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Exudative Pleural Effusion: Approach to Management

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INTRODUCTION

The normal pleural space contains approximately 1 ml of fluid. Pleural fluid is filtered in the parietal pleural compartment from the systemic capillaries down a small pressure gradient into the pleural space. Pleural fluid secretion is greatest at the apex while absorption is maximum towards the diaphragm and mediastinum, where the parietal lymphatics are concentrated. The fluid is drained out predominantly through the stomata of the parietal lymphatics lying between the parietal mesothelial cells. These stomata merge into small lymphatic channels which, in turn, form larger vessels ultimately drain into the mediastinal lymph nodes. The parietal stomata possess valve-like structures to guarantee a unidirectional flow of fluid out of the pleural space[1]. The lymphatic drainage system can cope with up to several hundred milliliters of additional fluid per day without the development of an effusion. Therefore any pleural effusion represents a severe imbalance of pleural fluid formation and/or drainage capacity. In case of congestive heart failure, even a small pleural effusion signals a severe pulmonary fluid overload.

The visceral pleura does not play a significant role in pleural fluid turnover.

One implication of pleural fluid dynamics is that, despite statements to the contrary, effusions in CCF do not indicate right heart failure. It is actually a function of elevated pulmonary capillary wedge pressures rather than to pulmonary artery or right heart pressures[2]. This is due to left ventricular dysfunction with pathological flow of interstitial pulmonary fluid into the pleural space across the visceral side. In animal models of cardiogenic pulmonary edema, it has been shown that up to 25% of the edema fluid flows via the visceral pleura into the pleural space. Therapeutic centesis hence has a role in CCF by reducing systemic fluid overload and thus contributing to a decrease in pulmonary capillary pressures.

In several pathological states leading to increased formation or reduced drainage (Table 1), pleural fluid can accumulate, producing symptoms, and becomes a management issue. If correctly worked up, it also holds the key to correct diagnosis.

Pleural effusion can be transudative or exudative; this review will deal exclusively with the latter.

Table 1: Pathological basis of pleural effusion

Condition	*Example*
1. Increased hydrostatic pressure	Congestive cardiac failure
2. Reduced oncotic pressure	Hypoalbuminemia
3. Lymphatic block	Malignancy
4. Increased permeability	Pneumonia
5. Decreased intra-pleural pressure	Atelectasis
6. Diaphragmatic defects	Hepatic hydrothorax
7. Rupture of thoracic duct	Chylothorax

Definition

A pleural fluid protein level of > 35 gm/L is normally considered an exudate while a level of < 25 gm/L is suggestive of a transudate. However, a more precise diagnosis is made by using Light's criteria[3] (Table 2). Light's criteria needs measurement of both pleural and serum protein analysis. Criteria have also been suggested to diagnose exudative effusion based on pleural fluid analysis alone (Table 3). However, for all practical purposes, Light's criteria are most specific and

Table 2: Light's criteria

1. Pleural fluid serum protein ratio more than 0.5.
2. Pleural fluid serum LDH ratio more than 0.6.
3. Pleural fluid LDH levels more than two thirds normal serum value

Table 3: Defining exudate based on pleural biochemistry alone

1. Pleural fluid LDH level more than 0.45 of upper limit of normal serum value.
2. Pleural fluid cholesterol more than 45 mg%
3. Pleural fluid protein level more than 2.9 gm%.

sensitive. In a meta-analysis of 8 studies with 1448 cases, Light's criteria had the best discriminative value[4].

Caveat: In 20% of cases of transudates in persons exposed to diuretic therapy, such as in congestive cardiac failure, a chronic transudative can resemble an exudate by Light' criteria. If the serum minus pleural *protein* concentration is greater than 3.1 gm%, the effusion is transudative. A serum to effusion *albumin* gradient greater than 1.2 gm% also indicates that the pleural effusion is most likely a true transudative effusion[5].

Recently, serum and pleural fluid NT-proBNP concentrations of 4,000 ng/L was found to have sensitivities and specificities of 90 and 93%, respectively, for the diagnosis of heart failure and thus can be useful in a situation as described above[6].

Differential Diagnosis

An exhaustive list of conditions giving rise to an exudative effusion is given in Table 4. For all practical purposes, most of them are rare and the diagnosis is obvious. The first five are the commonest causes of pleural effusion in India.

