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Insights on Pleural Effusion

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ABSTRACT

Pleural effusion is not a disease, but it is the sign of many diseases it constitutes a major problem in all areas of clinical medicines. Pleural effusion occurs when fluid collects between the parietal and visceral pleura. Any conditions that may lead to fluid effusion increase into the pleural space can cause pleural effusion. In this regard, different baseline mechanisms suggested for pleural effusion include empyema, abnormal capillary permeability leading, increased hydrostatic or decreased oncotic pressure in the setting of normal capillaries, abnormal lymphatic clearance, and also hemothorax. Pleural fluid is accumulated when the rate of formation exceeds the rate of absorption or when the rate of absorption is decreased. Symptoms include Chest Pain, Dry Cough (non-productive), Breathlessness, Fever, Loss of weight and Loss of appetite. Diagnosis criteria include Clinic presentation: Patient's history and physical examination. Radiology: Conventional radiography, ultrasonography, computerized tomography. Thoracentesis: pleural fluid analysis. Bronchoscopy, Pleural fine needle biopsy and Video assisted thoracoscopic surgery (VATS) - Tauroctony (open pleural biopsy). Treatment include therapeutic thoracentesis, tube thoracostomy, pleural sclerosis and video assisted thoracoscopic surgery.

Keywords: Bronchoscopy, chest pain, empyema, pleural sclerosis, tube thoracostomy

INTRODUCTION

Pleural effusion is defined as a fluid collection between the pleural leaves due to local/systemic disease of the pleura, lung or extra pulmonary organs. Normally, 0.1 to 0.2 ml/kg of fluid is present in the pleural leaves to facilitate pleural movement. When the balance between the production and reabsorption of this fluid deteriorates, it becomes pleural effusion.

In India, total 17% cases of extra pulmonary tuberculosis were reported in 2016[1]. Tuberculous pleural effusion has been reported as the most common form of extra pulmonary tuberculosis in certain areas of India but worldwide pleural TB is the second commonest manifestation of extra pulmonary TB [2]. Pleural involvement is a common form of extra pulmonary disease and may occur in the presence or absence of pulmonary parenchymal disease on the chest radiograph with frequency of ranging from 3.5-30% [3,4]. Pleural effusion is not a disease, but it is the sign of many diseases it constitutes a major problem in all areas of clinical medicines [5]. Tuberculosis pleurisy is the second most common form of extra pulmonary tuberculosis

(TB) [6,7] and a common cause of pleural effusion in endemic TB areas [8,9]. Pleural effusion is defined as a fluid collection between the pleural leaves due to local/systemic disease of the pleura, lung or extra pulmonary organs. Normally, 0.1 to 0.2 ml/kg of fluid is present in the pleural leaves to facilitate pleural movement. When the balance between the production and reabsorption of this fluid deteriorates, it becomes pleural effusion [10]. Pleural effusion is accumulation of fluid in pleural cavity due to disequilibrium in the formation and removal of pleural fluid. Detecting pleural effusion is easy but finding the etiological cause is difficult since both pulmonary and extra pulmonary conditions cause pleural effusion [11]. The pleura is the serous membrane that covers the lung parenchyma, the mediastinum, the diaphragm, and the rib cage [12]. Amount of fluid in the right pleural space in normal individuals is 8.4 ±4.3 ml. Normally, the volume of fluid in the right and left pleural spaces is quite similar [13]. Pleural effusion occurs when fluid collects between the parietal and visceral pleura [14]. Approximately 1.5 million patients develop a pleural effusion each year [15]. There are approximately 320 new cases of pleural effusions per 1,00,000 people each year in industrialized countries [16,17]. In India 6% of the extra pulmonary tuberculosis are pleural effusions and 66% of the exudative effusions are of pulmonary tuberculosis [18]. The first step in the evaluation of pleural effusion is to determine whether the effusion is a transudate or exudate [19]. The causes of effusions can be categorized into transudative or exudative using light's criteria [20]. As many as 15% to 20% of all pleural effusions remain undiagnosed despite intensive effort [21]. It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion [22]. Pleural biopsy provides diagnostic value for patients with exudative effusions who remain undiagnosed after thoracentesis [23].

