

# Diagnostic Work-Up of Pleural Effusions

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## Key Words

Pleural effusion, diagnosis • Cytology • Thoracoscopy

## Abstract

A wide range of diseases may be the cause of an accumulation of fluid in the pleural space. Pleural effusion is a major diagnostic problem, since the pleura is an inner cavity with no direct access. The aim of this review is to provide a practical approach to the investigation of the patient presenting with pleural effusion. This should help to accurately diagnose pleural effusion and keep time-consuming, but necessary, invasive investigations to the minimum.

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## Introduction

The pleural space normally contains between 7 and 16 ml of fluid. Any accumulation of fluid in the pleural space is the result of an increased production exceeding the rate of fluid removal [1]. Pleural effusion as initial manifestation in a patient without accompanying symptoms is a major diagnostic problem. A large number of diseases may be the cause of pleural effusion. Different pathogenetic mechanisms are involved in the creation of pleural effusion: elevated hydrostatic pressure gradient (transudation); increased extravasation of the pleural vessels (exudation) due to a local inflammatory/infiltrative process; decrease in lymphatic drainage caused by a mechanical obstruction, and decreased oncotic pressure [1, 2].

Time may be wasted before an accurate diagnosis is made in patients with pleural effusion, as the pleura is an inner cavity with no direct access, adding some difficulty to the diagnosis. The aim of this review is to provide a practical approach to the investigation of the patient presenting with pleural effusion as an initial manifestation. This should assist in accurate diagnosis, keeping the number of time-consuming, but sometimes necessary, invasive investigations to a minimum.

## Clinical History and Assessment

Pleural effusion may initially be present with or without associated symptoms, with or without a previously known cause, or as a pleural effusion in the evolution of a known disease. Therefore an initial clinical assessment with detailed history should be directed at identifying clues to the possible underlying cause of pleural effusion [3, 4]. The diagnostic approach must be specific to each case as the patient's therapy and prognosis relies on this. A second practical issue is to consider whether there is bilateral pleural effusion, as this is strongly suggestive of transudate, and therefore no thoracentesis needs to be performed [3].

The etiology of pleural effusion may be pleural, pulmonary or extrapulmonary (table 1). Symptoms and signs may be specific to the respiratory system, or non-specific general ones. Dyspnea is a major, although non-specific, respiratory symptom which accompanies pleural effusion, commonly with progressive worsening [3, 4]. It is present in up to 50% of patients with malignant

**Table 1.** Causes of pleural effusion

Transudates
Congestive heart failure
Cirrhotic liver disease
Renal failure
Nephrotic syndrome
Hypoalbuminemia
Atelectasis
Hypothyroidism
Pulmonary embolism (10–20%)
Malignancy (5%)
Exudates
Parapneumonic effusion – empyema
Malignancy
Mesothelioma
Tuberculosis
Pulmonary embolism
Connective tissue disorders
Pancreatitis
Drug-induced
Post-coronary artery bypass surgery
Chylothorax
Esophageal rupture
Asbestos-related benign pleuritis
Sub-diaphragmatic abscess
Paragonimiasis
Ovarian hyperstimulation syndrome
Yellow-nail syndrome

pleural effusion [5]. The pathogenesis of dyspnea caused by a large pleural effusion has not been clearly elucidated but several factors may be involved, including a decrease in the compliance of the chest wall, contralateral shifting of the mediastinum, a decrease in ipsilateral lung volume, and reflex stimulation from the lungs and chest wall [5, 6].

The presence of chest pain may be helpful diagnostically as it implies a degree of inflammatory process suggestive of exudate such as pleural infection, mesothelioma, or pulmonary infarction [3, 7]. Hemoptysis may also help in the diagnosis of associated endotracheal and/or endobronchial lesions [5, 8] or pulmonary embolism [9]. Cough is a nonspecific symptom that may involve both the lungs and pleura. History may also provide useful information, such as exposure to asbestos suggesting mesothelioma or drug-induced pleural effusion [10, 11]. Specific exposure may be overlooked by the patient and it is important to elicit and document any occupational exposure, although sometimes difficult [10]. Drugs may also occasionally be a cause of misdiagnosed pleural effusion [3, 11, 12]. The website [www.pneumotox.com](http://www.pneumotox.com) provides an exhaustive list of drugs causing pleural effusion (table 2).