Table 4: Causes of exudative pleural effusion

1. Parapneumonic
2. Tuberculous
3. Malignancy
4. Pulmonary embolism
5. Collagen-vascular (rheumatoid arthritis, lupus)
6. Postcardiac injury syndrome
7. Pancreatitis
8. Trauma
9. Sarcoidosis
10. Esophageal perforation
11. Radiation pleuritis
12. Drug-induced (Amiodarone, nitrofurantoin)
13. Asbestos-related (Benign Asbestos Pleural Effusion, BAPE)
14. Parasitic (Echinococcus, filarial, paragonimiasis)
15. Chylothorax
16. Meigs syndrome
17. Yellow nail syndrome

Investigations

Investigations are of three types[7]. Initial investigations are biochemical and imaging. However, the gold standard is a tissue diagnosis based on pleural fluid cytology or pleural biopsy.

Pleural Aspiration

A diagnostic pleural fluid sample should be gathered with a fine bore (21G) needle and a 50 ml syringe. The sample should be placed in both sterile vials and blood culture bottles and analysed for protein, lactate dehydrogenase (LDH, to clarify borderline protein values), pH, Gram stain, ZN stain, cytology, and microbiological culture.

Pleural aspiration should not be done if a transudate is suspected, which can be done easily based on the clinical picture.

The appearance and odour of the fluid can be diagnostic some conditions:

- Purulent fluid indicates an empyema.
- Bile stained-chylothorax – biliary fistula
- Anchovy sauce-ruptured amoebic liver abscess
- Milky, opalescent fluid-chylothorax—secondary to lymphatic obstruction by malignancy or thoracic duct injury by trauma or surgery.
- Bloody fluid with hematocrit level of more than 50% of the peripheral hematocrit level is a hemothorax – due to malignancy, embolism and trauma (Hct < 1% is not significant)
- Putrid odor suggests an anaerobic empyema.
- Uriniferous smell suggests urinothorax (in ipsilateral obstructive uropathy). Pleural fluid creatinine is more than serum creatinine.
- Turbidity persisting after centrifugation is suggestive of a chylothorax or a pseudo-chylothorax. Chylothorax has triglyceride level of > 110 mg%, while pseudo-chylothorax has cholesterol level of > 200 mg%.

Biochemical Investigations

Pleural fluid and serum protein and LDH are essential for diagnosing an exudative effusion. Sometimes, a cholesterol value is also useful.

Glucose and pH

The next set of investigations is a pH value and glucose levels, which are interlinked and is reduced in most conditions. Pleural fluid pH does not change

significantly over several hours if collected in a heparinized syringe.

- Pleural fluid pH less than 7.2 indicates the need for urgent drainage of the empyema.
- Pleural fluid pH more than 7.3 suggests that the effusion may be managed with systemic antibiotics alone.
- Pleural glucose concentration of <30 mg % indicates rheumatoid pleuritis or empyema.
- Levels of 30-60 mg% suggest malignant, tuberculous or lupus effusion, or esophageal rupture.

Adenine Deaminase (ADA)

ADA is produced by most cells and catalyzes the conversion of adenosine to inosine[8]. There are several isoforms of ADA, but the prominent ones are ADA1 and ADA2, which are coded by different gene loci. ADA1 isoenzyme is found in all cells, with the highest concentration found in lymphocytes and monocytes, whereas ADA2 isoenzyme appears to be found only in monocytes. ADA2 is the predominant isoform in the tuberculous pleural effusion, accounting for 88% of total ADA activity. In clinical practice, the difference in the use of total ADA and isoform ADA2 is not significant and total ADA value is taken to represent ADA2.

False-positive results can occur in less than 3% cases; this occurs with lymphoma, rheumatoid arthritis, SLE, and rarely adenocarcinoma. A different isoenzyme (ADA-1) is elevated in the presence of empyema, accounting for 70% of ADA activity. This cause for elevated total ADA activity can be distinguished by doing isoenzyme studies but as this test is expensive, it best avoided by not ordering, or ignoring ADA when cytology is suggestive of empyema.

Elevated pleural fluid ADA level (> 40 U/L) in a lymphocyte predominant exudate predicts tuberculous pleural effusion with a sensitivity of 90 to 100% and a specificity of 89 to 100%.