The Normal Pleura: The pleura is the serous membrane that covers the lung parenchyma, the mediastinum, the diaphragm, and the rib cage. Pleura is divided into the visceral and the parietal pleura. The visceral pleura covers the lung parenchyma, not only at its contact with the chest wall, mediastinum, and diaphragm but also in the interlobar fissures. Parietal pleura lines the inside of the thoracic cavity, and it is subdivided into the costal, mediastinal and diaphragmatic parietal pleura. The potential space between the two pleural layers is termed as pleural space. A thin layer of fluid is normally present between the parietal and visceral pleura. This thin layer of fluid acts as a lubricant and allows the visceral pleura covering the lung to slide along the parietal pleura lining the thoracic cavity during respiratory movements [24].

Pleural Fluid: Normally, a small amount of pleural fluid is present in the pleural space [24].

1	Volume	8.4 ± 4.3 ml. or 0.1 - 0.2 ml / kg body weight
2	WBC	1700 cells/mm^3
3	Macrophages	75%
4	Lymphocytes	23%
5	Mesothelial cells	1-2%
6	Eosinophils	1.20%
7	RBC	700 / mm^3
8	Proteins	1-1.5 gr / dl
9	pH	7.45 - 7.60
10	Glucose	≈ plasma level
11	LDH	50% of plasma level

Table 1: Normal composition of pleural fluid

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Pathogenesis of Pleural Effusions: Any conditions that may lead to fluid effusion increase into the pleural space can cause pleural effusion. In this regard, different baseline mechanisms suggested for pleural effusion include empyema, abnormal capillary permeability leading, increased hydrostatic or decreased oncotic pressure in the setting of normal capillaries, abnormal lymphatic clearance, and also hemothorax [25]. Pleural fluid is accumulated when the rate of formation exceeds the rate of absorption or when the rate of absorption is decreased.

PATHOLOGY: On histopathological examination tuberculous lesions shows granulomatous inflammation. A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. In the usual haematoxylin and eosin stained tissue sections, the epithelioid cells have a pale pink granular cytoplasm with indistinct cell boundaries, often appearing to merge into one another. The nucleus is less dense than that of a lymphocyte, is oval or elongate, and may show folding of the nuclear membrane. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Frequently, epithelioid cells fuse to form giant cells in the periphery or sometimes in the centre of granulomas. These giant cells may attain diameters of 40 to 50 µm. They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell). Squamous cell carcinoma histologically, characterized by the presence of keratinization and/or intercellular bridges. Keratinization may take the form of squamous pearls or individual cells with markedly eosinophilic dense cytoplasm These features are prominent in the well-differentiated tumors, are easily seen but not extensive in moderately differentiated tumors, and are focally seen in poorly differentiated tumors. Mitotic activity is higher in poorly differentiated tumors. Adenocarcinoma histologically from well-differentiated tumours with obvious glandular elements to papillary lesions resembling other papillary carcinomas to solid masses with only occasional mucin-producing glands and cells. About 80% contain mucin {24}.

SIGNS AND SYMPTOMS: Accumulation of pleural fluid produces a restrictive ventilatory defect and decreases total lung capacity, functional capacity, and forced vital capacity [26]. It may cause ventilation-perfusion mismatches due to partially atelectatic lungs in dependent areas and, if large enough, may compromise cardiac output by causing ventricular diastolic collapse [27]. The symptoms depend on the amount of fluid and the underlying cause. Many patients have no symptoms at the time a pleural effusion is discovered. Possible symptoms include pleuritic chest pain, dyspnoea, and dry nonproductive cough. Physical findings are reduced tactile fremitus, dullness on percussion, and diminished or absent breath sounds. A pleural rub may also be heard during late inspiration when the roughened pleural surfaces come together [28].

