitoneal injection of technetium-99m ($^{99m}$Tc)-sulfur colloid [11].

*Nephrotic syndrome*

Another cause of a chronic transudative pleural effusion is the nephrotic syndrome. More than 20% of patients with the nephrotic syndrome have pleural effusions, which are usually bilateral [12]. Therefore, all patients with chronic transudative pleural effusions should be evaluated for proteinuria and hypoproteinemia. It should be remembered that the incidence of pulmonary emboli is high with the nephrotic syndrome [13], and this possibility should be considered in all patients with the nephrotic syndrome and a pleural effusion.

*Urinothorax*

A transudative pleural effusion can result when there is retroperitoneal urinary leakage secondary to urinary tract obstruction or trauma with subsequent dissection of the urine into the pleural space [14,15]. This diagnosis is easy if it is considered as the pleural fluid looks and smells like urine. Confirmation of the diagnosis can be made by demonstrating that the pleural fluid creatinine is greater than the serum creatinine [15,16]. The pleural fluid with urinothorax may also have a low glucose level and a low pH level. The only other instances in which a transuda-

tive pleural effusion has a low glucose or low pH level is when there is systemic hypoglycemia or acidosis, respectively [4].

*Cerebrospinal fluid leak to the pleura*

On rare occasions, cerebrospinal fluid (CSF) can collect in the pleural space and produce a pleural effusion. This most commonly occurs after ventriculopleural shunting [17] but can also occur after penetrating injuries and fractures of the thoracic spine as well as after thoracic spinal surgery [18,19]. The diagnosis should be suggested by the appearance of the pleural fluid, which appears to be CSF. The protein levels are usually very low. The diagnosis can be confirmed by radionuclide cisternography [19]. Another way to establish the diagnosis is by demonstrating the presence of $\beta_2$-transferrin in the pleural fluid [20]. This substance is normally present only in CSF [20].

## Exudative pleural effusions

*Malignant pleural effusion*

There is no doubt that malignancy causes more persistent undiagnosed exudative pleural effusions than any other cause. It should be emphasized that there is no huge hurry to establish this diagnosis, however, because (1) the presence of the effusion indicates that the patient has metastases to the pleura and the malignancy cannot be cured surgically, (2) most malignant pleural effusions are attributable to tumors that cannot be cured with chemotherapy, and (3) there is no evidence that attempts to create a pleurodesis early improve the quality of the patient's life.

Most patients who have a pleural malignancy usually have other characteristics suggesting malignancy. For example, in the series of 211 patients reported by Poe and coworkers [21], the needle biopsy of the pleura was negative in 29 patients who were eventually proven to have malignant pleural effusions. All these patients were strongly suspected of having a malignant effusion by clinical criteria, such as weight loss, constitutional symptoms, or a history of a previous cancer, however [21]. Ferrer and coworkers [22] recently evaluated the characteristics of patients undergoing thoracoscopy who turned out to have a malignancy. They found four clinical characteristics that were suggestive of malignancy: symptoms for more than 1 month, absence of fever, blood-tinged pleural fluid, and chest CT scan findings suggestive of malignancy [22]. All 28 patients who had all four characteristics had a malignancy, whereas none of the 21 patients with one criterion at most had a malignancy [22].

When patients with pleural effusions attributable to the most common types of tumors are analyzed, some interesting observations can be made. The tumor that causes the highest number of pleural effusions is lung cancer [7]. When patients with lung cancer are first evaluated, approximately 15% have a pleural effusion [23], but 50% of patients with disseminated lung cancer develop a pleural effusion [7]. The tumor that causes the second highest number of pleural effusions is breast cancer [7]. Patients with breast carcinoma rarely present with a pleural effusion. The mean interval between the diagnosis of the primary tumor and the appearance of a pleural effusion is 2 years [24]. Hematologic malignancies (lymphomas and leukemias) cause the third highest number of malignant pleural effusions [7]. Approximately 10% of patients with Hodgkin's lymphoma and 25% of patients with non-Hodgkin's lymphoma have pleural effusions at presentation. Those who do almost invariably have intrathoracic lymph node involvement [25]. If the patient has AIDS and cutaneous Kaposi's sarcoma, the likely diagnosis is a pleural effusion attributable to Kaposi's sarcoma. This diagnosis is usually established at bronchoscopy, which demonstrates erythematous or violaceous macules or papules in the respiratory tree [26].

