

Pleural Effusion: A Rationale Approach to Diagnosis and Management.

Abstract:

Background: Pleural effusion is a most common pleural disorder which can be due to multiple underlying pulmonary or systemic causes. The management of pleural effusion is based on history, clinical, radiologic and then analysis of pleural fluid with complete biochemical, cytologic, microbiological, histopathological examination. As a protocol the Lights criteria was applied to distinguish transudate and exudate effusion. The management also depends up on underlying disease for that acquisition of histopathological biopsy sample is required with use of precise and selective diagnostic tool.

Results: Study included 103 cases of pleural effusions, predominantly middle aged individuals with a mean age of 45.6 years. Males constituted the majority at 74.8%, reflecting a male predominance in the affected population. Cough (75.7%), breathlessness (73.8%), and chest pain (65.0%), were the main symptoms. The predominant etiology in the study population was TB (49%), followed by malignant effusions (19%) and Syn-pneumonic effusions in 17% accounted 17% of cases. Diagnostic and therapeutic procedures such as pleurocentesis (96%), intercostal drain (ICD) insertion (32%), and the therapeutic procedures i.e. fibrinolytic, adhesion and septation removal, and pleurodesis (24%) were also performed. The diagnostic yield improved with the use of simirigid thoracoscope and fiberoptic bronchoscopy by 13% and 12% respectively.

Discussion: The clinical examination and chest x-ray (CXR) are the simplest way to detect PLEF. Apart from the examination of PLEF for bio/ cyto/ microbes, the acquisition/ procurement of tissue for histological analysis becomes mandatory especially for undiagnosed cases. There are two known options for tissue biopsy: 1) a blind/ or closed pleural biopsy (CPB) with Abrams or Tru-cut needle and 2) a 'gold standard' surgical biopsy. However the USG guided pleural interventions are safe, cost effective, least invasive, radiation free and can be performed bed site with a comparable yield, where ever the computed tomography and thoracoscopy facilities are lacking. An image-guided Tru-cut biopsies and the medical thoracoscopy (pleuroscopy) to directly visualize disease site under local anesthesia have become more acceptable and popular tool since past decade.

Conclusion: The pleural effusion is most common ailment with underlying local, focal and generalized or systemic causes. The presentation of PLEF is wide and variable thus for the selection of diagnostic and therapeutic tool the patients comfort, consent, cost effectiveness, least complication, easy availability and feasibility should be considered. The mis or undiagnosed cases of PLEF should be again considered for a complete repeat examination after a suitable interval.

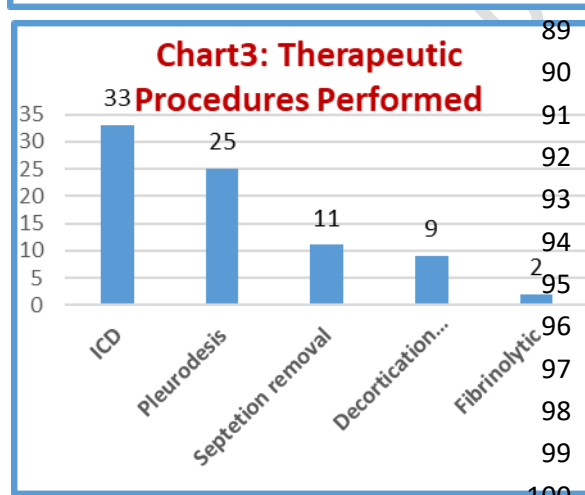
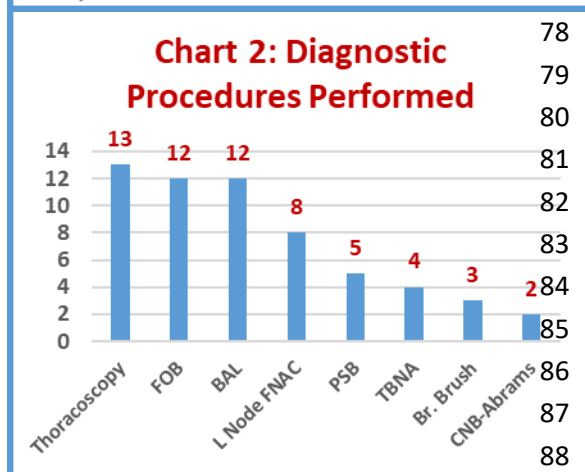
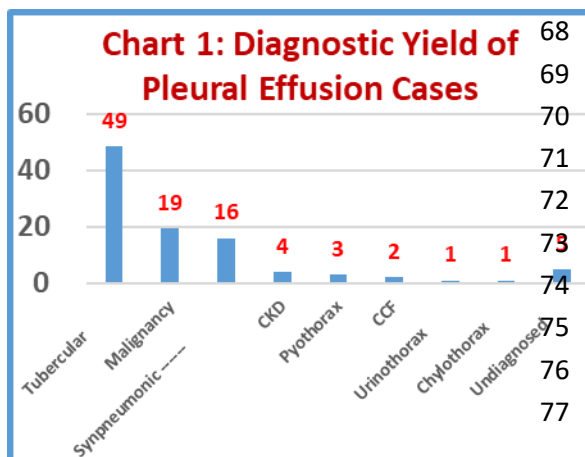
Key words: Adenosine deaminase (ADA), Close pleural biopsy (CPB), Malignant pleural effusion (MPE), Medical thoracoscopy (MT), pleurodesis, Tubercular pleural effusion (TPE), fiberoptic bronchoscopy (FOB)