CAUSES OF PLEURAL EFFUSION:

1) Transudative pleural effusions: The causes of transudative pleural effusion are- Congestive heart failure, Cirrhosis, Nephrotic syndrome, Kidney failure, Peritoneal dialysis, Hypoalbuminemia, Atelectasis, Sarcoidosis, Pulmonary embolism, Vena cava superior syndrome, Meigs syndrome, Constrictive pericarditis and Cerebrospinal fluid leakage to pleural space.

2) Exudative pleural effusion: The causes of exudative pleural effusion include- Neoplastic diseases, Metastatic diseases, Mesothelioma, Lymphoma, Infectious diseases, Bacterial infections, Tuberculosis, Fungal infections, Parasitic infections, Viral infections, Pulmonary embolism, Cardiovascular diseases, Coronary artery bypass surgery, Postcardiac injury syndrome, Pericardial diseases, Gastrointestinal diseases, pancreatic diseases, Subphrenic, intrahepatic, intrasplenic abscess, Esophageal perforation, Liver transplantation, Rheumatoid pleurisy, Systemic lupus erythematosus and Drug induced (Nitrofurantoin, Dantrolene, Ergot alkaloids, Amiodarone, Interleukin-2, Procarbazine, Methotrexate, Clozapine and Bromocriptine).

3) Miscellaneous: Asbestos exposure, Lung transplantation, Bone marrow transplantation, Trapped lung, Radiation exposure, Drowning, Amyloidosis, Thoracotomy, Electrical burns, Extramedullary hematopoiesis, Syphilis, Hemothorax and Idiopathic pleural effusions [29].

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CLINICAL MANIFESTATIONS AND DIAGNOSIS OF PLEURAL EFFUSION: Normally the presence of moderate to large amount of pleural fluid produces symptoms and characteristic findings on physical examination [24].

Symptoms-

1) Chest Pain

2) Cough which is dry (non-productive)

3) Breathlessness

4) Fever

5) Loss of weight, Loss of appetite.

Diagnostic Approach in Pleural Effusion:

1. Clinic presentation: Patient's history and physical examination

2. Radiology: Conventional radiography, ultrasonography, computerized tomography

3. Thoracentesis: pleural fluid analysis

4. Bronchoscopy

5. Pleural fine needle biopsy

6. Video assisted thoracoscopic surgery (VATS) - Tauroctony (open pleural biopsy) [29].

PHYSICAL EXAMINATION:

General examination: Lymphadenopathy suggests Malignancy, Tuberculosis, lymphoma or sarcoidosis, HIV. Clubbing, presence of hypertrophic osteoarthropathy suggests Malignancy.

Respiratory System

- **Inspection:** The hemithorax will be larger and the usual concavity of the intercostals spaces will be blunted or even convex. Respiratory movements on the side of effusion decreased and shift of the mediastinum opposite side, if associated with collapse of lung mediastinum shifted towards same side.
- **Palpation:** In areas of the chest where pleural fluid separates the lung from the chest wall, tactile fremitus is absent or attenuated because the fluid absorbs the vibrations from the lung. Tactile fremitus is much more reliable than percussion for identifying both the upper border of the pleural fluid and the proper site to attempt a thoracentesis. Palpation may also reveal that the cardiac impulse is shifted to one side or the other. Position of the trachea should always be ascertained because it indicates the relationship between the pleural pressures in the two hemi thoraces.
- **Percussion:** Percussion note over a pleural effusion is dull or flat. The dullness is maximum at the lung bases, where the thickness of fluid is the greatest, light percussion is better than heavy percussion for identifying small amount of pleural fluid. If the dullness to percussion shifts as the position of the patient is changed one can be almost certain that free fluid is present.
- **Auscultation:** Auscultation characteristically reveals decreased or absent breath sounds. Near the superior border of the fluid, however breath sounds may be accentuated and takes on a bronchial characteristic. This phenomenon has been attributed to increased conductance of breath sounds through the partially atelectatic lung compressed by the fluid.

CVS: The effusion is probably due to congestive heart failure if the patient has cardiomegaly, neck veins distension, or peripheral oedema.

Musculo Skeletal System: Signs of joint disease or subcutaneous nodules suggest the effusion is due to rheumatoid disease or lupus erythematosus.