There are several primary tumors of the pleura that should be considered if the patient has an undiagnosed pleural effusion. If the patient has a history of asbestos exposure, mesothelioma should be considered. Thoracoscopy or thoracotomy is usually necessary to make this diagnosis [7]. If the patient has AIDS and has a lymphocytic pleural effusion with a high LDH level, the diagnosis of a primary effusion lymphoma is likely [27]. This diagnosis can usually be established with pleural fluid cytology and flow cytometry [27]. If the patient had received an artificial pneumothorax many years previously, a likely diagnosis is pyothorax-associated lymphoma [28].

*Parapneumonic effusion*

The diagnosis of parapneumonic effusion is easy in the patient with an acute febrile illness, purulent sputum, and pulmonary infiltrates. On occasion, however, particularly with anaerobic infections, the patient may present with a chronic illness. In one study of 47 patients with anaerobic parapneumonic effusions, the median duration of symptoms before

presentation was 10 days and 60% of the patients had substantial weight loss (mean of 29 lb) [29]. Therefore, if the patient has a chronic illness with predominantly neutrophils in the pleural fluid, it is imperative to obtain anaerobic cultures of the pleural fluid. Because patients with actinomycosis and nocardiosis sometimes have a chronic pleural effusion with predominantly neutrophils, cultures for these organisms should be obtained in patients with chronic neutrophilic pleural effusions.

*Tuberculous pleural effusion*

Throughout the world, tuberculosis remains one of the principal causes of pleural effusion. It is important to make this diagnosis, because if the patient has pleural tuberculosis and is not treated, the effusion resolves but the patient has a greater than 50% chance of developing active pulmonary or extrapulmonary tuberculosis over the next 5 years [30]. Therefore, all patients with a chronic undiagnosed pleural effusion should be evaluated for tuberculosis. The easiest way to do this is to measure the pleural fluid level of ADA or $\gamma$-interferon. If the level of ADA is less than 40 IU/L or the level of $\gamma$-interferon is less than 140 pg/mL, the diagnosis can be virtually excluded [31]. In one study, Ferrer and colleagues [32] followed 40 patients with a chronic undiagnosed pleural effusion and a pleural fluid ADA level less than 43 IU/L for a mean of 5 years, and none developed tuberculosis. Patients with lymphocytic pleural effusions because of other etiologies almost always have pleural fluid ADA levels less than 40 IU/L [33]. If the pleural fluid ADA level is greater than 40 IU/L or the level of $\gamma$-interferon exceeds 140 pg/mL and empyema and rheumatoid pleuritis are excluded, the patient probably has tuberculous pleuritis [31].

*Pulmonary embolus*

The diagnosis of a pulmonary embolism should be considered in every patient with an undiagnosed pleural effusion. Pleural effusions occur in at least 30% of patients with pulmonary emboli [34], and they are almost always exudative [35]. Most pleural effusions associated with pulmonary emboli are small, and it is uncommon for the effusion to occupy more than one third of the hemithorax [34]. Patients with undiagnosed pleural effusions should have the possibility of a pulmonary embolism investigated with a spiral CT scan [36]. The spiral CT scan not only identifies vascular filling defects, which are highly suggestive of pulmonary embolism, but demonstrates concomitant parenchymal and pleural abnormalities and mediastinal lymphadenopathy.

*Fungal pleural effusions*

Fungal disease is responsible for a small percentage of pleural effusions [7]. At times, however, blastomycosis and coccidioidomycosis may cause a chronic lymphocytic pleural effusion [7]. Accordingly, cultures for fungi should be obtained in the patient with a chronic undiagnosed pleural effusion with predominantly lymphocytes in the pleural fluid. It is unknown whether the lymphocytic effusions attributable to fungal diseases have a high ADA level.

*Chronic pancreatic pleural effusion*

This is one diagnosis that should always be considered in a patient with a chronic undiagnosed pleural effusion. Some patients with a pancreatic pseudocyst develop a direct sinus tract between the pancreas and the pleural space [37]. The sinus tract decompresses the pancreas; therefore, the patient presents with symptoms usually referable only to the chest. The patient with a chronic pancreatic pleural effusion is usually chronically ill and looks like he or she has cancer. The diagnosis is virtually established if the level of amylase in the pleural fluid is greater than 1000 U/L [37]. It is important to consider this diagnosis, because the patient can be cured with appropriate surgery.