Tumor Markers

A panel of 4 tumor markers (carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA 125), carbohydrate antigen 15-3 (CA 15.3), and cytokeratin 19 fragments) was used to differentiate malignant from benign effusions—at least one was elevated in 54% of cancer cases while none was in benign cases. However, due to low sensitivity and specificity, it is suggested that presence of elevated levels of tumor markers in the pleural fluid should only serve as a *pointer* for a more invasive procedure to establish the diagnosis of malignancy and in itself, *should not be used to establish* the diagnosis[10].

Markers for Connective Tissue Disorders

Measurement of C4 complement in pleural fluid may be of help, with levels below 0.04 g/l in all cases of rheumatoid pleural disease. Rheumatoid factor can be measured on the pleural fluid and often has a titer of >1:320. However, it can be present in effusions of other etiology and often mirrors the serum value. The presence of LE cells in pleural fluid is diagnostic of SLE. However, ANA values are of no use—although they are elevated in most lupus effusions, they usually mirror serum values, and false positives are common, especially in malignancies[11].

Amylase

Elevated levels (higher than the upper limits of normal for serum, or the pleural fluid/serum ratio is >1.0) occurs in acute pancreatitis, pancreatic pseudocyst, esophageal rupture, ruptured ectopic pregnancy, or pleural malignancy (especially adenocarcinoma). Approximately 10% of malignant effusions have raised pleural amylase levels. Pleural amylase due to esophageal rupture is of salivary origin while that due pancreatitis is of pancreatic origin, and this can be distinguished by isoenzyme analysis. This is useful test as occasional effusions are due to occult pancreatic origin.

Imaging

Chest X-ray

Costophrenic angle is blunted in PA view if > 200 ml fluid is present.

Posterior CPA in a lateral film is blunted with as little as 50 ml fluid.

Lateral decubitus film is useful to distinguish between pleural thickening and free fluid. Thickness of free fluid of 10 mm or more predicts "tappable" fluid.

In a supine film (as in a critically ill patient), evidence of pleural effusion include haziness of hemithorax with preserved vascular shadows, loss of silhouette of the hemidiaphragm and thickening of minor fissure.

Subpulmonic effusion can be missed on erect PA view and can be demonstrated on decubitus films or by ultrasound scan.

Ultrasound Scan

Thoracic ultrasound is useful in:

- Estimating the amount of pleural fluid (more accurate than CXR PA)
- Guided tap when fluid is minimal or loculated and when a blind tap fails[12]
- Distinguishing transudates from exudates: those with septated and homogenously echogenic patterns are always exudates, whereas hypoechoeic effusions may be either.

CT Scan

Contrast enhanced helical CT scan diagnose pulmonary embolism better than a VQ scan; it also can detect the site of the origin of the thrombus[13].

Contrast enhanced CT scan performed after full drainage of pleural effusion can differentiate between benign and malignant pleural disease. CT scan features suggestive of malignant disease include (Leung's criteria[14]:

- Nodular pleural thickening,
- Mediastinal pleural thickening,
- Parietal pleural thickening greater than 1 cm
- Circumferential pleural thickening.

Infiltration of chest wall or diaphragm is also characteristic of malignancy.

CT scan also differentiates parenchymal lung abscess from empyema—commonly displays the *'split pleura sign'*, with lenticular opacification of the infected fluid.

Perfusion Scan

This was useful in diagnosing pulmonary thromboembolism, but this role is being gradually supplanted by helical CT scans.

MRI

A comparative study of CT versus MRI[15] showed that high signal intensity in relation to intercostal muscles on T2-weighted and/or contrast-enhanced T1-weighted images in MRI were significantly suggestive for a malignant disease. Using morphologic features in combination with the signal intensity features, MRI had a sensitivity of 100% and a specificity of 93% in the detection of pleural malignancy. The authors concluded that MRI is superior to CT in differentiation of malignant from benign pleural disease.

PET Scan

Positron emission tomography (PET) scans are useful for differentiating between benign and malignant pleural diseases (sensitivity 97% and specificity 88.5% in one study). It has been reported as helpful in evaluating the extent of disease in mesothelioma.

Tissue Diagnosis

Cytology

Cytology can give a clue about the etiology based on the predominant cell (Table 5). Cytology is of importance to establish the diagnosis of malignancy in a lymphocyte predominant effusion where ADA levels are normal. In four major series totaling 1370 patients, malignant cells were detected only in 60% (range 40-87%); however, success rates increased with:

- Repeat samples (first sample 65% positive, second additional 27% and third, further 5%).
- Combining with pleural biopsy (+ 7%)
- Preparing both cell blocks and smears.