GIT: An enlarged, nontender nodular liver suggests metastatic disease, as in bronchogenic carcinoma. Abdominal tenderness suggests a subdiaphragmatic process, whereas tense ascites suggests cirrhosis.

Radiological Diagnosis

- **Chest – X-Ray:** The normal pleural space contains 10-15 ml of pleural fluid. At least 200 ml of fluid is necessary to blunt the costophrenic angle on a chest X-ray PA view. 50 ml of fluid causes blunting of posterior costophrenic angle on lateral chest X-Ray, and up to 500 ml of fluid can be present in some cases with no appreciable blunting a lateral decubitus film is the most sensitive view and can detect as little as 5 to 10 ml of free fluid [29,30]. In PA view homogenous

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opacity with obliteration of lateral costophrenic angle and typical upper surface meniscus shaped shadow suggests pleural effusion. Homogenous opacity with obliteration of posterior costophrenic angle or obliteration of posterior part of one or both diaphragms suggest pleural effusion in lateral view. Chest radiographs can also provide important clues to the cause of an effusion. Bilateral effusions accompanied by cardiomegaly are usually caused by congestive heart failure. Large unilateral effusions without contralateral mediastinal shift suggest a large atelectasis, infiltration of the lung with tumour, a mesothelioma, or a fixed mediastinum due to tumour or fibrosis [31].

- **Ultra sound:** On ultra sound effusion is characterized by echo free (anechoic) complex, septate if there are fibrin strands or septa floating inside the anechoic pleural effusion, non-septate if homogenously echogenic spaces are present between parietal and visceral pleura [32,33]. Ultrasound is useful in pleural effusion as follows.
    1. Determining whether the pleural fluid is present, as minimum as < 50 ml.
    2. Identification of the appropriate location for an attempted thoracentesis, pleural biopsy, chest tube placement.
    3. Identification of pleural fluid loculations.
    4. Identification of pleural thickening.
- **CT scan:** It is usually performed in patients with pleural effusions of unknown aetiology and suspected malignant or complicated parapneumonic effusions and empyema. It differentiates pleural effusions from the lung parenchymal and extra pleural diseases of chest wall. Contrast enhanced CT Scan is useful in differentiation of pleural thickening as benign or malignant and differentiation of an exudative from a transudative, with enhancement always indicating an exudative effusion [34].

Specific tests of pleural fluid:

pH: The pH of the normal pleural fluid is around 7.64, owing to active transport of HCO_3 into the pleural space. A pleural fluid pH below 7.2 in this situation indicates the patient is at increased risk for poor outcome and indicates the need for drainage [35] In the case of malignancy, patients with extensive tumour burden of the pleura have a pleural fluid with a low pH (<7.28) and low glucose. In general, these patients have a poor short-term survival rate, but pleural pH alone has insufficient accuracy for clinical use in identifying patients who should not undergo pleural sclerosis, in view of poor procedure success (see Pleural sclerosis, below) [36,37].

Pleural biopsy: The main conditions that can be established with needle biopsy of the pleura are tuberculous pleuritis and malignancy of the pleura. Needle biopsy is currently recommended when tuberculous pleuritis is suspected and the pleural fluid adenosine deaminase or interferon-gamma levels are not definitive (see Tuberculosis, below). A parietal pleural biopsy specimen is positive for granulomas in up to 80% of cases of tuberculous pleurisy, acid-fast staining is positive in 26%, and culture is positive in 56%. At least one of these three tests are positive in 91% of cases [38].

Pleural needle biopsy: It is indicated in patients who cannot be diagnosed by less invasive methods. Pleural biopsy; closed pleural biopsy, biopsy under CT or thoracoscopic biopsy. Under CT, pleural biopsy provides reliable results when the pleural thickening is over 1 cm [39,40].

Video assisted thoracoscopic surgery (VATS) - Thoracotomy (Open pleural biopsy): Pleural biopsy with VATS provides both inspecting pleural surfaces, performing biopsy from the suspicious regions of the pleura and draining the effusion at the same time [41]. It can be done under intubated general anaesthesia; also, can be done under non-intubated general anaesthesia or paravertebral block/ thoracic epidural anaesthesia.

