Objectives

1. To help the reader understand the pathophysiology of pleural fluid accumulation in disease.
2. To describe the symptoms, chest radiograph, and time to resolution of pleural fluid in different causes of pleural effusions.
3. To describe the pleural fluid findings that will diagnose or narrow the differential diagnosis of a pleural effusion.
4. To help the reader understand the approach to management of pleural effusions.

Key words

chest radiograph; diagnosis; malignancy; management; pleural effusion; pneumonia

Abbreviations

BAPE = benign asbestos pleural effusion; LDH = lactate dehydrogenase

Pleural effusions are a mirror of systemic disease. Disease affecting virtually any organ can result in a pleural effusion. Therefore, the clinician not only needs to consider chest disease as a cause of pleural effusions, but diseases of organs below the diaphragm (splenic infarction), systemic diseases (systemic lupus erythematosus), and diseases of the lymphatic system (yellow nail syndrome) need to be thought of as well, in the appropriate clinical setting.

Pathophysiology of Pleural Fluid Accumulation

There are a limited number of mechanisms responsible for the accumulation of pleural fluid: (1) increased hydrostatic pressure (congestive heart failure); (2) decreased oncotic pressure (hypoalbuminemia); (3) decreased pleural pressure (atelectasis); (4) increased endothelial permeability (pneumonia); (5) decreased
lymphatic drainage (malignancy); (6) movement from the peritoneal space (hepatic hydrothorax); (7) thoracic duct rupture (chylothorax); and (8) iatrogenic (extravascular migration of central venous catheter).¹

When pleural fluid formation exceeds efflux from the pleural space, a pleural effusion will accumulate and, when large enough (> 200 to 300 mL), can be detected on a posteroanterior chest radiograph. Smaller amounts of fluid can be detected by lateral decubitus view, ultrasonography, and CT scan.

Pleural fluid formation related to disease in the lungs results from an increased interstitial-pleural pressure gradient. When fluid moves from the intravascular space into the interstitium of the lung because of increased hydrostatic pressure (as in congestive heart failure) or increased capillary permeability (pneumonia), pressure in the interstitium of the lung increases and results in a driving force towards the pleural space, which has a mean negative pressure. The interstitial fluid moves between mesothelial cell junctions into the pleural space. If fluid formation exceeds removal by the parietal pleural lymphatics, a pleural effusion will develop.²

**Symptoms at Presentation**

Awareness of the symptoms and signs of specific diseases in patients who present with pleural effusions may be helpful in narrowing the differential diagnosis of the exudative effusion. For example, patients with postcardiac injury syndrome,³ lupus pleuritis,⁴ and malignant mesothelioma⁵ usually are symptomatic at presentation with a pleural effusion. In contrast, about 75% of patients with carcinomatous malignant effusions,⁶ 50% of patients with rheumatoid pleurisy,⁷ and less than half of the patients with benign asbestos pleural effusion (BAPE)⁸ may be symptomatic at presentation.

**Chest Radiograph**

*Pleural Fluid as the Only Abnormality With Primary Disease in the Chest*

When the only abnormality on chest radiograph is a pleural effusion, several diseases originating in the chest should be considered, such as infections (tuberculous and viral pleurisy), malignancy (cancer, non-Hodgkin's lymphoma, and leukemia), pulmonary embolism, drug-induced lung disease, BAPE, lymphatic abnormalities (chylothorax and yellow nail syndrome), uremic pleurisy, constrictive pericarditis, and hypothyroidism.⁹

**Bilateral Effusions**

Bilateral pleural effusions are commonly transudative due to congestive heart failure,¹⁰ nephrotic syndrome, hypoalbuminemia, peritoneal dialysis, and
constrictive pericarditis. Patients with exudative effusions can also present with bilateral effusions, most commonly malignancy (extrapulmonic primary carcinomas, lymphoma), lupus pleuritis, and yellow nail syndrome.

**Diseases Below the Diaphragm**

Patients with diseases of the abdomen and pelvis can present with chest radiographs that reveal only a pleural effusion while other abnormalities are not present or cannot be visualized. These include transudates such as hepatic hydrothorax, nephrotic syndrome, urinothorax, and peritoneal dialysis and exudates such as pancreatic disease, chylous ascites, subphrenic abscess, and splenic abscess or infarction.