**Table 2.** Common drugs and therapies causing pleural effusion ([www.pneumotox.com](http://www.pneumotox.com))

Amiodarone
Bromocriptine
Carbamazepine
Cyclophosphamide
Ergots
Granulocyte colony-stimulating factor
Methotrexate
Nitrofurantoin
Penicillamine
Phenytoine
Procainamide
Propylthiouracil
Radiation therapy
Sulfamides

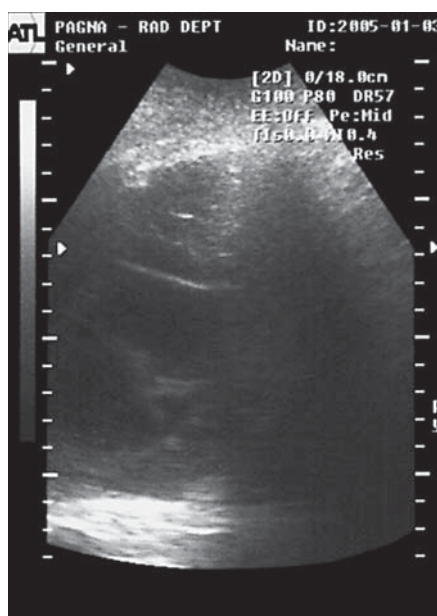
Constitutional nonspecific symptoms, such as fever, night sweats, weight loss, anorexia and restriction of daily activity, may be associated [5, 13, 14]. A great deal of pulmonary and extrapulmonary diseases may give the same symptomatology. Malignancies, such as lung cancer, breast cancer, gastric cancer, ovarian cancer and lymphoma, are often the cause of pleural disease either as an initial manifestation or during disease progression [5, 8, 15]. Connective tissue disorders may also be associated with pleural effusion and their existence should be systematically searched for by meticulous interrogation [13, 16].

Physical examination must be complete, searching for signs that may give a diagnostic clue. Typically on physical examination of the chest, a pleural syndrome is confirmed by the chest radiograph, which shows the extent of the pleural effusion [3, 4]. About 25% of the patients are totally asymptomatic and pleural effusion is discovered only after a routine chest radiograph [17]. The synthesis of the symptoms and signs from the clinical assessment and history must at least suggest the differential diagnosis in up to 75% of the cases, differentiating between the possibility and probability of a transudate or exudate [13]. Table 1 shows the causes of pleural effusion.

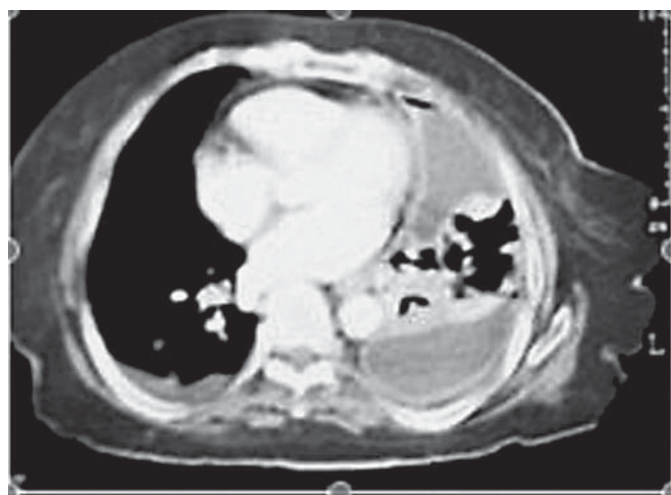
## Imaging

### *Chest Radiography*

The postero-anterior chest radiography is abnormal when pleural fluid is >200 ml. In addition, the lateral radiography may show blunting of the posterior costo-diaphragmatic angle when the fluid exceeds 50 ml. The pres-