*Intra-abdominal abscess*

Subphrenic, intrahepatic, intrasplenic, and intrapancreatic abscesses are all associated with a pleural effusion in a large percentage of patients [7]. Patients with an intra-abdominal abscess are usually chronically ill with fever and weight loss. The pleural fluid is sterile and contains predominantly neutrophils. The diagnosis can be made with a CT or ultrasound scan of the abdomen.

*Effusion after coronary artery bypass graft surgery*

Approximately 10% of patients who undergo coronary artery bypass graft (CABG) surgery have a pleural effusion that occupies more than 25% of their hemithorax 28 days after surgery [38]. The primary symptom (if any) of a patient with a post-CABG pleural effusion is dyspnea; chest pain and fever are distinctly unusual [38]. The pleural fluid in these patients is an exudate characterized by a predominance of lymphocytes and an LDH level

approximately equal to the upper limit of normal for serum [39]. Although the pleural fluid is similar to the pleural fluid in patients with tuberculous pleuritis, these two entities may be differentiated by the pleural fluid level of ADA; the ADA level is less than 40 U/L in patients with a post-CABG effusion [33]. The importance of these effusions is to know that they can persist for years on rare occasions [40] and not to be too aggressive in pursuing a diagnosis if the pleural fluid findings are as expected.

*Postcardiac injury syndrome*

Postcardiac injury syndrome (PCIS), also known as Dressler's syndrome, is characterized by the development of fever, pleuropericarditis, and parenchymal pulmonary infiltrates in the weeks after trauma to the pericardium or myocardium [41]. The PCIS has been reported after myocardial infarction, cardiac surgery, blunt chest trauma, percutaneous left ventricular puncture, pacemaker implantation, and angioplasty. The PCIS differs from the pleural effusion after CABG surgery, because fever and chest pain invariably occur with the PCIS and are rare after CABG surgery. After cardiac injury, symptoms usually develop between the first and third weeks but can develop any time between 3 days and 1 year [41]. The pleural fluid is frankly bloody in approximately 30% of patients, and the differential cell count may reveal predominantly neutrophils or mononuclear cells, depending on the acuteness of the process [42].

*Pericardial disease*

Approximately 25% of patients who have a pericardial effusion have a concomitant pleural effusion [43]. In patients with inflammatory pericarditis, most of the associated pleural effusions are unilateral and left-sided [43]. The characteristics of the pleural fluid seen in conjunction with pericardial disease are not well described [7]. The possibility of pericardial effusion should be evaluated in any patient with cardiomegaly and an isolated left pleural effusion.

Approximately 60% of patients with constrictive pericarditis have a concomitant pleural effusion [44]. The associated pleural effusion is bilateral and symmetric in most of these patients. In one report of four patients with constrictive pericarditis, the pleural fluid was transudative in one and exudative in three [44]. We recently reported one patient with constrictive pericarditis who had a pleural fluid protein level of 4.0 g/dL [45]. When a patient is seen with edema and an exudative pleural effusion, the diagnosis of constrictive pericarditis should be considered. It is important to realize that the findings of echocardiography may be normal in the patient with constrictive pericarditis and that cardiac catheterization may be necessary to establish the diagnosis [45].

*Meigs' syndrome*

Meigs' syndrome is the constellation of a benign pelvic neoplasm associated with ascites and pleural effusion in which surgical extirpation of the tumor results in permanent disappearance of the ascites and pleural effusion [7]. The pleural fluid is an exudate with a relatively low cell count, which may sometimes have an elevated CA-125 level [46]. The importance of Meigs' syndrome is that not all patients with a pelvic mass, ascites, and a pleural effusion have metastatic disease.

*Ovarian hyperstimulation syndrome*

This syndrome is a serious complication of ovulation induction. The clinical picture is characterized by massive ovarian enlargement with multiple cysts, hemoconcentration, and the third space accumulation of fluid. Patients with the syndrome present within 2 to 3 weeks after receiving the human chorionic gonadotropin with abdominal pain and distention; a nonproductive cough; and dyspnea caused by the ascites, pleural effusion, or both. The pleural effusion is usually bilateral, and the pleural fluid is an exudate with predominantly neutrophils and a relatively low LDH level [7].