**Interstitial Lung Disease**

When pleural effusions are associated with interstitial lung disease, the differential diagnosis includes congestive heart failure, rheumatoid arthritis, asbestos-induced disease (BAPE and asbestosis), lymphangitic carcinomatosis, lymphangioleiomyomatosis, viral and mycoplasma pneumonias, Waldenström's macroglobulinemia, sarcoidosis, and *Pneumocystis carinii* pneumonia.

**Pulmonary Nodules**

The association of pleural effusions with pulmonary nodules most commonly occurs with metastatic carcinoma from a nonlung primary tumor. Less common causes include Wegener's granulomatosis, rheumatoid arthritis, septic emboli, sarcoidosis, and tularemia.

**Resolution of Pleural Effusion**

Awareness of the spontaneous resolution rates of exudative pleural effusions is helpful in arriving at a presumptive cause of the pleural effusion. For example, in patients with pulmonary embolism without a radiographic infarction (consolidation), the effusion usually resolves completely within 7 to 10 days; when a radiographic infarction is present, resolution may require 2 to 3 weeks. The pleural effusion associated with acute pancreatitis will resolve as the pancreatic inflammation subsides, typically within 1 to 2 weeks. With continued hemodialysis, a uremic pleural effusion resolves in 4 to 6 weeks. Persistence of the uremic effusion suggests that either a trapped lung or fibrothorax has developed, which can be successfully treated with decortication. A tuberculous pleural effusion has a spontaneous resolution rate of 4 to 16 weeks; corticosteroid therapy will shorten resolution time but does not appear to have an effect on pleural space sequelae. Rheumatoid pleural effusions have a typical resolution time of 4 to 6 months, with a range of a few
weeks to 9 months. In patients with BAPE effusions typically resolve in 3 to 4 months, with some persisting for \( \geq 1 \) year and some resolving in \(< 1\) month. Effusions that persist for \( > 1\) year have a limited differential diagnosis that includes trapped lung, yellow nail syndrome, lymphangiectasia, Noonan's syndrome (chylothorax), and, rarely, rheumatoid pleurisy, BAPE, and malignancy.

**Value of Pleural Fluid Analysis**

In a prospective study of 78 patients with new-onset pleural effusion, a definitive diagnosis was established by the initial pleural fluid analysis in 25% and a presumptive diagnosis in 55%, with the remaining 20% having a nondiagnostic pleural fluid analysis. However, in the latter group of patients, the pleural fluid analysis was helpful by excluding possible diagnoses such as infection. Thus, the initial pleural fluid analysis is either definitively or presumptively diagnostic in 80% of patients and is valuable clinically in about 90% of cases.

Diagnoses that can be definitively established by pleural fluid analysis include empyema (pus), malignancy, tuberculous pleural effusion, fungal pleural effusion, lupus pleuritis (lupus erythematosus cells), chylothorax (triglycerides \(< 110\) mg/dL or presence of chylomicrons), hemothorax (pleural fluid/blood hematocrit \(< 0.5\)), urinothorax (pleural fluid/serum creatinine \( > 1.0\)), peritoneal dialysis (total protein \(< 0.5\) g/dL and glucose 200 to 400 mg/dL), esophageal rupture (increased salivary amylase and pH \(< 7.00\)), rheumatoid pleurisy (pleural fluid cytology), and extravascular migration of a central venous catheter (high glucose level or pleural fluid simulating the infusate).

**Exudates Vs Transudates**

Pleural fluid/serum protein ratio, pleural fluid lactate dehydrogenase (LDH) compared with the upper limits of normal of serum LDH, and pleural fluid cholesterol level can help discriminate accurately between a transudate and exudate. Helpful values include a pleural fluid/serum protein ratio of \( > 0.5\), a pleural fluid LDH of \( > 0.45\), between 0.67 and 0.80 of the upper limit of normal of serum LDH, and a pleural fluid cholesterol \( > 45\) mg/dL or \( > 60\) mg/dL. The presence of any one of the above values makes it highly likely that the effusion is exudative. When pleural fluid LDH suggests an exudate and the pleural fluid/serum protein ratio suggests a transudate, malignancy or an effusion secondary to *Pneumocystis carinii* pneumonia should be considered. It is important to remember that no laboratory test is 100% sensitive and specific and prethoracentesis diagnosis and clinical judgment must be used in the interpretation of pleural fluid analysis.
Pleural Fluid Nucleated Cell Count

The total nucleated cell count is rarely helpful in establishing a definitive diagnosis; however, it may provide useful information. If the nucleated cell count is < 500/µL, the fluid is usually a transudate. If the nucleated cell count is > 50,000/µL, it usually represents pleural space bacterial infection (typically empyema). Nucleated cell counts between 25,000 and 50,000/µL are usually seen only with uncomplicated parapneumonic effusions, acute pancreatitis and acute pulmonary infarction.