**Fig. 1.** Chest ultrasonography of a 44-year-old male patient showing multiple loculations.



**Fig. 2.** Chest computed tomography of a 76-year-old female patient showing an empyema with pleural thickening involving both the parietal and visceral pleura.

ence of massive effusion will lead to a malignant etiology. Furthermore, chest radiography may show additional lesions, either pleural (pleural thickening, plaques, masses), pulmonary parenchymal (consolidation, atelectasis, tumor, diffuse reticulonodular), or mediastinal (enlargement), that will direct diagnosis [17].

### *Chest Ultrasound*

Ultrasonography (US) will detect the presence of as little as 5–50 ml of pleural fluid and is 100% sensitive for effusions [17, 18]. The superiority of US is particularly apparent for small or loculated effusions [19]. Effusions with loculations and fibrous septa may appear as mass lesions on the chest radiograph as fluid climbs into the fissure. Chest ultrasound is helpful in this case (fig. 1). It may also detect tumors in relation with the parietal pleura and the chest wall, aiding biopsy with significant diagnostic yield, low complication rate and cost [19]. Overall, chest US is an important bedside tool in the detection and diagnosis of pleural effusion [17, 20].

### *Chest Computed Tomography*

Computed tomography (CT) of the chest is unequalled in its ability to image the entire pleural space [20]. CT also has the advantage of simultaneously imaging the pulmonary parenchyma and mediastinum. CT is more sensitive than both conventional chest radiography and US for differentiating pleural fluid from pleural thickening and for the identification of focal masses involving the pleura or the chest wall [20] (fig. 2). When more detailed information about the pleural space in relation to other intrathoracic structures is required, CT is superior to US [20].

### *Magnetic Resonance Imaging*

Magnetic resonance imaging has a limited role in the investigation of pleural disease due to poor spatial resolution and motion artifacts [18]. T1-weighted images, obtained after intravenous gadolinium contrast medium, can occasionally be of value in detecting pleural enhancement [18].

### **Pleural Thoracentesis**

Not all patients with pleural effusion should undergo thoracentesis [3]. Obviously patients presenting with transudative effusion according to the history and clinical assessment, such as heart, renal and hepatic failure, should not undergo thoracentesis unless adequate treatment fails. Upon presentation, patients with diseases that may express exudative effusion, such as pulmonary infarction, pancreatitis and connective tissue disorders, should not undergo pleural fluid analysis.

When thoracentesis is considered, pleural fluid must be analyzed for pleural lactate dehydrogenase (LDH) and proteins in order to establish an exudate or a transudate according to Light's [21] criteria (table 3), pleural pH, Gram,

acid-fast bacilli stains and cultures, and cytological analysis. Together with the analysis of the pleural fluid it is important to note the appearance of the fluid that may give important information about the origin of the effusion.

#### *Appearance*

The appearance of the pleural fluid might be useful. Massive and hemorrhagic or sero-hemorrhagic pleural effusions are likely to be malignant [22]. Pus is characteristic of pleural empyema and cloudy fluid may be due to parapneumonic pleural effusion and/or to empyema. An underlying disease such as lung carcinoma should be systematically researched. A chocolate or gelatinous pleural fluid may be the consequence of paragonimiasis. A green-colored fluid may indicate rheumatoid effusion and a 'milky' appearance chylothorax. Classically transudates are limpid, clear yellow-colored fluids. It is also important to smell the pleural fluid because an unpleasant smell suggests infection by anaerobic bacteria [23].

