Differential Diagnosis of Pleural Effusions

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Abstract

A variety of disease states are associated with the development of pleural effusions, which sometimes makes the differential diagnosis problematic. Pleural effusions can be classified into two categories, transudative and exudative, based on the characteristics of the pleural fluid. While transudative effusions are the result of changes in hydrostatic or oncotic pressure with no pathological change in the structure of the pleural membrane or condition of the vascular wall, exudative effusions collect in the pleural cavity as a result of pathological changes or structural breakdown of the pleura. In recent years, Light's diagnostic criteria have been most commonly used to differentiate between these two categories of pleural effusion and to help delineate the underlying cause, including malignant tumors, infectious diseases (such as tuberculosis), collagen vascular disease, liver disease, pancreatic disease, iatrogenic causes, and gynecological diseases. Pleural mesothelioma secondary to asbestos exposure has been recognized as a cause of pleural effusion, but diagnostic confirmation is difficult in some cases. When pleural effusion cannot be controlled despite treatment of the underlying cause, pleurodesis can be performed as a potentially permanent method of treatment.

Key words Pleura, Effusion, Transudate, Exudate, Mesothelioma, Thoracentesis

Introduction

A variety of disease states are associated with the development of pleural effusions (Table 1), and depending on the disease, the pleural effusion can either exhibit specific or nonspecific characteristics. A diagnosis of pleural effusion may be suggested by characteristic symptoms (e.g., chest pain, dyspnea) and physical exam findings (e.g., dull lung bases on auscultation and percussion) but definitive diagnosis requires radiological imaging. In particular, X-rays taken with the patient in the decubitus position have high diagnostic sensitivity, and computerized tomography imaging can detect even small amounts of pleural effusion and thus play a significant role in the assessment of intrapulmonary and extrapulmonary lesions. Thoracic ultrasound examination is another effective method of confirming the presence of pleural fluid and determining appropriate access sites for thoracentesis. Because intrapulmonary lesions can go undetected when the pleural effusions are large, CT imaging should be repeated once the fluid has been drained. Further, special attention should be paid to the rate and volume of fluid aspiration during thoracentesis, as rapid or large volume drainage may result in re-expansion pulmonary edema.

Pathophysiology of Pleural Effusions

Pleural fluid is continually secreted by blood capillaries in the visceral and parietal pleural membranes, but most of this fluid is normally secreted from the parietal pleura. Typically, the amount of fluid produced is equal to the amount reabsorbed by the flow of lymph from the visceral pleura. Consequently, the fluid keeps the pleural surface moist and reduces friction between the pleural membranes during respiratory excursion without accumulating in the pleural cavity. This balance between fluid production and absorption

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Table 1 Causes of pleural effusions

Infectious diseases	All pneumonic pleural inflammations, acute empyema, chronic empyema, tuberculosis pleuritis, parasitic infection (lung fluke, etc.)
Malignant tumors	Primary lung cancer, metastatic lung cancer, thymoma (pleural metastasis, pleural seeding), leukemia, Hodgkin's disease, multiple myeloma, malignant pleural mesothelioma
Collagen diseases	Rheumatoid arthritis, SLE, Churg-Strauss syndrome
Gastrointestinal diseases	Liver cirrhosis, acute pancreatitis, liver abscess, subphrenic abscess, peritonitis, esophageal perforation
Cardiovascular diseases	Congestive heart failure, lung infarction, ruptured thoracic aortic aneurysm, Dressler syndrome
Renal disease	Nephrotic syndrome
Gynecological diseases	Meigs syndrome, pleural endometriosis
Iatrogenic diseases	Drugs, post-thoracic/abdominal surgery complications, radiation
Other	External injury, spontaneous pneumothorax, benign asbestos pleurisy, sarcoidosis, yellow nail syndrome, pulmonary lymphangiomyomatosis

Table 2 Light's criteria

1. Ratio of pleural fluid protein to total serum protein is 0.5 or more.

2. Ratio of pleural fluid LDH to total serum LDH is 0.6 or more.

3. Pleural fluid LDH is two-thirds or more of the upper limit for serum LDH.

is maintained through multiple forces, including plasma osmolality, hydrostatic pressure, venous pressure, and capillary wall permeability.

A transudate results from fluid that accumulates in the pleural cavity as a result of a breakdown in the balance between pleural fluid production and absorption in the context of a normal pleural membrane, vascular wall, and lymphatic vessel structure. For example, in some cases pleural fluid accumulates as a result of an increase in fluid production due to increases in hydrostatic pressure, reductions in oncotic pressure, or reductions in absorption. By contrast, an exudate results from fluid that accumulates in the pleural cavity as a result of structural breakdown or increased vascular permeability. In such cases, further tests are often necessary to determine the underlying cause of this pathologic phenomenon.[1]