Introduction:

Pleural effusion is the collection of fluid in the pleural space. The causes of pleural effusion varies by geographical areas and the local pattern of incident and prevalent of diseases. In

developed countries the common causes of pleural effusions in adults which varies around 320/
Lac of population ⁽¹⁾ includes; cardiac failure, malignancy, and pneumonia, conversely in
developing countries, tuberculosis is an important cause, para pneumonic effusions as is
malignancy (lung or metastatic) being more prevalent. The accumulation of effusion is
associated with various medical conditions that predispose to fluid buildup through various
mechanisms (isolated or in combined) like increased pulmonary capillary pressure, decreased
oncotic pressure, increased pleural membrane permeability, and lymphatic obstruction ⁽²⁾.

There is no need to emphasize that a meticulously taken history of the patient with thorough
clinical examination plays a pivotal role in differential diagnosis of PLEF. A patient with pleural
effusions typically present with dyspnea because of compressed and displaced lung and
mediastinum with reduced vital capacity. They may also have cough, sharp pleuritic chest pain
(radiating/ nonradiating), there may accompanying fever (denotes underlying
infection/inflammation), expectoration (Parenchymal disease), haemoptysis (Pulmonary
thromboembolism) and clinical findings suggestive of collapse or consolidation are some of the
examples. Apart from the diseases of the pleura itself (e.g. mesothelioma) and the lung, there are
wide spectrum of systemic diseases including the co-morbidities i.e. cardiac, renal, liver,
pancreatic, thyroid (myxedema), drug induced, post radiotherapy, ovarian hyperstimulation
syndrome and connective tissue or autoimmune disorders (like rheumatoid arthritis or lupus) etc.
are some of the other rarer causes of PLEF. The pleural fluid has to be carefully drained, with
under perfect aseptic precautions to investigate the etiology. The physical appearance of drained
PLEF may provides a clue toward diagnosis e.g. odor, color, transparent or opaque/ turbid etc
and it could be further classified according to the Light's criteria as exudative or transudative.
These two type of fluids enable to narrow the differential diagnosis; however PLEF could be
serosanguinous (watery and pinkish-red due to blood mixed with serum), haemorrhagic
(haemocrate value >50%), turbid to frank pus (empyema), and or milky (Chylous) etc that may
also contribute to underlying etiology. Apart from the clinical, biochemical, microscopy and
bacteriologic examination of PLEF, a chest x-ray (PA/ Lateral and decubitus position) prior and
after the aspiration is desirable, however USG and or CT thorax may require to further precisely
delineate the site and size of underlying ailment and enable to optimized interventions. The
histopathology and or immuno-histochemistry is the ultimate to establish diagnosis and that
required to procure pathological biopsy tissue samples from pleura, lung, or lymph nodes (intra
or extra thoracic) and from the primary sites which may be variable in each case. The optimal
use of available modalities and procedures are the key to success e.g. FNAC, Abrams or Tru-cut
needle closed pleural biopsy (CPB), thorascopic or bronchoscopic biopsies are some of the
examples. The present study is carried out at a rural based Medical college to understand the
diagnostic yield with optimal use of various tools.



Results: A total of 103 admitted cases of pleural effusion were considered for a prospective observational study in the department of respiratory medicine. The mean age of participant was 46 yrs and among them more than 57 % cases were above the age 40 years with nearly three times male predominance ie 77 males and 26 females. Pleurocentesis was carried out in all the cases after taking complete history and clinical examination, followed by chest x-ray/

USG thorax, and were investigated for biochemical, pathological, microbiological etc to establish the diagnosis and management. However 4 cases showed dry tap and later on diagnosed as tuberculosis. The diabetes, COPD, HIV and hypertension as a systemic diseases were detected as comorbidities in 8%, 8%, 5% and 4% patients respectively. Similarly less common diseases known to cause PLEF were also detected as CKD (4%), CCF (2%), and 1% each with urinothorax, CAD and CLD. However the case of urinothorax was due to per cutaneous nephro-lithotomy and was also managed successfully which resolved spontaneously after an aspiration. Pleuroscopy was done with the video assisted semi rigid thoracoscope in 13% cases and fibreoptic bronchoscopy was performed in 12% cases and their results displayed on bar **Chart: 1&2**. A close needle biopsy (CNB) yielded 100% with Abrams in 2 cases with having ample of pleural fluid and finally diagnosed as of TB origin. A fine needle aspiration cytology (FNAC) in 8% cases with

101 cervical lymphadenopathy had revealed TB in 2 and Malignancy in 6 cases.