Table 5: Differential diagnosis of cytology report

Neutrophil predominant (> 50%):
With parenchymal opacities:
Parapneumonic effusion
Pulmonary embolism
Bronchogenic carcinoma
Without parenchymal opacity:
Pulmonary embolism
Viral infection
Acute tuberculosis (10%)
Benign asbestos pleural effusion (BAPE)
Eosinophilic effusion (> 10% eosinophils)
Parapneumonic effusion
Tuberculosis
Drug induced (nitrofurantoin, bromocryptine, dantrolene)
Pulmonary embolism
Churg Strauss syndrome
Parasitic disease (paragonimiasis)
BAPE
Malignancy (rare)
Air or blood in pleural cavity
Lymphocyte Predominant (> 50%):
Tuberculosis
Malignancy
Sarcoidosis
Chylothorax
Rheumatoid disease

Immunohistochemistry (IHC) studies are useful to distinguish mesotheliomas from adenocarcinoma, and amongst the latter, to identity primary site if unclear (e.g., breast versus lung). Flowcytometry is useful to subtype lymphomas.

Cytology can be negative if:

- the effusion is due to another etiology (e.g. embolism associated with cancer)
- Some cancers like squamous cell cancer, sarcomas and Hodgkin's lymphoma.

Pleural Biopsy

Pleural biopsy can be blind (Abrams' or Copes needle), or image guided (cutting needle) biopsy.

Blind pleural biopsy using an Abram's needle is a safe procedure in experienced hands, with a high positivity for tuberculous and malignant effusion. The diagnostic yield is similar to that of Copes needle but the sample size is bigger[16]. At least 4 samples should be taken and from the *same* site—changing the site does not increase diagnostic yield.

With tuberculous effusion, the initial needle biopsy is positive for granulomas in 50–80% of patients; a second biopsy will be positive 10–40% of the time. A specimen of the pleural biopsy should also be cultured for mycobacteria as the combination of microscopy and culture of the pleural biopsy makes a positive diagnosis in more than 80% of patients.

Needle biopsies are less reliable in malignancies (45% positivity), whereas fluid cytology is likely to be more positive. This is due to the late involvement of parietal pleural, which also tends to be patchy in nature. However, the combination of cytology and biopsy should establish the diagnosis in > 80% cases.

Complications of Abrams' pleural biopsy include site pain (1–15%), pneumothorax (3–15%), vasovagal reaction (1–5%), hemothorax (<2%), site hematoma (<1%), transient fever (<1%) and, very rarely, death secondary to hemorrhage. If a pneumothorax occurs, only 1% requires chest drainage.

Pleural malignant deposits tend to occur near midline and near diaphragm, where image guided biopsies are safer. A diagnostic accuracy of 90% is possible. In a direct comparison of blind vs CT guided biopsy, the latter had a far higher sensitivity (87% versus 47%) with a specificity of 100%. Repeat biopsy is avoided in 40% of patients (with fewer passes) if CT-guided biopsy is used as the preliminary investigation.

Thoracoscopy

> 20% of patients with pleural effusion undergoing pleural fluid analysis and closed-needle pleural biopsy remain undiagnosed, and in up to 22% of cases, a malignancy is detected later. Thoracoscopy is helpful in such cases and is of two types: medical and surgical (Video assisted thoracoscopic surgery or VATS). Medical thoracoscopy is generally characterized as thoracoscopy performed under local anesthesia in the endoscopy suite with the use of nondisposable instruments, and is generally for diagnostic purposes. In contrast, VATS is a keyhole surgical procedure in the operating room, under general anesthesia with one-lung ventilation using disposable instruments, generally for therapeutic purposes[17].

Thoracoscopy can detect malignancy (if present) in > 90% of cases; however, more than 50% cases of idiopathic effusion referred for thoracoscopy will be negative. In one series of 620 patients[18], non-invasive workup established the diagnosis in all except 48 cases (8%). Thoracoscopy established the diagnosis of malignancy in another 24 cases (50%), and benign conditions in 16 (33%); which still left 8 cases undiagnosed (17%).