### **Pleural Fluid Biochemical Analysis**

The first question to be stressed is: is this fluid an exudate? The answer in most cases is given by pleural protein. Exudates have a higher protein concentration ( $>30$  g/l) due to an increase in capillary permeability and/or impaired lymphatic drainage [24, 25]. Pleural fluid protein measurements should be interpreted in light of the serum protein. In cases with abnormal serum protein or pleural fluid protein levels close to 30 g/l, the ratio pleural/serum LDH according to Light's [21] criteria (table 3) is highly sensitive (98%) for the diagnosis of exudates, with 83% specificity [26]. To date, no other fluid parameters studied to separate transudates from exudates have given such increased accuracy as Light's criteria [24, 27, 28]. However, rarely it may misidentify a transudative effusion as an exudate, commonly in heart or renal failure patients treated with diuretics. In such cases other criteria such as pleural fluid cholesterol determination have been recommended. A value of  $>60$  mg/dl (1.55 mmol/l) is indicative of exudates [29].

A low pleural fluid pH ( $<7.3$ ) may follow bacterial metabolism and is often associated with a reduced pleural fluid glucose ( $<3.3$  mmol/l) or pleural fluid/serum glucose ratio of  $<0.5$ . This combination is relatively specific for parapneumonic pleural effusions and/or empyemas, but may be seen also in case of rheumatoid, lupus pleural effusions or in malignant pleural effusions due to tumor cell metabolism. A pleural fluid/serum rheumatoid fac-

**Table 3.** Light's [21] criteria differentiating exudates and transudates

The pleural fluid is an exudate if one or more of the following criteria are met:

- Ratio pleural fluid protein/serum protein  $>0.5$
- Ratio pleural fluid LDH/serum LDH  $>0.6$
- Pleural fluid LDH more than two thirds the upper limit of normal serum LDH

tor ratio of  $\geq 1$  can confirm the diagnosis of rheumatoid effusion in patients with clinical symptoms of the disease [30]. Patients with pleural effusions caused by systemic lupus erythematosus usually have pleural fluid/serum antinuclear antibody ratios of  $>1$ . The levels of complement in pleural fluid are low in both rheumatoid and lupus pleural effusions [31]. Pleural effusion of rheumatoid arthritis and systemic lupus erythematosus commonly resolves after adequate treatment of the disease [16, 23].

An increase in intrapleural amylase is characteristic of effusion due to pancreatitis but also may be found in pleural effusion caused by esophageal disruption. The disruption or obstruction of the thoracic duct by a tumor or trauma may result in a chylothorax with the characteristic 'milky' pleural fluid. Confirmation of chylothorax is made by determining the levels of triglycerides in the fluid, which must be  $>110$  mg/dl, and contain chylomicrons but not cholesterol crystals [32].

### **Pleural Fluid Microbiologic Analysis**

Pneumonia is associated with an exudative pleural effusion in up to 57% of cases and is the most common cause of pleural effusion in young patients. Resolution is obtained with antibiotic treatment, but a certain number will progress to an infected pleural space [33, 34]. Significant progress in the treatment of complicated parapneumonic effusion has been shown with the use of intrapleural fibrinolytics [35, 36]. However, the mortality from empyema is as high as 15% and up to 40% of these patients require surgery because medical treatment has failed [33]. Therefore rapid recognition of such patients is important. The bacteriology of pleural infection varies as there are significant differences between community- and hospital-acquired infections [37, 38].

Thoracentesis is essential for a diagnosis of pleural infection. Aspiration may be difficult in empyema or loculated effusions (fig. 3). In such cases chest US should be





**Fig. 3.** Loculations seen during thoracoscopy in a 36-year-old male patient with complicated parapneumonic effusion.

used to localize pleural fluid. The appearance of the fluid must be noted and samples must be taken for Gram's stain and culture [34, 38]. Another sample should be collected in a heparinized syringe to determine pleural fluid pH in a blood gas machine, but only in non-purulent pleural infections [38]. However, pleural fluid cultures are negative in up to 30% of the cases of infection, because either the patient has already received previous antibiotic treatment or the aspiration fluid was not adequately manipulated. Diagnostic accuracy may be increased by analyzing fluid samples in blood culture bottles [34, 37].