102 Some of the therapeutic procedures were also performed i.e. insertion of intercostal tube
 103 drainage (ICD) with under water seal (in 32% cases), pleurodesis (in 25%), pleuroscopy with
 104 adhesion/ septations removal during pleuroscopy (in 13%), fibrinolysis (in 2% cases), and 9%
 105 chronic recalcitrant cases referred to thoracic surgical unit for decortications **Chart: 3**.

Discussion: The parietal pleura is richly supplied with sensory nerve and the inflamed or diseased pleura become painful due to friction with visceral part, however the pain may later disappear with the collection of reactionary fluid or again reappear after pleurocentesis due to direct contact of both pleura and inflammation in the pleural space. The dyspnea is the most common presentation with a filling of more than a half of the hemithorax with fluid. The clinical examination and chest x-ray (CXR) are the simplest way to detect PLEF in the free form (meniscus), loculated (D sign) or subpulmonic and even a small amount of free fluid can be diagnosed with chest radiograph taken in decubitus position. However in a tedious situations the radiation free USG guided pleurocentesis remained the best choice.

In the present study the drained PLEF samples (99 cases) were examined for biochemical, bacteriologic and cell cytology and was classified as exudative (92%) and transudative (8%) according to the Light's criteria. The exudative PLEF was in majority and among them 49%, 19% and 17% cases were of TB, malignancy and synpneumonic effusion respectively. In the Indian context upfront molecular testing with or without ADA (value >40 unit) test may have higher yield in diagnosing tuberculosis along with rifampin resistance, nevertheless the bacillary population is sparse/ paucibacilli in PLEF. In the absence of mycobacterium the sensitive individuals may developed TPE that could be due to delayed type hypersensitivity ⁽³⁾. The present study observed 20% (10/50 cases) as bacteriologically positive by CBNAAT and among them 2/50 (4%) rifampin resistant cases were also detected that remained creditable. Similarity Damanjit Duggal et al had reported that in majority of their patients 77 (86%) MTB could not be detected by the GENEXPERT test and concluded insufficient tool for TPE ⁽³⁾. Rahul Gupta et al mentioned that TPE is second most common extrapulmonary TB while the positivity of CBNAAT was higher in lymph node TB (TBLN) patients (57.8%) as compared to TPE (23.7%) patients ⁽⁴⁾. A microbiol culture and sensitivity test was performed for turbid or frank pus (empyema) to initiate appropriate chemotherapy. The synpneumonic PLEF (pneumonia or infected lung with PLEF) as usually responded, very well with the same antibiotic treatment, thus intervention are usually not required as happened with our 17 (17%) cases, however 3 cases of pyothorax were managed with intercostal tube drainage.

A predominant lymphocytes and the value of ADA (>40 IU) with the ratio of LDH/ADR may help to distinguished TB from synpneumonic and malignancy effusion e.g. a lower ratio around <10 favor tubercular etiology against >14 or >45 suggests parapneumonic and malignant origin respectively ⁽⁵⁾. The intercostal tube drainage (ICD) with an under water seal should invariably be placed to manage pleural fluid whenever the pH is <7.2 or found to be turbid/ frank pus (empyema) without considering the underlying etiology. In the present small series of 103 cases the ICD was placed in 33 (32%) cases after the therapeutic or post diagnostic procedures.

In the present study 8 cases were clinically detected with additional finding of cervical lymphadenopathy, and among them a simple FNAC revealed TB (in 2 cases) and malignancy (in 6 cases), had contributed to the ultimate diagnosis. A pleural fluid cell block should invariably be examined for exfoliative cytology but none of the cases in our study reported any abnormality

145 i.e. malignant or fungal hyphae etc in the sputum or pleural fluid. In 4 (4%) cases the PLEF
146 sample could not be collected due to minimal amount nevertheless the clinical, radiologic and
147 pathological findings had supported in making a diagnosis of TB in these cases. The co
148 morbidities may also play a pivotal role in management e.g. eight cases of our study group had
149 transudative effusion due to cardiac and renal disease which resolved with diuretic, dialysis, and
150 supportive management etc, and did not require further evaluation. Similarly among them a case
151 of urinothorax followed by PCNL (percutaneous nephrolithotomy) also resolved spontaneously.