Characteristics of Pleural Fluid

The characteristics of pleural fluid differ according to the underlying pathological condition but can be broadly classified into two categories, transudative and exudative, and then further into subcategories, such as purulent, bloody, and chylous, according to appearance and smell. Although the classic Rivalta reaction can also be of assistance, Light's diagnostic criteria (Table 2) are most commonly used to differentiate between transudative and exudative effusions. According to this method, an exudative effusion is diagnosed if one or more of three criteria are satisfied. When the pleural effusion is diagnosed as exudate by this criterion in spite of clinically being considered as transudate, the difference of albumin concentration between serum and effusion is greater than 1.2 mg/dl, then the effusion is diagnosed as transudate. The amount of LDH present in the pleural fluid is a rough indicator of the extent of pleural inflammation and is useful in assessing treatment outcomes. Transudative pleural fluid is often present in both sides of the chest and is caused by heart failure, nephrotic syndrome, low-protein leukemia, malnutrition, hypothyroidism, and other systemic diseases.[2]

Since the condition often resolves with treatment of the underlying cause or with diuretics, thoracentesis is typically not required unless there is ventilatory impairment or significant mediastinal displacement.

Diagnosis of Exudative Effusions

In 25% of cases, pleural effusion result from malignant disease. In another 20–40% of cases, biochemical testing, bacteriological examination, and pathological cytology of the pleural fluid fail to identify any underlying cause of disease. In such cases, either cytology is repeated or a pleural biopsy is performed.

Malignant tumors

With malignant tumors, the pleural effusion is often bloody, but ordinary exudative pleural effusion is also possible. Malignant effusion can result from primary cancer of the lungs, pleural mesothelioma, leukemia, lymphoma, or metastatic spread of other tumors to the lung.

The sensitivity of a single pleural fluid cytology examination ranges from 40–80%; thus, in the case of a negative result, the test should be repeated. Pleural effusion is usually unilateral in distribution but can also be bilateral if effusion spreads to the contra lateral pleural membrane. Pleural fluid CEA and other tumor markers are useful diagnostic adjuncts. When there is no tumor detected in the lungs, metastasis from other organs is suspected, and evaluation of the stomach, pancreas, large intestine, ovaries, and breasts should be conducted to identify occult tumors. Indeed, in patients with a history of breast cancer, the disease can recur and manifest with pleural effusions more than 10 years after the original cancer has been ostensibly cured. In other cases in which adenocarcinoma cells are found in the pleural fluid without the identification of any primary tumor, the condition is often designated as carcinomatous pleurisy resulting from primary lung cancer.

Approximately 30–80% of patients with pleural mesothelioma also have pleural effusions, less than half of which are bloody. In such cases, cytological diagnosis is difficult, and detection of elevated levels of pleural fluid hyaluronic acid, which are caused by the accumulation of large amounts of hyaluronic acid in mesothelial cells, may be necessary for correct diagnosis. Measurement of serum mesothelin-related protein (SMRP) also has high specificity for a diagnosis of pleural mesothelioma, but only a limited number of facilities in Japan are able to perform this procedure.

Infectious diseases

Tuberculous pleural effusion is straw-colored fluid contains fibrin and comprises approximately 70% lymphocytes. The incidence of tuberculous bacilli positive culture from pleural fluid cultures is up to 20%, and the data of PCR testing is various results. A pleural ADA of greater than 50 IU/L is suggestive of tuberculosis, but pleural ADA can also be elevated in the context of thoracic empyema, RA, and Hodgkin's disease. Pleural fluid IFNγ levels may also be elevated in the context of tuberculosis, but determination of IFNγ levels is seldom performed.

Parapneumonic effusions secondary to bacterial pneumonia typically resolve with treatment of the underlying pneumonia. However, a foul-smelling purulent pleural fluid containing a large amount of neutrophil cells (e.g., thoracic empyema) may also develop. Diagnostic evaluation of the pleural fluid in patients with empyema typically reveals high numbers of white blood cells, high LDH, low glucose, and sometimes isolation of bacteria. In cases in which the pleural fluid $pH < 7.0$, drainage of the pleural cavity is necessary, and pleural lavage is performed if purulence is strong. Causative microorganisms include *Pneumococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *E. coli*, *Streptococcusmilleri group*, *Mycoplasma pneumoniae*, and anaerobic bacterias such as *bacteroides*. *Nocardia, Actinomyses* species, fungi, and parasitic infections, such as *Paragonimus miyazaki*, *Paragonimus westermani*, and *Echinococcus* are also with pulmonary effusions. Parasitic pleural effusion often contains large amount of eosinophils.

Collagen diseases

Rheumatoid arthritis and SLE can also cause exudative effusions. RA with pleural effusion is more frequently in man than in woman in spite of strong predilection of arthritis for woman. Pleural effusions may sometimes be the initial presenting manifestation of RA. In patients with RA, pleural effusions are characterized by a low blood glucose concentration ($<30\,mg/dl$) in more than 78% of cases due to changes in pleural

membrane permeability. Also, LDH tends to be high, pH tends to be slightly low, and complements, especially C4, are reduced to less than 4 mg/dl.[3]

In SLE, pleural effusion can manifest as aseptic meningitis, pericarditis, and peritonitis. Common symptoms include fever, abdominal pain, and peritoneal signs, which can be confused with a diagnosis of diffuse peritonitis and result in exploratory laparotomy. In patients with SLE, the pleural fluid is often positive for antinuclear antibodies and lupus erythematosus cell. Further, in patients with Churg-Strauss syndrome, the pleural fluid may be rich in eosinophils.