*Rheumatoid pleuritis*

Chronic pleural effusions may be a manifestation of rheumatoid pleuritis, and the diagnosis is usually straightforward. Classically, the effusion occurs in older men who have subcutaneous nodules. The pleural fluid is an exudate with low glucose, low pH, and high LDH levels. The first manifestation of rheumatoid disease is virtually never a pleural effusion [7].

*Systemic lupus erythematosus*

In contrast to rheumatoid pleuritis, patients with systemic lupus erythematosus (SLE) may present with a pleural effusion. The possibility of drug-induced lupus should always be considered in a patient with an undiagnosed pleural effusion. Drugs that are most commonly incriminated in drug-induced lupus are hydralazine, procainamide, isoniazid, phe-

nytoin, and chlorpromazine [7]. The diagnosis of SLE with pleural involvement is based on the usual criteria for the diagnosis of lupus. Measurement of the pleural fluid antinuclear antibody (ANA) levels [47] or performance of lupus erythematosus preparations on the pleural fluid [7] do not assist in the diagnosis.

*Drug-induced pleural disease*

When a patient is evaluated with a chronic undiagnosed pleural effusion, the list of drugs that the patient is taking should be carefully reviewed, because the ingestion of certain drugs can lead to the development of a pleural effusion. The primary drugs associated with the development of a pleural effusion are nitrofurantoin (a urinary antiseptic), dantrolene (a muscle relaxant), and the ergot alkaloids, such as bromocriptine or pergolide, that are used to treat Parkinson's disease [7]. Other drugs that have been reported to induce pleural effusions include methysergide, amiodarone, procarbazine, methotrexate, clozapine, dapsone, metronidazole, mitomycin, isotretinoin, propylthiouracil, simvastatin, warfarin, and gliclazide [7,48]. Most patients who have drug-induced pleural effusions have peripheral eosinophilia. When the drug is discontinued, the effusion usually resolves rapidly [48].

*Asbestos pleural effusion*

Exposure to asbestos can lead to the development of an exudative pleural effusion. In one series of 1135 asymptomatic asbestos workers, the prevalence of pleural effusion was 3% [49]. In this series, all the patients developed effusions within 20 years of the initial exposure and many had done so within 5 years of the initial exposure [49]. The prevalence of pleural effusion was directly related to the total asbestos exposure. Patients with asbestos pleural effusions are usually asymptomatic [49,50]. The effusion tends to last several months and then clears, leaving no residual disease. The pleural fluid is an exudate and can contain predominantly neutrophils or mononuclear cells [50]. If a patient with a pleural effusion has a history of asbestos exposure and is asymptomatic, the patient can probably be observed to determine if the effusion disappears spontaneously.

*Yellow nail syndrome*

The yellow nail syndrome consists of the triad of deformed yellow nails, lymphedema, and pleural effusions [7]. The three separate entities may become manifest at widely varying times. The pleural effusions are bilateral in approximately 50% of patients and vary in size from small to massive [7]. Once a pleural effusion has occurred with this syndrome, it tends to persist and recur rapidly after a thoracentesis. The pleural fluid is usually a clear yellow exudate with a normal glucose level and predominantly lymphocytes in the pleural fluid differential. The pleural fluid LDH level tends to be low relative to the pleural fluid protein level.

*Uremia*

The prevalence of pleural effusions with uremia is approximately 3% [51]. As many as 50% of patients on long-term hemodialysis have a pleural effusion [52]. There is not a close relation between the degree of uremia and the occurrence of a pleural effusion [51]. More than 50% of the patients are symptomatic, with fever (50%), chest pain (30%), cough (35%), and dyspnea (20%) being the most common symptoms [51]. The pleural fluid is an exudate, and the differential usually reveals predominantly lymphocytes [51]. Tests of renal function should be obtained in every patient with an undiagnosed exudative effusion.