152 Apart from the examination of PLEF for bio/ cyto/ microbes, the acquisition/ procurement of
153 tissue for histological analysis becomes mandatory especially for undiagnosed cases. There are
154 two known options for tissue biopsy: 1) a blind/ or closed pleural biopsy (CPB) with Abrams or
155 Tru-cut needle and 2) a 'gold standard' surgical biopsy. The biopsy could also be performed under
156 image (USG or CT) guided is much safer procedure especially for pleural or Peripheral lung
157 lesions. Yuqing Wei et al in their meta-analysis study of exudative effusion had mentioned that
158 the close pleural biopsy (CPB) yielded comparable to medical thoracoscopy (MT) 69% and 68%
159 respectively in non malignant cases, so they concluded that the CPB may be considered as first
160 choice ⁽⁶⁾. However they further mentioned that CPB could not properly visualise the
161 diaphragmatic, apical and mediastinal pleura and they also stated that the diagnostic yield in
162 malignant PLEF remained higher with MT (92%) vs. CPB (72%). The most common
163 complication associated with CPB includes pneumothorax, pain, haemothorax, hematoma,
164 vasovagal reaction and transient fever etc reported to be 8- 18% ⁽⁷⁾. Boy DP et.al. has stated that
165 USG guided pleural interventions are safe, cost effective, least invasive, radiation free and can be
166 performed bed side with a comparable yield, where ever the facilities of computed tomography
167 and medical thoracoscopy facilities are not available ⁽⁸⁾. He further mentioned and added a
168 recommendation that the US-guided procedures should be encouraged and adopted as an integral
169 part of the respiratory physician curriculum ^(8,9).

170 Giles Dixon et al had mentioned that since last more than a decade an image-guided Tru-cut
171 biopsies and medical thoracoscopy (pleuroscopy) under local anesthesia have become more
172 acceptable and popular tool ⁽¹⁰⁾. We too preferred and adopted a minimal invasive video-assisted
173 semi-rigid thoracoscope in 13% cases with diagnostic dilemma to visualize the pleural space and
174 surrounding structure and enable biopsy under direct vision. Similarly the fiberoptic
175 bronchoscopy was performed in 12 cases with suspected lung malignancy and biopsy, bronchial
176 brushing and BAL fluid were collected and TBNA was also carried out in 2 cases with enlarged
177 sub carinal lymph nodes detected on CECT thorax. Along with FOB a protected sample biopsy
178 (PCB) were also performed in 3 cases of delayed resolving synpneumonic effusion for culture
179 and sensitivity test however, ICD was also placed in them. The MT may also ease therapeutic
180 procedures like Fibrinolytic (2% cases), removing fluid and adhesions in loculated/ complex
181 effusions (found in 12% cases) to allow lung expansion and also help in deciding a candidate for
182 decortication with pleural peel or trapped lung. 9% cases referred to thoracic surgeon for
183 decortication. The present study also performed pleurodesis in 24% (24cases) with doxycycline
184 after full expansion of the lung nevertheless with a failure rate of 16% (4/24). Our study reported

4% undiagnosed cases as against Wei et al. mentioned 15-20 % PLEF cases may remain undiagnosed ⁽⁶⁾. In India the medical thorascopies are performed more frequently than ever before yet most the general practionars are still managing PLEF empirically which leads to mised or delayed diagnosis and untoward complications due to improper treatment ⁽¹¹⁾.

The prognosis of PLEF depends upon the underlying etiology with complete cure to disastrous end of life, as in malignant pleural effusion (MPE) which has the worst (TNM-stage 4) prognosis and it also depends on the amount i.e. massive effusion irrespective of histological type of lung cancer, which may require prolonged indwelling ICD and palliative management ⁽¹¹⁻¹⁴⁾.

Conclusion: The pleural effusion is most common ailment with underlying local and generalized or systemic causes. The PLEF may presents with a certain variable clinical and radiological features that themselves will incline us to choose/ opt a particular procedure. Thus a definite algorithm cannot be implanted while the minimal invasive with least complication and maximum yielded procedures should be planned for each individual case. Patient comfort, consent are all component of a patient's centric care to ensure full cooperation in removing fluid and preventing its reaccumulation. The CPB may be more suitable in exudative and lymphocytic predominant with diffuse pleural involvement cases when USG/ CT facilities are unavailable or when patient cannot tolerate medical thoracoscopy. The misdiagnosed cases of PLEF should be followed up regularly and should be again considered for a complete repeat examination after an interval.

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