Ferrer[19] has put forward four criteria that were strongly predictive of malignancy:

- CT scan suggestive of cancer
- Symptomatic period of greater than 1 month
- Sero-sanguinous effusion
- Absence of fever.

Malignancy was detected by thoracoscopy in all patients who fulfilled the four criteria and in 74% of those with three criteria. It is suggested that a conservative approach may be adopted and thoracoscopy not performed in the subgroup of patients with one or none of the described criteria. This approach seems to be more logical than the use of tumor markers.

Common adverse events include subcutaneous emphysema (6.9%), cardiac arrhythmia (0.35%), air embolism (rare); no deaths have been reported.

Fibreoptic Bronchoscopy (FOB)

FOB has a limited role in pleural effusion. In patients with an isolated pleural effusion, with no hemoptysis or pulmonary abnormality on the chest radiograph, the yield from bronchoscopy is low (16%) whereas pleural investigation yielded a positive diagnosis in 61%. If bronchoscopy is deemed necessary, it should be performed after pleural drainage in order to perform

adequate bronchoscopy without extrinsic airway compression by pleural fluid.

APPROACH TO DIAGNOSIS

Three questions arise when confronted with a pleural effusion[20]:

1. Should a thoracocentesis be performed?
2. Is it a transudate or an exudate?
3. If it is an exudate, what is the etiology?

While most patients with pleural effusion need a diagnostic or a therapeutic tap, in two situations, this should be deferred; one, if it is too small and two, if there is congestive cardiac failure. In a lateral decubitus film, if the thickness of fluid is < 10 mm, a tap is not recommended as the chance of obtaining fluid is less than the chance of puncturing the lung. However, an ultrasound guided tap can be done if the thickness is 10-15 mm.

The second step is to confirm the presence of an exudate by Light's criteria. A lymphocyte predominant exudate should undergo ADA analysis and a value of > 40 U/L establishes the diagnosis of TB. The excluded group is a cause for worry as a high percentage of them are likely to harbor a malignancy. They should undergo an imaging procedure; CT scan/MRI/PET scan. CT scan would establish a pulmonary embolism or suggest a malignancy. The diagnosis of the latter can be then confirmed by a blind pleural biopsy or one guided by CT scan. Persons fulfilling Ferrer's criteria above can proceed to a thoracoscopy as the possibility of a malignancy is high. Those remaining undiagnosed and fulfilling the 6 criteria given below (see undiagnosed effusions) can be observed safely.

TUBERCULOUS PLEURAL EFFUSION

Tuberculous pleural effusion usually resolves spontaneously, but in more than two-third cases, will relapse within 5 years with parenchymal disease. Hence, the necessity to diagnose and treat this condition. However, as the Mantoux test is negative in 30% and pleural fluid culture is negative in 75% (as the fluid is due to a delayed hypersensitivity reaction to rupture of a Ghon's focus into the pleural cavity), specific diagnosis of tuberculous effusion presents a problem[21].

Needle biopsy of the pleural for histology and culture significantly improves diagnosis in up to 86% of cases; this combined with pleural fluid and sputum cultures increase the yield to 90%. Studies have reported variable results for the diagnosis of tuberculous pleural effusion; reported sensitivities range from 10 to 47% for pleural fluid culture, 39 to 84% for pleural biopsy histology and 56 to 82% for pleural biopsy culture. However, the last facility does not exist in many centers, and is invasive and time consuming. 10 to 20% of patients will not have positive culture results or granulomas on biopsy specimen.

Five tests are available to help the clinician. They are polymerase chain reaction (PCR), lysozyme levels, interferon gamma and interleukin 16 levels, and adenine deaminase levels. Polymerase chain reaction has a relatively low sensitivity in pleural fluid (0.42 to 0.81) and is fairly expensive. The sensitivity of an elevated interferon level appears better (0.89 to 0.99) but this test is not freely available. Recently, interleukin 16 (IL-16) has been found to be significantly elevated in tuberculous effusion and has been found useful for differentiating this from malignant effusions. Lysozyme pleural fluid to serum ratio improves the sensitivity of the pleural fluid ADA.

ADA level of > 40 U/L in a lymphocyte predominant exudate is highly specific and sensitive for tuberculous effusion. However, it is often recommended that ADA should not be used as a diagnostic test or as an alternative to biopsy and culture[9].