Diagnosis is confirmed with a frankly purulent pleural fluid and/or the presence of microbes on Gram's stain or culture [33]. When those criteria are not met, the patient's clinical presentation associated with a pH of  $<7.20$  is suggestive of pleural infection [33]. In pleural infections with multiple loculations [28] and/or a *Proteus mirabilis* infection [39], the possibility of aspirating fluid from a compartment that has a pH of  $>7.20$  should not exclude a complicated parapneumonic effusion, which may also be supported by increased pleural LDH ( $>1,000$  IU/l) and low glucose ( $<35$  mg/dl) [34, 38].

Common causes of community-acquired infection include the *Streptococcus milleri* group (including *S. intermedius*, *S. constellatus* and *S. inonia*), *Streptococcus pneumoniae* and staphylococci, sometimes with associated anaerobes [37, 38]. Less common organisms responsible include other streptococci, enterobacteria, *Haemophilus influenzae*, *Pseudomonas* spp., tuberculosis and *Nocardia*. Hospital-acquired infection, mostly due to pneumo-

nia, surgery, trauma or pleural procedures, is frequently caused by methicillin-resistant *Staphylococcus aureus* or enterobacteria [37].

In TB effusions, fluid smears and culture have a low yield (10–20 and 25–50%, respectively) [40]. Culture of pleural fluid and biopsy improves the diagnostic yield to about 90% [40, 41]. Pleural fluid adenosine deaminase (ADA) may be raised but is nonspecific or negative in HIV infection and is of value in high endemic areas [41, 42]. In association with increased lymphocytes, ADA has 95% sensitivity and 89% specificity in tuberculous pleurisy [43]. Anti-TB treatment is reasonable to consider in the undiagnosed recurrent effusion with a positive tuberculin test (positive in 70% of TB effusions) with a lymphocytic exudate [41].

### Pleural Fluid Cytological Analysis

Differential cell counting adds little diagnostic information. Pleural lymphocytosis is common in malignant and tuberculous effusions but can also be attributable to rheumatoid disease, lymphoma, sarcoidosis, and chylothorax. Eosinophilic ( $>10\%$  eosinophils) pleural effusions are often benign, associated with blood or air in the pleural space, but can be attributable to underlying malignancy in up to 10% of cases and therefore still need to be investigated fully [44]. Causes of pleural eosinophilia include parapneumonic effusion, benign asbestos pleural effusion, Churg-Strauss syndrome, pulmonary infarction, parasitic disease, and drugs. Coronary artery bypass grafting may also cause early left-sided, hemorrhagic, eosinophilic pleural effusions followed later by small lymphocyte predominant effusions [45, 46].

Morphologic analysis of the cells recovered from an effusion may not be sufficient to reach a diagnosis of malignancy [47, 48]. Commonly, the distinction between atypical mesothelial cells and metastatic carcinoma is impossible because of the notorious reactivity of mesothelial cells [47]. When considering the primary site of a metastatic malignancy three factors are crucial: (1) the type of cell present in the effusion; (2) the location of the effusion in relation to the age and sex of the patient, and (3) the presence and nature of a tumor in a distant site [47]. If any of these three crucial data is missing, the puzzle may be resolved by astute interpretation of cytologic details and the use of ancillary methods such as immunocytochemistry [47].

Pleural fluid cytology is the simplest definitive method to obtain a diagnosis of malignant pleural effusion.

Malignant effusions can be diagnosed by a single pleural fluid cytology specimen in 60% of the cases for carcinomatous effusions but only 20–30% for mesothelioma [48]. This yield is only slightly increased if repeated cytology specimens are analyzed [48]. The cytological yield is higher for adenocarcinoma and when smears and blocks are used [48]. Overall, the diagnostic yield of pleural cytology shows large variation in different series. The diagnostic yield is dependent on such factors as the extent of disease and the nature of the primary malignancy [5]. Immunohistochemical epithelial and glandular markers may help to confirm epithelial malignancy and differentiate mesothelioma from adenocarcinoma [48].