THERAPY

Therapeutic thoracentesis: Any pleural effusion large enough to cause severe respiratory symptoms should be drained regardless of the cause and regardless of concomitant disease-specific treatment. Relief of symptoms is the main goal of therapeutic drainage in these

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patients. The only absolute contraindication to thoracentesis is active cutaneous infection at the puncture site. Some relative contraindications include severe bleeding diathesis, systemic anticoagulation, and a small volume of fluid. Possible complications of the procedure include bleeding (due to accidental puncture of a vessel or lung parenchyma), pneumothorax, infections (soft-tissue infection or empyema), laceration of intra-abdominal organs, hypotension, and pulmonary edema [42]. In general, no more than 1,000 to 1,500 mL of fluid should be removed at one time. Rapid drainage of fluid may predispose patients to the rare complication of reexpansion pulmonary edema in the underlying lung or rapid fluid shift from the intravascular space to the pleural space (post-thoracentesis shock). These complications appear to be related to the creation of excessive negative pressure in the pleural cavity during thoracentesis. Large-volume thoracentesis can be undertaken with monitoring of the intrapleural pressure [43,44].

Tube thoracostomy (**Chest Tube**): Tube thoracostomy allows continuous, large volume drainage of air or liquid from the pleural space. Specific indications for placement of a chest tube include spontaneous or iatrogenic pneumothorax (especially if large and symptomatic), hemothorax, penetrating chest trauma, complicated parapneumonic effusion or empyema, chylothorax, and pleurodesis of symptomatic pleural effusions. In symptomatic or clinically unstable patients, there is no absolute contraindication to chest tube placement. In patients with complicated pleural spaces due to multiple loculations or previous pleurodesis, a contrast chest CT scan should be obtained to guide the placement of the chest tube. For drainage and pleurodesis of malignant pleural effusions, a silicone polymer (Silasticchest tube 20 to 24 F is usually adequate, although small-bore catheters (8–14 F) placed under fluoroscopic, ultrasound, or CT guidance have also been successful [45,46]. Complicated parapneumonic effusions and frank empyema require drainage with a large-bore chest tube (28–36 F) to control the local pleural inflammatory reaction, which may not otherwise respond to intravenous antibiotics. In multiloculated complicated effusions, image-guided placement of small-bore catheters (10–14 F) should be considered [47,48]. If appropriate drainage is not obtained despite correct positioning of the tubes (verified with chest CT), fibrinolytic therapy can be used [49,50]. Agents such as streptokinase, urokinase, and alteplase can lyse fibrin and improve drainage.

Pleural Sclerosis: Pleural sclerosis (pleurodesis) is considered for patients with uncontrolled and recurrent symptomatic malignant effusions, and rarely, in cases of benign effusions after failure of medical treatment. A sclerosing agent is instilled into the pleural cavity via a tube thoracostomy to produce a chemical serositis and subsequent fibrosis of the pleura. Pleural sclerosis should be attempted only if the lung expands fully after fluid removal. The visceral and parietal pleura need to be approximated closely, obliterating the pleural cavity so that fibrotic healing achieves pleural symphysis. The overall success rate with fibrosing agents (talc, doxycycline, and tetracycline) is 75%, compared with a complete success rate of only 44% for antineoplastic agents (bleomycin) [51]. Talc is the most effective agent, with a complete success rate of 93%.49,50 Pleurodesis failure is usually the result of suboptimal technique or inability to approximate the pleural surfaces.

Surgical therapy: Video-assisted thoracoscopic surgery is very useful in managing incompletely drained parapneumonic effusions. With thoracoscopy, the loculi in the pleura can be disrupted, the pleural space can be completely drained, and the chest tube can be optimally placed [52].

In cases of empyema with uncontrolled sepsis or progression to the fibroproliferative phase, a full thoracotomy with decortication is performed with removal of all the fibrous tissue and evacuation of all the pus from the pleural space. Decortication in this situation will eliminate the septic source and allow the lung to expand.

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