The differential diagnosis of an exudate pleural fluid with a lymphocyte count of > 80% of the total nucleated cells includes tuberculous pleurisy, chylothorax, lymphoma, yellow nail syndrome, chronic rheumatoid pleurisy, sarcoidosis, trapped lung, and acute lung rejection. The differential diagnosis of pleural fluid eosinophilia (> 10% of the total nucleated cells are eosinophils) includes most commonly pneumothorax and hemothorax, as well as BAPE, pulmonary embolism with infarction, previous thoracentesis, parasitic disease (paragonimiasis), fungal disease (histoplasmosis and coccidioidomycosis), drug-induced lung disease (nitrofurantoin, dantrolene, propylthiouracil, valproic acid, isotretinoin, and bromocriptine), Hodgkin's lymphoma, and carcinoma. The prevalence of pleural fluid eosinophilia is similar in carcinomatous and noncarcinomatous pleural effusions.

Pleural Fluid pH and Glucose

A pleural fluid pH < 7.30, in the setting of a normal blood pH, narrows the differential diagnosis of the exudative effusion to empyema, complicated parapneumonic effusion, chronic rheumatoid pleurisy, esophageal rupture, malignancy, tuberculous pleurisy, and lupus pleuritis. Finding a pleural fluid glucose < 60 mg/dL or pleural fluid/serum glucose < 0.5 provides the same differential diagnosis of the exudate as a low pleural fluid pH. Urinothorax, most commonly caused by obstructive uropathy, is the only cause of a low pH transudate. Empyema and rheumatoid pleurisy are the only effusions that can present with glucose concentrations of 0 mg/dL. A pleural fluid pH < 7.00 is usually seen only with empyema, whether it be parapneumonic or associated with esophageal rupture. Pleural fluid acidosis is due to increased acid generation by neutrophils and bacteria in empyema and an abnormal pleural membrane that inhibits glucose end products, CO₂ and lactic acid, from exiting the pleural space at a normal rate. Complicated parapneumonic effusion/empyema, rheumatoid pleurisy, and pleural paragonimiasis are the only effusions with the triad of a pH < 7.30, a glucose < 60 mg/dL, and an LDH > 1,000 U/L (upper limit of normal of serum 200 IU/L).
Common Diseases Associated With Pleural Effusions

**Congestive Heart Failure**

Patients with pleural effusions from congestive heart failure will provide a history of orthopnea and paroxysmal nocturnal dyspnea typical of left ventricular failure. The usual chest radiograph will demonstrate cardiomegaly, bilateral pleural effusions (right greater than left), and evidence of pulmonary edema as demonstrated by peribronchial cuffing, interstitial or alveolar infiltrates, or Kerley-B lines. The degree of pulmonary edema correlates with the volume of pleural effusion.\(^{47}\) The pleural space serves as a "reservoir" for pulmonary edema fluid, which moves from the interstitium of the lung into the pleural space through mesothelial cell junctions along a pressure gradient. Pleural effusions are associated with elevated pulmonary capillary wedge pressures, typically 24 mm Hg or greater, a level that is associated with Kerley's B lines on chest radiograph.\(^{47}\) However, pleural effusions can occur with lower pulmonary capillary wedge pressures, particularly if the oncotic pressure is low. There is no significant relationship between right atrial pressure and the development of pleural effusions.