Treatment of tuberculous effusion is as for parenchymal TB, with the standard EHRZ for 2 months followed by HR for four months. The role of initial steroids is controversial with some centers using a short course for 2 to 4 weeks; there is no evidence for or against this practice[22]. Intercostal tube drainage of tuberculous effusion has not been found to be useful[23].

EMPYEMA

Pneumonia is associated with an exudative pleural effusion in up to 57% of cases. The majority resolves with antibiotic treatment, but some can progress through an exudative phase ('simple parapneumonic effusion') to a fibrinopurulent stage ('complicated parapneumonic effusion'), eventually organizing into fibrotic scar tissue formation, or proceeding to a frankly purulent empyema[24] (Table 6). Other causes of empyema included thoracic surgery (20%), trauma (5%), esophageal perforation (5%); rare causes include thoracocentesis, pneumothorax and abdominal infection. Empyema may also present as an indolent illness with constitutional symptoms and be confused with malignancy. Complications of empyema include bronchopleural fistula, lung abscess, and "empyema necessitatis" (spontaneous perforation through the chest

Table 6: Parapneumonic effusions

Type of effusion	*Appearance*	*Biochem/microbiol*	*Treatment*
Parapneumonic effusion-simple	Clear fluid	Exudate	Drainage not needed
Parapneumonic effusion – complicated	Fluid clear or turbid, although infected	pH < 7.2 Glucose < 30 mg% LDH > 1000 IU/L Gm stain/culture maybe positive	Drainage needed
Empyema	Purulent fluid	Gm stain/culture may be positive	Drainage needed

wall). Early diagnosis is essential as the mortality of empyema is as high as 15% and up to 40% of these patients require surgery because medical treatment fails[25].

A chest radiograph showing consolidation with effusion should raise the possibility of empyema. Patients with pneumonia not responding to antibiotics should be assessed for the presence of pleural infection. CT scanning can help differentiate empyema from abscess and pleural thickening, with the former having a typical encapsulated and biconvex configuration. All patients with suspected parapneumonic effusion should undergo diagnostic pleural fluid sampling, ideally with ultrasound localization. Recommendations include:

1. the pleural fluid pH should be measured in all parapneumonic effusions except for those that are frankly purulent or have a positive Gram stain (immediate indication for tube drainage, regardless of the pH);
2. glucose measurements correlate well with pH and do not add relevant information and are not essential, unless there is doubt about the quality of the pH measurement;
3. pH values <7.0 should usually lead to tube drainage, in all other cases the pH should not be the sole criterion to decide on the necessity of a chest tube;
4. effusions with pH 7.0–7.2 should be observed closely (repeat thoracocentesis);
5. effusions with pH >7.2 should be observed; those with pH values >7.3 are very unlikely to take a complicated course.

Small tubes are as effective as larger ones; double lumen tubes can be used to irrigate the cavity with saline; irrigation with antibiotics is not recommended. Antibiotic regimens remain the same, but anaerobic cover is recommended as 15% are caused exclusively by anaerobic bacteria.

Use of intrapleural fibrinolytics were previously recommended and included streptokinase (2.5 lakh units) and urokinase (1.0 lakh units). The fibrinolytic substance is diluted in 100 ml saline and instilled via the chest tube. The tube is then clamped for 1 to 4 hours. The instillation is usually repeated once daily, and is continued for several days, sometimes for periods of up to 2 weeks.

The recently published MIST1 study[26] was the first large double-blind, randomized, controlled trial (454 patients) to address this issue. Results revealed that there was no improvement in outcomes with STK. There was an increase in adverse events with STK, especially chest pain and allergic reactions. Also, there was an elevated antibody response to STK which raised concerns about receiving STK in any future thrombotic events. The authors concluded that intrapleural streptokinase should generally be avoided in pleural infections. A subsequent meta-analysis[27] also came to the same conclusion but added that selected patients may still benefit by this approach.

Recombinant deoxyribonuclease (dornase alpha) has been used successfully in some cases[28]. Surgical intervention is frequently necessary in patients who fail to improve with medical management alone; however, the optimal timing and nature of surgery is unknown. Control of infection is the major indication for early surgery; even thick pleural peels resolve slowly and surgery can be delayed.

MALIGNANT PLEURAL EFFUSION

Lung cancer is the most common metastatic tumor to the pleura in men and breast cancer in women. Together, both malignancies account for approximately 50-65% of all malignant effusions. Lymphomas, tumors of the gastrointestinal and genitourinary tract account for a further 25%. Pleural effusions from an unknown primary are responsible for 7-15% of all malignant pleural effusions (Table 7)[29].