*Trapped lung*

When there is intense inflammation in the pleural space, a fibrous peel may form over the visceral pleura. This peel can prevent the underlying lung from expanding; therefore, the lung is said to be trapped [53]. The initial event producing the pleural inflammation is usually a pleural infection or a hemothorax, but it can be a spontaneous pneumothorax, thoracic operations (particularly CABG surgery) [40], uremia, or collagen vascular disease. The pleural fluid is usually clear yellow and is a borderline exudate with predominantly mononuclear cells. The diagnosis can be made by measuring the pleural pressure while fluid is withdrawn during a thoracentesis. If the initial pleural pressure is less than $-10$ cm $H_2O$ or if the pleural pressure falls more than 20 cm $H_2O$ per 1000 mL of fluid removed, the diagnosis is confirmed provided that the patient does not have a bronchial obstruction [53].

*Chylothorax and pseudochylothorax*

When pleural fluid is found to be milky or extremely turbid, the possibility of a chylothorax or a pseudochylothorax should be considered. When turbid fluid is found, the first step is to centrifuge

the fluid. If the supernatant remains turbid, the turbidity is attributable to a high lipid content in the pleural fluid and the patient has a chylothorax or a pseudochylothorax.

A chylothorax is usually easy to differentiate from a pseudochylothorax on clinical grounds. Patients with a chylothorax have an acute illness, and their pleural surfaces are normal on CT. In contrast, patients with a pseudochylothorax usually have had a pleural effusion for more than 5 years, and their pleural surfaces are markedly thickened on CT. Measurement of the lipid levels in the pleural fluid is also useful in distinguishing these two conditions. Pleural fluid from a chylothorax has a triglyceride level greater than 110 mg/dL, and the ratio of the pleural fluid to serum cholesterol is less than 1.0. In contrast, fluid from a pseudochylothorax has cholesterol crystals or a cholesterol level greater than 200 mg/dL and higher than the simultaneous serum level [7].

## Tests to consider for patients with persistent undiagnosed pleural effusion

### *History*

There are certain points in the patient's history that should receive special attention if the patient has a persistent undiagnosed pleural effusion. If a patient has a transudative pleural effusion, particular attention should be paid to symptoms of congestive heart failure, such as dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and nocturia. In addition, historical evidence of cirrhosis, alcoholism, or chronic hepatitis should be sought with the possibility of a hepatic hydrothorax in mind. A history of trauma or surgery to the thoracic spine should be sought with the diagnosis of a CSF leak in mind.

If the patient has an exudative pleural effusion, a history of malignancy should be sought. Malignant pleural effusions have been known to develop as long as 20 years after the primary tumor was diagnosed [54]. A history of exposure to asbestos should be sought, because this would suggest mesothelioma or an asbestos pleural effusion. A history of fever suggests a chronic anaerobic, tuberculous, or fungal infection or an intra-abdominal abscess. A history of alcoholism or previous pancreatic disease raises the possibility of a chronic pancreatic pleural effusion. A history of CABG surgery or myocardial trauma suggests a post-CABG surgery pleural effusion or the PCIS, respectively. A history of rheumatoid disease raises the possibility of rheumatoid pleuritis. The patient should be questioned carefully regarding the medications he or she is taking to determine whether he or she is taking a medication that causes a pleural effusion or is associated with drug-induced lupus erythematosus. The patient should be questioned carefully about previous pleural problems, which raise the likelihood of a pseudochylothorax or a trapped lung.

### *Physical examination*

In the patient with a chronic undiagnosed pleural effusion, it is worthwhile to repeat a careful physical examination. If the patient has a transudative pleural effusion, signs of congestive heart failure, such as basilar rales, an $S_3$ gallop, or distended neck veins, should be sought. In addition, evidence of ascites should be carefully sought. The presence of pedal edema suggests congestive heart failure, cirrhosis with hepatic hydrothorax, nephrotic syndrome, pericardial disease, or the yellow nail syndrome.

If the patient has an exudative effusion, a careful search for lymphadenopathy or other masses that would suggest malignancy is indicated. In women, a careful breast examination and a careful pelvic examination should be done to evaluate these locations for masses. Abdominal tenderness suggests an intra-abdominal abscess. Distant heart sounds, a pericardial friction rub, or Kussmaul's sign (increased jugular venous pressure that increases during inspiration) suggests pericardial disease. Ascites and a pelvic mass raise the possibility of Meigs' syndrome. Deformed joints and subcutaneous nodules make rheumatoid pleuritis likely. The presence of yellow nails establishes the diagnosis of the yellow nail syndrome.