### Other Markers

Several tumor markers, such as carcinoembryonic antigen, CA-125, CA-19-9, CYFRA 21-1, nonspecific enolase, have been tested in patients with malignant pleural effusion [49–51]. Although the results seem to be controversial as to the usefulness of these tumor markers in the differential diagnosis of pleural effusions, even between malignant and nonmalignant, some authors propose specific tumor markers for the diagnosis of pleural effusions due to bronchogenic carcinoma [52, 53]. A reasonable attitude may be that tests should be performed in a selected population of patients with negative cytology and 'suspect' clinical outcome [54].

There are a number of studies on various novel markers, such as acute phase proteins [55], oncogenes [56], cytokines involved in inflammation [57, 58], and matrix metalloproteinases [59], in the differential diagnosis between transudates and exudates and/or between malignant and benign pleural effusions. Although some may be adequate markers for pleural effusion differentiation, they are not as sensitive, specific, or cost- and time-efficient as the easily available standard tests [60]. Biochemical or biological markers in malignant pleural effusions, as well as in the serum, cannot replace routine cytopathologic examination in the diagnosis of the disease and predicting the outcome of the patient without firm diagnosis [61].

### Pleural Biopsy Procedures

#### *Blind Pleural Biopsy*

The diagnostic yield of closed pleural biopsy alone in malignant pleural effusions is about the same as pleural cytology. A combination of both techniques seems to im-

prove diagnostic yield [5, 62]. The low diagnostic yield of closed pleural biopsy is due to factors such as early stage disease with small pleural extension, location of tumors in areas of the pleura unreachable by the needle, including the visceral pleura [63], as well as the inexperience of the physician [64]. The diagnostic yield of blind biopsy increases with the number of specimens taken in malignant pleural effusion [65]; at least 4 biopsy samples are needed for accurate diagnosis [65]. As pleural invasion is preferentially located at the base of the hemithorax, it is recommended that the sample be taken from the lowest part of the costal pleura in order to achieve a higher diagnostic success [63, 66].

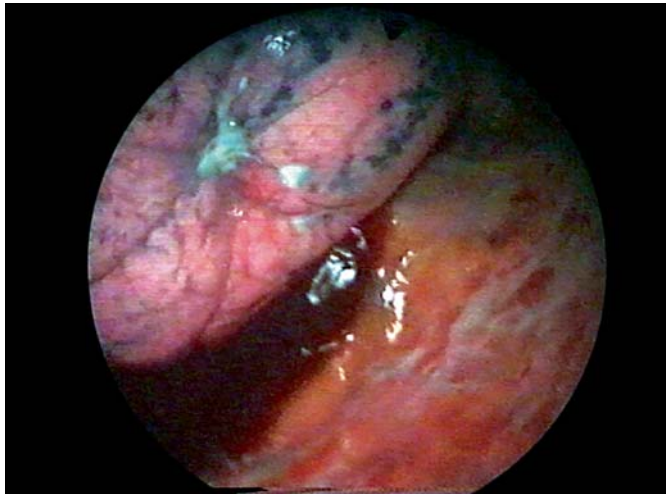
In benign pleural effusion the diagnostic yield of blind pleural biopsy depends on the etiology. For tuberculous pleurisy the diagnostic accuracy is about 100% when it is associated with culture of acid-fast bacteria, as well as in combination with pleural ADA and a lymphocyte/neutrophil ratio of  $\geq 0.75$  [43]. In patients with suspected TB pleurisy, one biopsy sample might be sufficient for diagnosis, as multiple samples do not increase the diagnostic yield since the disease is widely spread in the pleural cavity [65].