Massive pleural effusions are defined as those effusions occupying the entire hemithorax. While only 10% of patients have massive pleural effusions on presentation, malignancy is the most common cause of

massive pleural effusion. An absence of contralateral mediastinal shift in these large effusions implies fixation of the mediastinum, mainstem bronchus occlusion by tumor (usually squamous cell lung cancer), or extensive pleural involvement (as seen with malignant mesothelioma). About 15% of patients, however, will have pleural effusions < 500 ml in volume and will be relatively asymptomatic. Most present with dyspnea, cough or chest pain.

Table 7: Primary malignancy in cases of malignant effusion*

Primary site	*Percentage*
Lung	37.5
Breast	16.8
Lymphoma	11.5
GU tract	9.4
GI tract	6.9
Other	7.3
Unknown primary	10.7

*Summary of 5 series with total of 2040 patients

Pleural effusions found with malignancy are not always due to metastatic spread. For example, 5% of lung cancers have effusions that are non-metastatic. The term *"paramalignant effusions"* is reserved for those effusions that are not the direct result of neoplastic involvement of the pleura[30]. Reasons include post-obstructive pneumonia with parapneumonic effusion; chylothorax; pulmonary embolism; and transudative effusions secondary to post-obstruction atelectasis and/or low plasma oncotic pressures secondary to cachexia; treatment related (radiation and drugs such as methotrexate, procarbazine, cyclophosphamide, bleomycin); and concurrent nonmalignant disease. Conversely, postmortem studies have shown that more than 50% of cases with pleural spread may not have effusion.

Diagnosis is based on pleural fluid cytology, pleural biopsy, and in rare cases, by thoracoscopy. As little of 10 ml of fluid is enough for diagnosis in some cases[31]; however, success increases with repeat sampling. Management depends on degree of symptoms (performance status), curability of the tumor, and the expected life span[32-34].

- In a patient in poor condition with short life span (< 3 months), observation or repeated tapping (therapeutic thoracocentesis) is preferred, with the likelihood that 100% of the effusions will recur within the month.
- Pleural effusions in patients with extremely chemosensitive tumors (lymphomas, testicular tumors, small cell lung cancer) can be ignored as most will disappear with systemic chemotherapy.
- However, this still leaves a percentage of patients with metastatic disease but with relatively long life span (> 6 months at least) who needs long-term relief from large effusions (e.g., non-small cell lung cancer, breast cancer, colon cancer). These are best managed with pleurodesis. Less commonly used options in this group include indwelling catheters, pleuroperitoneal shunts, pleurectomy, or thoracoscopy with talc poudrage.

The steps of chemical pleurodesis used in our center are outlined below:

- Pleural fluid is drained out using small bore (10-14 Fr) intercostal tube.
- Lung re-expansion is confirmed by chest X-ray.
- Wait until pleural fluid drainage is less than 150 ml daily.
- Sclerosant is instilled after premedication and the tube is removed.
- Patient is rotated to ensure even spread of the sclerosant.
- Repeat chest X-ray is taken 24 hours later to reconfirm lung expansion.

Each of the above steps is not without controversies and is explained below. While it is traditional to insert large bore tubes to avoid clogging, two small series showed that small bore tubes are equally effective; rare instances of clogging can be cleared with guide wires. The effusion should be drained slowly initially (< 1.5 L at each setting to prevent re-expansion pulmonary edema); this can be repeated frequently (every 4-6 hours or so) in the first 24 hours until the fluid is completely drained. If pleural fluid pressure can be measured and does not decrease below - 20 cm H_2O, much more fluid can be removed safely. In patients with contralateral mediastinal shift on chest radiograph, removal of several liters of pleural fluid is probably safe, so long as he tolerates thoracocentesis without chest tightness, cough, or dyspnea.

The presence of lung re-expansion as seen on X-ray is more important indicator for pleurodesis than waiting for fluid drainage of < 150 ml/day. A randomized trial has shown that success rate of 80% can be achieved with early pleurodesis as soon as lung expansion is achieved (usually within 24 hours); it is not necessary for fluid drain to be < 150 ml before pleurodesis. This also cuts down on hospital stay and patient discomfort. However, our center prefers to wait till drainage is less than 150 ml per day.