A diagnostic thoracentesis is indicated in suspected congestive heart failure when there is fever, pleuritic chest pain, a unilateral effusion, a left effusion greater than the right effusion, effusions of disparate size, and a PaO\(_2\) inconsistent with the clinical presentation. With the typical presentation, thoracentesis can be withheld while observing the response to treatment. If response is not appropriate, diagnostic thoracentesis should be performed. Acute diuresis can transform a transudative congestive heart failure fluid into a pseudoexudate.\(^{48}\)

**Hepatic Hydrothorax**

An hepatic hydrothorax results when ascitic fluid moves from the peritoneal to pleural space along a pressure gradient through congenital diaphragmatic defects that have been opened by increased peritoneal pressure. Hepatic hydrothorax occurs in approximately 5% of patients with clinical ascites but can result even in the absence of clinical ascites.\(^{14}\) These effusions are most commonly right-sided but may be unilateral on the left (15%) or bilateral (15%).\(^{14}\) A presumptive diagnosis can be established in the appropriate clinical setting by demonstrating that pleural and ascitic fluid characteristics are similar. For a definitive diagnosis, a radionuclide study should be performed. Radionuclide appearing in the chest within 1 to 2 h following injection into the ascitic fluid confirms the diagnosis.\(^{49}\)

Management of hepatic hydrothorax includes sodium restriction, diuretic therapy and intermittent therapeutic thoracentesis. Refractory effusions can be
managed with a transjugular intrahepatic portal systemic shunt or video-assisted thoracoscopic surgery repair of the diaphragmatic defect and pleurodesis in patients with a reasonable expected survival who can tolerate a surgical procedure. Chest tube drainage is contraindicated in hepatic hydrothorax, as it causes protein and lymphocyte depletion and can cause an iatrogenic empyema, precipitate renal failure, and be a source of continuous fluid leak through the thoracostomy site.

**Atelectasis**

Atelectasis causes a small transudative pleural effusion due to a decrease in pleural pressure. As the collapsed portion of the lung moves away from the chest wall, it causes a localized decrease in pleural pressure that results in an increased parietal pleural-interstitial pleural space gradient, causing increased formation of pleural fluid. As fluid moves into the pleural space, the pleural-interstitial pressure gradient returns to normal with pleural fluid formation equaling pleural fluid removal. Atelectatic effusions are commonly found in patients in ICUs but can also occur when lung cancer obstructs a mainstem or lobar bronchus, with pulmonary embolism without infarction, and any cause of lower chest or upper abdominal pain. Most atelectatic effusions are small in volume and resolve quickly when the atelectasis resolves.

**Nephrotic Syndrome**

Patients with nephrotic syndrome have an estimated 20% prevalence of small bilateral pleural effusions, which have a tendency to be subpulmonic in location. Thrombotic complications including deep venous thrombosis, renal vein thrombosis, arterial thrombosis, and pulmonary embolism are a common occurrence in this hypercoagulable state. The hypercoagulable state is due, in part, to loss of clotting inhibitors (protein S, protein C, and antithrombin III) in the urine, volume depletion, and platelet abnormalities. The presence of a large volume of pleural fluid, a unilateral effusion, effusions of disparate size, pleuritic chest pain or acute dyspnea, or an exudate, hemorrhage, or neutrophil predominance on pleural fluid analysis should prompt an immediate evaluation for pulmonary thromboembolic disease.

**Parapneumonic Effusions**

Approximately a million patients per year in the United States present with parapneumonic effusions. Parapneumonic effusions can be uncomplicated (small, free-flowing effusion with pleural fluid pH > 7.30, resolves with antibiotics alone) or complicated (large, loculated effusion with pleural fluid pH < 7.30, requires pleural space drainage for resolution of pleural sepsis). The end stage of a complicated parapneumonic effusion is an empyema.
Empyema is defined as pus in a body cavity and, therefore, empyema thoracis is pus in the pleural space. Pus assumes its character because it is composed of coagulable pleural fluid, cellular debris, fibrin, and collagen. Pus appears as a thick, yellow-white, opaque fluid.

The three stages of a parapneumonic effusion are the exudative (capillary leak) stage, the fibrinopurulent (transitional) stage, and the organizational (empyema) stage. The exudative stage covers the approximate time period from the beginning of pleural fluid collection and the next 5 to 10 days. When neutrophils migrate to the lung to control pneumonitis, they adhere to the capillary endothelium and release oxygen radicals and proteases that result in capillary leak. With its high protein concentration, this extravascular fluid moves along a pressure gradient from the interstitium of the lung to the pleural space. If formation exceeds removal, a pleural effusion will develop. This effusion is usually small to moderate in volume and exudative, with a neutrophil predominance, a pH > 7.30, a glucose > 60 mg/dL, and an LDH < 700 IU/L. Almost all patients treated with appropriate antibiotics for pneumonia in this stage will have complete resolution of the pleural effusion over 1 to 2 weeks without clinically significant pleural space sequelae.