In connective tissue disorders associated with pleural effusion, blind biopsies offer little to the diagnosis as typical histological findings of the disease are occasionally found. Most patients present a nonspecific histological appearance of chronic and/or granulomatous or fibrotic pleuritis [67]. However, patients with pleural effusion associated with connective tissue disorders are more likely to be diagnosed according to the associated findings on clinical presentation and/or laboratory tests. Studies are lacking to evaluate the diagnostic accuracy of different bioptic techniques in such patients.

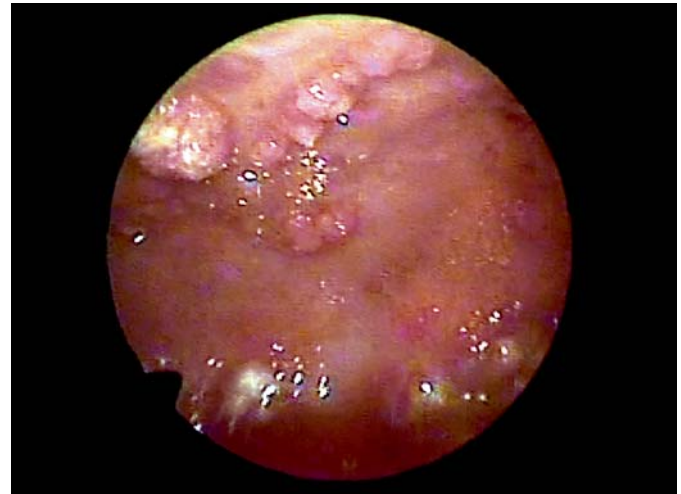
#### *Thoracoscopy*

Thoracoscopy is the 'gold standard' in the diagnosis of pleural effusion as it is indicated when less invasive tests have failed [3, 68–70]. It is a simple and safe method with a diagnostic yield of 93–97% [71–74] in patients with malignant pleural effusion. The method is performed either under local or general anesthesia by one or two ports of entry [75, 76]. Before thoracoscopy is indicated, and to avoid complications, the performance status of the patient should be considered together with limitations such as coagulation problems, with or without anticoagulant therapy, thrombocytopenia, severe respiratory insufficiency with hypercapnea, and unstable cardiac status.

In developed countries, thoracoscopy is very important as there is a significant likelihood of malignancy in



**Fig. 4.** Peripheral lung adenocarcinoma of the left lower lobe with satellite nodules on the visceral pleura also invading the parietal pleura in a 41-year-old male patient.



**Fig. 5.** Masses from an epithelial mesothelioma of the parietal pleura in a 56-year-old patient.

**Table 4.** Primary tumor site in patients with malignant pleural effusion

Lung carcinoma	37.5%
Breast carcinoma	16.8%
Lymphoma	11.5%
Genitourinary carcinomas	9.4%
Gastrointestinal carcinomas	6.9%
Other carcinomas	7.3%
Unknown primary	10.7%

Modified from Antunes et al. [91].

patients with undiagnosed pleural effusions [13]. Indeed, in developed countries where the incidence of tuberculosis is low, more than 50% of the cases of undiagnosed pleural effusion are due to carcinomas, the second most common (10%) being tuberculosis [71, 77, 78]. After thoracoscopy less than 10% of the cases of initially suspected pleural effusion are diagnosed as having nonspecific (idiopathic) pleuritis [71, 77]. During the follow-up period of those with nonspecific pleuritis, only 4–8% of patients present a malignancy after repeated thorascopies [79, 80]. Most of the cases (up to 80%) follow a true benign course with spontaneous resolution, while few cases are ‘idiopathic’ [79, 80].