### *Laboratory examinations*

Several blood tests should be routinely obtained in patients with a persistent undiagnosed pleural effusion. The level of albumin and globulin should be measured to determine whether the patient has cirrhosis or the nephrotic syndrome, and liver function tests should be obtained to ascertain if there is chronic hepatitis. Additionally, I obtain a complete blood cell count with a differential. A serum ANA test should be obtained with the diagnosis of SLE in mind. Blood urea nitrogen (BUN) and creatinine levels should be obtained to evaluate the possibility of uremia, and a urinalysis should be obtained to detect proteinuria.

Several special tests on the pleural fluid are also indicated. The least expensive test is to smell the

pleural fluid. If the pleural fluid smells like urine, the patient probably has an urinothorax, whereas if the pleural fluid smells feculent, the patient probably has an anaerobic pleural infection. As mentioned previously, the ADA or γ-interferon should be measured in the pleural fluid to assess whether the patient has pleural tuberculosis. Flow cytometry on the pleural fluid is indicated if lymphoma is suspected [55]. If the pleural fluid is milky or cloudy, it should be centrifuged, and if the supernatant remains milky or cloudy, the pleural fluid should be sent for measurement of cholesterol and triglycerides. Every time a thoracentesis is performed in a patient with a persistent undiagnosed pleural effusion, a pleural fluid LDH level should be determined. If this LDH level tends to decrease with time, the pleural process is resolving and one can be conservative in the approach to the patient. Alternatively, if the LDH level is increasing with time, the process is getting worse and one should be aggressive in pursuing a diagnosis [7].

*Imaging procedures*

Most patients with an undiagnosed persistent pleural effusion should have a spiral CT scan of the chest. With the spiral CT scan, the diagnosis of pulmonary emboli can be established [56]. In addition, parenchymal infiltrates and masses, pleural masses or thickening, and mediastinal lymphadenopathy can be identified. Finally, pericardial thickening and pericardial effusions can be identified on the CT scan. While the patient is receiving the CT scan, it is reasonable to obtain abdominal cuts also. These can demonstrate abdominal masses, lymphadenopathy, and ascites. An echocardiogram is indicated if congestive heart failure is suspected but is not definitely established and if a pericardial effusion is suspected. It is important to remember that the echocardiogram may not reveal any abnormality if the patient has constrictive pericarditis [45]. If constrictive pericarditis is suspected, the patient should undergo right heart catheterization.

*Needle biopsy of the pleura*

For the past 50 years, most cases of tuberculous pleuritis have been diagnosed with a needle biopsy of the pleura. In the past 10 years, however, it has been demonstrated that markers for tuberculosis obtained from the pleural fluid, such as the ADA or γ-interferon, are efficient at establishing this diagnosis. The other diagnosis that can be established with a needle biopsy of the pleura is pleural malignancy. In most series, however, cytology is much more sensitive in establishing the diagnosis. Moreover, if the cytology of the fluid is negative, the pleural biopsy is usually nondiagnostic. In one series of 118 patients from the Mayo Clinic who had a malignancy involving the pleura but negative pleural fluid cytology, the needle biopsy of the pleura was positive in only 20 (17%) patients [57]. Because thoracoscopy is diagnostic in more than 90% of patients with a pleural malignancy and negative cytology, it is the preferred diagnostic procedure in patients with a cytology-negative pleural effusion who are suspected of having a pleural malignancy. A needle biopsy of the pleura is indicated if the patient has an undiagnosed pleural effusion that is not improving and thoracoscopy is not available. A needle biopsy of the pleura is also indicated if pleural tuberculosis is suspected and a pleural fluid marker for tuberculosis is unavailable or equivocal [7]. If the patient has pleura thickening on contrast-enhanced CT, consideration should be given to performing an image-guided cutting needle biopsy of the pleura. In one report [58], the diagnosis of mesothelioma was established in 18 (86%) of 21 patients.