If the infection remains untreated or inappropriately treated, the effusion evolves into the fibrinopurulent stage, which is characterized by increasing pleural fluid volume, continued fever, and pleural fluid that contains a large number of neutrophils and possibly organisms identified by Gram's stain or culture. Later in this stage, which covers a period of approximately 7 to 14 days following initial fluid formation, loculation ensues and pleural fluid pH falls to < 7.30, the glucose decreases to < 60 mg/dL, and the LDH rises to > 1,000 IU/L. However, the fluid may not be purulent. Without treatment or inadequate therapy over the next 2 to 3 weeks, an empyema will develop. The empyema may reside in a single loculus or in multiple loculi, and aspiration of the pleural fluid demonstrates pus that will usually culture an organism, if the patient has not been on prior antimicrobial therapy and the fluid is placed immediately in transport media. The most common organisms responsible for empyema are anaerobes, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and Gram-negative aerobes, with the responsible organism(s) dependent upon the patient's underlying risk factors for pneumonia. Once a patient enters the late fibrinopurulent stage or empyema stage, a contrast chest CT scan should be obtained to better delineate pleural space anatomy and to evaluate the underlying lung parenchyma. Depending on the pleural space pathologic findings, these patients require treatment with either surgery (video-assisted thoracoscopic surgery or thoracotomy) or image-guided chest tubes and fibrinolytic therapy. There is a high failure rate if patients in the late fibrinopurulent or empyema stage are treated with antibiotics alone, therapeutic thoracentesis, or chest tube drainage without imaging; and a second procedure is usually necessary to resolve pleural sepsis. Furthermore, mortality is highest in patients with complicated parapneumonic effusions and...
Empyemas treated with medical therapy alone, therapeutic thoracentesis, or chest tube drainage.

Clinical features that increase the likelihood that a parapneumonic effusion will require drainage include prolonged symptoms, anaerobic infection, failure to respond to antibiotic therapy, and virulence of the bacterial pathogen.\textsuperscript{58,67} Chest radiograph and CT findings that increase the likelihood that a parapneumonic effusion requires drainage includes an effusion > 40% of the hemithorax, an air/fluid level, loculation, multiple loculations, large loculations, and pleural enhancement or thickening on CT scan.\textsuperscript{58,67} Pleural fluid characteristics that increase the likelihood that a parapneumonic effusion requires drainage include empyema, positive Gram's stain or culture, low pleural fluid pH (< 7.30), low pleural fluid glucose, and high pleural fluid LDH.\textsuperscript{58,67,68}

The options for pleural space drainage of a complicated parapneumonic effusion and empyema include chest tube drainage with or without fibrinolytic therapy, image-guided catheter drainage with or without fibrinolytic therapy, thoracoscopy with decortication, standard thoracotomy with decortication, and open drainage. The clinical decision concerning drainage is relatively straightforward for the patients in the exudative stage or those with empyema; the former need antibiotics alone without drainage, while the latter always require pleural space drainage. Patients in the fibrinopurulent stage must be evaluated thoughtfully to estimate the probability of needed drainage. Factors such as the volume of pleural fluid, pleural fluid analysis, presence or absence of loculation, duration of the pneumonia, comorbid disease, immune status, and presence or absence of positive pleural fluid bacteriology, and the organism involved must be considered in the clinical decision.

**Malignant Pleural Effusions**

There are approximately 300,000 cases of malignant pleural effusions diagnosed in the United States annually. Dyspnea is the most common presenting symptom, followed by cough.\textsuperscript{6} Of patients presenting with a massive pleural effusion, approximately two thirds will have malignancy.\textsuperscript{69} When there is contralateral mediastinal shift with a large or massive effusion, the effusion is usually caused by a carcinoma that is not a lung primary. When there is a large or complete opacification of the hemithorax without contralateral shift or ipsilateral shift, lung cancer is the most likely cause, usually squamous cell carcinoma involving the mainstem bronchus; other diagnoses to consider with this radiographic finding include a fixed mediastinum from malignant lymph nodes, malignant mesothelioma, and parenchymal tumor invasion. Bilateral effusions with a normal heart size should also suggest malignancy as the underlying cause; malignancy was the cause in 50\% of 78 patients who presented with these radiographic findings.\textsuperscript{12} The other 50\% of the patients had transudative effusions from hepatic...
hydrothorax, nephrotic syndrome, severe hypoalbuminemia, and constrictive pericarditis, and exudates from lupus pleuritis, esophageal rupture, and tuberculous pleurisy (rare except in HIV-positive patients).