Choice of the sclerosant is limited by availability. As shown in Table 8, sterile talc is the most effective agent, followed by tetracycline and doxycycline; however, these agents are not readily available in India. Our center uses Inj Bleomycin at a dose of 1 unit/kg body weight instilled in 100 ml of saline; patients are premedicated with antihistaminics and paracetamol as allergic reactions are common. Despite the figures in the table, head to head trials have shown that bleomycin is superior to tetracycline. 45% of the dose is absorbed systemically; however, this does not cause any cytotoxicity.

Table 8: Sclerosants for pleurodesis

Sclerosant	*Dose*	*Success rate*
Sterile talc	2-5 gm	90%
Tetracycline	1-1.5 gm	75%
Doxycycline	500 mg	65%
Bleomycin	60 units	60%

Patient rotation is not essential – studies with radioactive tetracycline have shown that it spreads evenly within seconds of instillation. However, this is a reasonable maneuver to perform which may add to the efficacy. Most centers recommend clamping of the tube for an hour after instillation and then removing it within 12 to 72 hours later, provided the fluid drain is less than 250 ml. In our center, the tube is removed immediately after instillation as there is no purpose served in keeping the tube as this could remove the sclerosant also.

40% of mesotheliomas tend to seed along the tube tract, or even at sites of pleural tapping/biopsy—these areas should be marked with India ink for future radiotherapy.

Failure of pleurodesis occurs in cases of partial re-expansion of the lung, or if the fluid could not be drained due to multiple loculations. Incomplete lung re-expansion may be due to a thickened visceral peel ("trapped lung"), pleural loculations, proximal large airway obstruction, or a persistent air leak. Where complete lung re-expansion or pleural apposition is not achieved and the patient is unsuitable for surgical intervention, pleurodesis should still be attempted. In the event of multi-loculated or septated malignant effusions, intra-pleural streptokinase (2.5 lakh units) can be safely instilled (without risk of allergic or hemorrhagic reactions) and has been shown to be effective.

A very interesting question is whether pleurodesis affects lung function, or rather, whether an intact pleural space has any useful function. Surprisingly, there is no clear cut answer to this. There is no evidence to suggest that lung function is significantly impaired post-pleurodesis. In elephants, the pleural space seems to be congenitally obliterated. It has been hypothesized that it could function as a "drip pan" for pulmonary edema fluid. However, there is no evidence of increased risk of pulmonary edema after pleurodesis, so even this role is unlikely to be of clinical relevance. The only apparent advantage of the pleural cavity is to thoracic surgeons – many surgeries would not have been possible without this cavity!

UNDIAGNOSED EFFUSIONS

If after the initial evaluation the diagnosis is not clear (as it happens in about 15% of patients) and the patients meet all the 6 criteria given below, further evaluation is not necessary as the patient will have a benign, self-limited illness:

- Patients are clinically stable
- Patients do not have weight loss
- The patient does not have a fever
- The effusion occupies less than 50% of the hemithorax
- The results of the Mantoux test are negative and the pleural ADA value is less than 40 U/mL
- The pleural fluid differential cell count has less than 95% lymphocytes.

20% of patients remaining undiagnosed and not meeting the above criteria will still have an underlying disease (usually a malignancy) and can be worked up with the knowledge that finding a curable disease is unlikely and invasive investigations have their own morbidity and mortality. These include surgical procedures such as thoracoscopy and open thoracotomy, which have a more than 90% chance of success.

Long-term (10 year) follow-up in a series of 40 patients[35] showed that 80% recovered spontaneously within a mean of 5.6 months (range: 1 week to 48 months). The diagnosis in the remaining 8 patients were asbestos related (3), adenocarcinoma (1), mesothelioma (1), CCF (1), cirrhosis (1), and rheumatoid arthritis (1). The recent isolation of Epstein Barr virus in some effusions may explain some of these 'idiopathic" effusions[36].

CONCLUSIONS

In conclusions, pleural effusion is a sign which, if worked up and interpreted correctly, can lead to the diagnosis of a systemic disorder in more than 95% cases. Common causes include infections (including TB) and malignancies; most of the other differential diagnoses are rare. Diagnosis can be established by relatively non-

invasive methods but on occasion, invasive techniques such as thoracoscopy can establish the diagnosis.

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