Gastrointestinal diseases

In patients with liver cirrhosis, ascites passes through the diaphragm (e.g., a transudate) and accumulates in the right side of the chest. In cases of subphrenic abscesses, exudative fluid accumulates in the pleural cavity. With pancreatitis, the pleural fluid usually accumulates in the left side of the chest, but cases of fluid accumulating in the right side or both sides have been reported. S-amylase rises if the effusion has been caused by esophageal perforation or rupture. Amylase is also elevated in approximately 10% of malignant pleural effusions.[4]

Chylous pleural effusion

Chylous pleural effusion is suspected when the pleural fluid is opaque and milky white, with a fatty supernatant even after centrifugation. Further, the opacity disappears when the pleural fluid is mixed with ether. Chylous pleural effusion is caused by lymph seeping into the pleural cavity following damage to thoracic ducts as a result of lymphangioleiomyomatosis (LAM), mediastinal lymphoma, external injury, or surgery. A change in diet to low-fat foods can be expected to slow the rate of accumulation and slightly reduce the amount of accumulated fluid.

Other

Sarcoidosis, Wegener's granulomatosis, eosinophilic pneumonia, and iatrogenic pneumonia can also cause fluid to accumulate in the pleural cavity. Benign asbestos pleurisy is diagnosed in cases in which there is a history of exposure to asbestos and in which no other plausible cause for the exudative effusion can be found. This diagnosis requires the absence of a malignant tumor for three years after the pleurisy diagnosis.

When no diagnosis can be made despite assessments of pleural fluid characteristics, cytology, bacteriological testing, or other forms of examination, a pleural biopsy is performed. Although the procedure is performed under local anesthesia using a needle designed especially for this purpose, it is not uncommon for the biopsy to find little more than nonspecific pleural inflammation. In such cases, thoracoscopic lung biopsy can be performed to achieve a definite diagnosis.

Treatment

Treatment of the underlying disease is the principle treatment for pleural effusions. Emergency procedures are required when there is a large amount of fluid, when breathing has been impaired, when cardiac function has been compromised, or when pleural bleeding resulting from external injury cannot be controlled. Drainage of the pleural space should also be instituted promptly in cases of acute thoracic empyema.

Small pleural effusions caused by malignant tumors will sometimes resolve with chemotherapy, but pleurosclerosis is performed after the fluid has been drained in cases where effusion reoccurs or when more that a moderate amount of effusion is present. If pleurodesis is performed on both sides, ventilatory function may decreases and consequently QOL may worsen. So this procedure is usually performed on only one side in Japan.

Drainage of the pleural cavity

The skin and pleura are sufficiently anesthetized, and a catheter is inserted into the pleural cavity. Atropine sulfate can be administered intramuscularly as a preanesthetic medication to prevent vagal reflex. A double-lumen tube may be easier to use when pleural lavage or chemical dosing is planned. Blood pressure may drop, and re-expansion pulmonary edema may occur if drainage is too fast; thus for elderly patients in particular, drainage should be kept to a maximum speed of 1,000 ml/hr and 1,000–2,000 ml/day. When using a large catheter to ensure that no air enters the pleural cavity when the catheter is inserted, it is important that careful attention is paid to the drainage speed, as 1,000–2,000 ml can quickly gush out as the catheter is being secured and connected. As the pleural fluid drains out

and decreases and the lungs expand, the patient should be warned that the procedure will likely provoke coughing. Vital signs should be checked during and after drainage to ensure that general condition is stable.

Pleurodesis

After the pleural effusion is thoroughly drained, medication is injected into the pleural cavity. A drainage tube is clamped securely to enable the medication to flow uniformly for 4–6 hours. After this period, the clamp is released. The tube is removed once drainage has dropped to less than 100 ml per day. This procedure sometimes ends in failure when pulmonary atelectasis occurs or when air enters the pleural cavity. The medication generally used in the case of pleural adhesions is picibanil, but minomycin and the chemotherapy drugs, cisplatin, adriamycin, and mitomycin, are also used.

Pleural lavage

When thoracic empyema is diagnosed, the pleural fluid must be drained. In such cases, pleural lavage is also performed to prevent irregular pleural adhesions and large-scale pleural thickening. After a sufficient amount of pleural fluid has been removed using as thick a catheter as possible, approximately 1,000 ml of sterile normal saline is injected and then drained. This is repeated several times until CRP and other inflammation observations improve. When pleural lavage does not go smoothly due to adhesion of the pleural membranes, one possible solution is to inject 120,000–240,000 units of urokinase, but this treatment is not covered by health insurance. If medical therapy is deemed to have limitations, surgical procedures should be used.

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