Lung and breast cancer are the most common causes of a malignant pleural effusion, accounting for about 65% of cases; ovarian and gastric cancer are the two next most common carcinomas to metastasize to the pleura and represent 6 to 10% of cases. Lymphoma represents about 10% of cases in series of malignant pleural effusions. Less than 10% of malignant effusions have an unknown primary tumor at the time of diagnosis.70

Virtually all cancers have been found to metastasize to the pleura. Paramalignant effusions are effusions associated with a known malignancy but malignant cells cannot be demonstrated in pleural fluid or pleural tissue.71 Lymphatic obstruction and increased capillary permeability caused by cytokines are important mechanisms causing pleural fluid formation. Endobronchial obstruction resulting in pneumonia and a parapneumonic effusion and atelectasis with a transudative effusion also are causes of a paramalignant effusion. Pulmonary embolism, superior vena cava syndrome, chylothorax, radiation therapy, drug reactions, and severe hypoalbuminemia also can cause paramalignant effusions.

Malignant pleural effusions are typically exudative but on rare occasion can be transudative.6,72 Transudative malignant effusions are most commonly caused by concomitant disease, particularly congestive heart failure, but also may be due to early lymphatic obstruction and endobronchial obstruction producing an atelectatic effusion. The pleural fluid glucose and the pH are low in about 30% of patients who present with malignant effusions.35 The low glucose is generally in the range of 30 to 50 mg/dL and the pH in the range of 7.05 to 7.29. Between 10 and 14% of patients with malignant pleural effusions are amylase-rich73,74; isoenzyme analysis shows that the amylase is primarily of salivary origin. The pleural fluid-to-serum ratio of amylase in malignancy is in the range of 5:1, much lower than in pancreatic disease.74

Finding a low pleural fluid pH (< 7.30) in malignant pleural effusions is associated with a poorer prognosis, a higher positive yield for malignant cells on cytology and pleural biopsy, and less success with chemical pleurodesis than when the pH is > 7.30.35 However, a meta-analysis of more than 400 patients with malignant effusions demonstrated that, even when the pH was in the range of 6.70 to 7.26, 46% of the patients were still alive at 3 months from the time of initial pleural fluid analysis.75 Furthermore, 65% of patients in the lowest quartile of pH (6.70 to 7.26) had successful pleurodesis, compared with 88% of patients who had a pH of > 7.27.76 Although pH directly correlates with survival and less successful pleurodesis, the relationships are not strong, and therefore pH should not be used as the sole criterion for whether or not to recommend pleurodesis; other factors, such as performance status77 and
primary tumor, also need to be considered. Patients should be evaluated on a case-by-case basis when deciding whether or not to recommend pleurodesis.

A low pH and low glucose level occur in far advanced malignant involvement of the pleural space when significant tumor burden and tumor-induced fibrosis involve the pleural surface. The tumor burden and fibrosis inhibit, but not completely, glucose transfer from blood to pleural fluid. The glucose that does move into pleural fluid is utilized at a rate similar to other noninfected pleural fluids, to its end products CO2 and lactic acid. Because these end products are not removed from the pleural space at a normal rate, they accumulate and result in a lower pH.

The yield of cytologic examination and pleural biopsy is high in malignant effusions with a pH of < 7.30 because of the larger tumor burden on the pleural surfaces. Pleurodesis tends to be unsuccessful when the pH is low because the lung may be trapped by tumor or fibrosis or because the tumor burden prevents the chemical agent from initiating mesothelial cell injury that initiates the inflammatory cascade that leads to fibrosis. Furthermore, tumor and fibrosis on the pleural surface may block submesothelial fibroblast migration into the coagulable pleural fluid, preventing collagen deposition.