*Thoracoscopy*

When one is dealing with patients with pleural effusions, thoracoscopic procedures should be used only when less invasive diagnostic methods, such as thoracentesis with cytology and markers for tuberculosis, have not yielded a diagnosis. In the series of 620 patients reported by Kendall and coworkers [59], only 48 (8%) required thoracoscopy for a diagnosis. The final diagnoses in these 48 patients were a malignancy in 24, a parapneumonic effusion in 7, a rheumatoid pleural effusion in 4, congestive heart failure in 3, and pulmonary interstitial fibrosis in 2. In 8 patients, no diagnosis was established with the combination of the clinical presentation and thoracoscopy; 6 of these patients were subsequently diagnosed has having a malignancy (mesothelioma in 3 patients and adenocarcinoma in 3 patients) [59].

In general, if the patient has a malignancy, thoracoscopy establishes the diagnosis in approximately 90% of cases [60–62]. The diagnosis of tuberculous pleuritis can almost always be established with thoracoscopy [63]. It should be emphasized, however, that thoracoscopy rarely establishes the diagnosis of benign disease other than tuberculosis [64]. One advantage of thoracoscopy in the diagnosis of pleural disease is that pleurodesis can be performed at the time of the procedure. In general, thoracoscopy is indicated in the patient with an

undiagnosed pleural effusion who is not improving spontaneously, provided that the patient has a significant likelihood of malignancy or tuberculosis.

*Bronchoscopy*

Bronchoscopy can be diagnostically useful in patients with a pleural effusion if the patient has one of the following four characteristics [65]; otherwise bronchoscopy is not indicated:

1. A pulmonary infiltrate is present on the chest radiograph or chest CT. If an infiltrate is present, particular attention should be paid to the area with the infiltrate at the time of bronchoscopy.
2. Hemoptysis is present. The presence of hemoptysis in the patient with a pleural effusion increases the likelihood of malignancy with an endobronchial lesion or pulmonary embolus. The former can be diagnosed with bronchoscopy.
3. The pleural effusion is massive. The most common cause of a massive pleural effusion is malignancy, particularly lung cancer, and this diagnosis can be established at bronchoscopy. The other two leading causes of massive pleural effusion are hepatic hydrothorax and tuberculous pleuritis; these diagnoses cannot be established with bronchoscopy.
4. The mediastinum is shifted toward the side of the effusion. With this finding, an obstructing endobronchial lesion is probably responsible, and this can be identified and biopsied at bronchoscopy.

*Open biopsy*

In many institutions, open thoracotomy with direct biopsy of the pleura has been replaced by video-assisted thoracoscopy. If both procedures are available, thoracoscopy is usually preferred because it is associated with less morbidity. The primary indication for an open pleural biopsy is progressive undiagnosed pleural disease in an institution where thoracoscopy is not available or when there is a contraindication for thoracoscopy, such as marked adhesions between the visceral and parietal pleura.

One should realize that even with an open biopsy of the pleura, a diagnosis is not always obtained. In one study, the experience at the Mayo Clinic between 1962 and 1972 with an open pleural biopsy for undiagnosed pleural effusion was reviewed. It was found that no diagnosis was established at open biopsy in 51 patients [66]. Thirty-one of the patients had no recurrence of their pleural effusion; however, 13 of these 51 patients were eventually found to have malignant disease (lymphoma in 6 patients, mesothelioma in 4 patients, and other malignancy in 3 patients). In another study of 21 patients subjected to open pleural biopsy for undiagnosed pleural effusion, no diagnosis was obtained in 7 (33%) [67].

## Summary

When faced with a patient with an undiagnosed pleural effusion, the first question to be answered is whether the patient has a transudate or an exudate. This is most commonly done with Light's criteria. If it seems clinically that the patient has a transudative effusion but Light's exudative criteria are met, the demonstration of a serum pleural fluid protein gradient of greater than 3.1 g/dL indicates that the effusion is transudative. The diagnosis of congestive heart failure is strongly suggested if the pleural fluid BNP level is greater than 1500 pg/mL. Patients with undiagnosed exudative effusions should have a spiral CT scan to evaluate the possibility of a pulmonary embolism and to demonstrate parenchymal, pleural, or mediastinal disease. Patients with a malignant pleural effusion usually have the following characteristics: symptoms for more than 1 month, absence of fever, blood-tinged pleural fluid, and chest CT scan findings suggestive of malignancy.

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