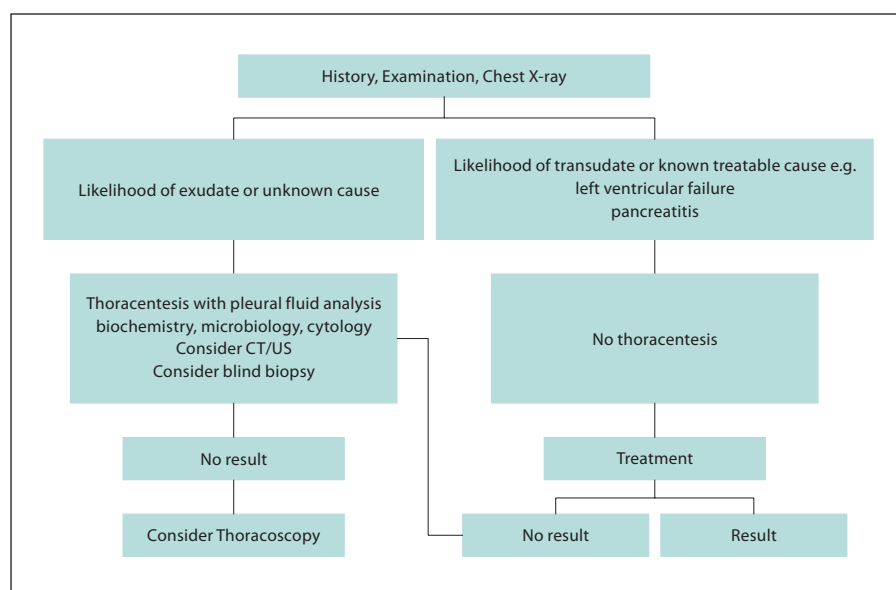
Thoracoscopy also provides information on the extent of underlying diseases such as lung carcinoma [8, 74, 81] and mesothelioma [82, 83]. In case of lung cancer, thoracoscopy is performed not only to diagnose but also to

detect pleural infiltration (fig. 4) and, for non-small-cell lung carcinoma, to determine T4 stage disease, which excludes surgical resection and indicates a poor prognosis for the patient [8, 81, 84]. The role of thoracoscopy in early stage mesothelioma is essential to determine the use of multimodality treatment based on extrapleural pneumonectomy [82]. Thoracoscopy in mesothelioma (fig. 5) is also necessary in advanced stage disease to diagnose and map lesions of the pleural cavity in order to evaluate the possible treatment response with a ‘second look’ [83].

Thoracoscopy with talc poudrage, under local anesthesia, provides palliation of dyspnea and discomfort due to the amount of pleural effusion in malignancies. Although the ideal sclerosing agent has not yet been found [85], talc poudrage is a safe, low-cost and more efficient method than pleurodesis (up to 90% success) [86, 87] and has mild side effects such as fever [87, 88].

### Bronchoscopy

When an endotracheal and/or endobronchial lesion is suspected, fiberoptic bronchoscopy is indicated [89]. After initial workup, pleural effusion of unknown origin is associated with bronchogenic carcinoma in more than 30% of the cases [89–91] (table 4). Also, fiberoptic bronchoscopy is useful in assessing the extent of the disease in the tracheobronchial tree, which is important for treatment and prognosis [89].



**Fig. 6.** Pleural effusion work-up.

## Conclusion

The diagnosis of pleural effusion is difficult, as the pleura is an inner cavity with no direct access. The various noninvasive diagnostic techniques are of limited diagnostic yield and generally very much dependent on the underlying disease, the disease distribution in the pleural cavity, and the experience of the physicians. These are the main reasons why time is wasted before diagnosis in patients with pleural effusion. This delay in diagnosis might

lead to important ‘side effects’ such as inadequate treatment and poor prognosis, together with discomfort and deterioration in the quality of life of the patient.

Thoracoscopy, performed under local anesthesia in the endoscopy suite, gives solutions in more than 95% of undiagnosed pleural effusions, with minimal and mild complications. It is a method widely applied by many respiratory physicians to whom a patient with pleural effusion must be referred immediately after a negative initial work-up (fig. 6).

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