Adenocarcinoma of the lung is the most common malignancy causing an amylase-rich pleural effusion, followed by adenocarcinoma of the ovary. These tumors produce an ectopic salivary-like isoamylase. A salivary-rich amylase effusion occurring in the absence of esophageal perforation has a high likelihood of being malignant.

**Pulmonary Embolism**

Pleural effusions are found in approximately 40% of patients with a pulmonary embolism. These effusions are virtually always less than a third of a hemithorax, present on the initial chest radiograph, and unilateral. Approximately 50% of patients have evidence of consolidation (pulmonary infarction) on chest radiograph at presentation. In a small series of 26 patients, 27% had transudates. Presumably, the exudative effusions are due to pulmonary ischemia/infarction; and the transudates are caused by atelectasis secondary to chest pain. Features that suggest that a pulmonary embolism is an unlikely cause for a pleural effusion include a large or massive effusion, bilateral effusions, effusions delayed in onset > 24 h from time of presentation, increase in the size of the effusion after 72 h, and effusions unaccompanied by ipsilateral chest pain. Pleural effusions that increase after 3 days with a documented pulmonary embolism suggest the following diagnoses: recurrent embolization, an infected pulmonary infarction, another diagnosis such as pneumonia, or spontaneous hemothorax with heparin therapy.

In summary, pleural effusions due to pulmonary embolism are small and
unilateral and their onset occurs soon after the initial symptoms. These effusions tend to reach their maximum size within a few days. Pulmonary infarctions are associated with larger hemorrhagic pleural effusions that resolve more slowly than effusions without infarction, which are smaller and serous. Ipsilateral chest pain occurs in virtually all patients with pleural effusions from pulmonary embolism. Effusions that are delayed in onset or increase in size later in the course tend to be associated with recurrent embolism, secondary infection or another diagnosis.

**Tuberculous Pleural Effusion**

Tuberculous pleural effusion presents a spectrum from an acute illness simulating pneumonia to indolent disease. The most common symptoms are fever (86%), cough (80%), and chest pain (75%). Tuberculous pleural effusions are small to moderate in size, and a parenchymal infiltrate is seen in ≤ 50% of patients on a standard chest radiograph. Approximately 80% of patients will have a subpleural infiltrate identified on CT. A purified protein derivative (PPD) skin test can be negative on presentation in up to 30% of patients and is probably best explained by mononuclear suppressor cells in the peripheral circulation that are not found in the pleural space. Over time, the PPD will become positive.

The classic pleural fluid analysis in tuberculous pleurisy shows 90 to 95% lymphocytes; however, in acute tuberculous pleurisy and tuberculous empyema, neutrophils predominate. The effusion is serous with a protein in the range of 4 to 5 g/dL. The pH is virtually always < 7.40 and is < 7.30 in approximately 20% of cases. Pleural fluid glucose is similar to serum glucose in most cases and is < 60 mg/dL in 20%. The finding of > 10% mesothelial cells and pleural fluid eosinophilia make the diagnosis unlikely. The nucleated cell count is generally < 5,000/µL.

The diagnostic test with the greatest sensitivity is percutaneous pleural biopsy. The sensitivity of pleural tissue culture ranges from 55 to 85%, and pleural tissue histology from 50 to 85%. The average sensitivity of pleural fluid culture is 30% with the pleural fluid acid-fast bacilli smear being positive in < 10% of patients. When pleural fluid and pleural tissue culture and histology are combined with sputum analysis, a diagnosis should be established in 80 to 90% of patients.

Tuberculous pleural effusion can be treated with a 6-month regimen of isoniazid and rifampin with pyrazinamide for the first 2 months, or with 6 months of isoniazid and rifampin alone in areas with a low percentage of isoniazid resistance. Patients with HIV infection may require longer treatment. Untreated patients with tuberculous pleurisy have a 65% chance of developing pulmonary or extrapulmonary tuberculosis in the ensuing 5 years. The administration of corticosteroids can result in more rapid lysis of fever and
resolution of the effusion; however, it probably does not affect pleural fibrosis.  

Rheumatoid Pleurisy

Rheumatoid pleural effusions occur most commonly in male patients with active articular disease and rheumatoid nodules. The most common time of onset is within the first 5 years following diagnosis. However, rheumatoid effusions can appear 3 years before or > 20 years after diagnosis is established. A rheumatoid pleural effusion may be turbid, have a yellow-green tint, or appear to contain debris. Nucleated cell counts vary from 100 cells/µL in chronic effusions to 15,000/µL in acute rheumatoid pleurisy. Neutrophils predominate in the acute disease and lymphocytes in the chronic form. The pleural fluid total protein can be as high as 7 g/dL. Chronic rheumatoid pleurisy has the classic triad of a glucose level of < 30 mg/dL, an LDH of > 1,000 IU/L, and a pH of 7.00; acute effusions usually will not have the triad. Pleural fluid complement levels are low and pleural fluid rheumatoid factor tends to be > 1:320, but this is a nonspecific finding. Definitive diagnosis of rheumatoid pleurisy can be made by cytologic examination. The pattern of round or oval giant multinucleated cells, large elongated "tadpole"- or "comet"-shaped cells, and a background of granular necrotic material is considered specific for rheumatoid pleurisy. This cytologic picture represents exfoliation of pleural inflammatory cells or necrobiotic nodules into the pleural space, predominantly from the visceral pleura. Corticosteroids may be effective in symptom resolution in acute disease but do not appear to alter the course of pleural fibrosis.

Trapped Lung

Trapped lung occurs when a fibrous membrane covers the visceral pleura, preventing lung expansion. Causes of trapped lung include empyema, rheumatoid pleurisy, malignancy, uremic pleuritis, BAPE, hemothorax, coronary artery bypass graft, and pneumothorax therapy for tuberculosis. Patients with trapped lung can be dyspneic if the area of lung trapped is large or asymptomatic with a small trapped lung. The effusion recurs rapidly following thoracentesis to the pre-thoracentesis volume. Pleural fluid forms with trapped lung because failure of lung expansion creates a space en vacuo, and this negative pressure space fills with fluid. The unilateral pleural effusion can vary from small to large, depending upon the extent of trapped lung.

The fluid is serous and is typically borderline between a transudate and exudate. If the inflammation is remote, the effusion is usually transudative; if there is active or recent inflammation, it is usually exudative. In chronic trapped lung, the nucleated cell count is generally < 1,000 and predominantly mononuclear; pH and glucose are normal. Closer to the time of acute...
inflammation, the cell count and percentage of neutrophils will be higher.

The diagnosis of trapped lung should be considered when an effusion has been present for several months or longer. The diagnosis is presumptive when there is failure of lung expansion on a chest radiograph immediately following thoracentesis (in the absence of endobronchial obstruction) and can be confirmed by finding an initial negative pleural liquid pressure (< 4 to 7 cm H₂O). A pleural space elastance > 19 cm H₂O also correlates strongly with trapped lung. Pleural space elastance is determined by measuring the change in pleural pressure following removal of a volume of pleural fluid. Others have found that the pleural elastance curve is not linear with higher values in the early and late phases of thoracentesis.

Decortication is effective if the underlying lung is relatively normal, and can be performed years after the diagnosis is established. Only patients with large trapped-lung effusions who are symptomatic should be considered for decortication.

Management of Pleural Effusions

The majority of pleural effusions will resolve with effective treatment of the underlying disease, such as congestive heart failure and lupus pleuritis. Chest tube drainage is used for complicated parapneumonic effusions, chylothoraces, and large hemothoraces. Chest tubes are also placed for symptomatic malignant effusions in preparation for chemical pleurodesis. Decortication is commonly used in the management of empyema and should be considered in patients with trapped lung or fibrothorax from any cause. If patients with trapped lung or fibrothorax have significant pulmonary impairment (FVC or total lung capacity < 40% predicted) and are good surgical candidates with relatively normal underlying lung parenchyma, decortication should be performed. Patients with lupus pleuritis, postcardiac injury syndrome, sarcoid pleurisy, and drug-induced pleural disease generally respond to corticosteroid therapy with rapid resolution of symptoms and effusion.

References


5. Antman K, Shermin R, Ryan L. Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over 2 decades 1965 1968. Int J Cancer 1988; 6:147153


38. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that
discriminate between exudative and transudative pleural effusions. Chest 1997; 111:970980


52. Runyon BA, Greenblatt M, Ming RHC. Hepatic hydrothorax is a relative contraindication to chest tube insertion. Am J Gastroenterol 1996; 81:566567

Medical Intensive Care Unit: prevalence, causes and clinical implications. Chest 1997; 111:1018-1023


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