

Role of Common Investigations in Aetiological Evaluation of Exudative Pleural Effusions

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ABSTRACT

Background: Pleural effusion is a common problem encountered in daily practice. To Establish aetiology of exudative effusions is a diagnostic challenge to general practitioners and even to pulmonologists especially in resource poor government hospitals with lack of investigations like thoracoscopy. Some recent studies had shown that around 2% of patients remained undiagnosed even after these investigations.

Aims and Objective: To evaluate the role of the commonly available investigations such as pleural fluid study, blind pleural biopsy, sputum examination, CT scan thorax, bronchoscopy in the aetiological evaluation of exudative effusions and to ascertain the proportion of cases which remain undiagnosed after all the above investigations.

Material and Methods: This was a prospective single-centred cross-sectional study carried out at the NRS Medical College, Kolkata, India from February 2008 to February 2013 which included 568 patients of exudative pleural effusions. We performed commonly available procedures like pleural fluid study, blind pleural biopsy, sputum examination, CT scan

thorax, bronchoscopic procedures to the diagnosis.

Results: Total number of patients studied were 568. Tuberculosis was the most common cause (54.57%) followed by malignancy (28.17%), empyema (10.56%), parapneumonic effusion (5.28%) and others. Carcinoma of the lung was the commonest cause of malignant effusions and bronchoscopic biopsy was given the highest yield of histological diagnosis (84.6%) followed by CT guided FNAC (77.6%) and pleural fluid cytology (55%). Highest yield to diagnose tubercular effusion was found in lymph node FNAC (81.5%) followed by pleural biopsy (62%). Sputum smear for AFB was positive in only 27.4% cases. Bleeding followed by pneumothorax were the most common complications. Complications are very less (1.3% and 0.9% respectively). 2 patients (0.34%) remained undiagnosed even after these all above said investigations.

Conclusion: Above mentioned commonly available investigations can ascertain diagnosis in most of the cases in the aetiological evaluation of exudative effusions and they are relatively safe procedures.

Key words: Pleural effusion, Exudative, Investigations, Pleural biopsy, Bronchoscopy, Malignancy, Tuberculosis

INTRODUCTION

Pleural effusion is one of the commonest problems presented to a pulmonologist. Around a million patients worldwide develop pleural effusion each year [1]. Aetiologies of these effusions may be diverse. To find it out and treat it properly is a challenge to the treating pulmonologist. The frequency of the various aetiologies of pleural effusion depends on the incidence of tuberculosis in the region where the study is conducted. In an area with a high incidence of tuberculosis, the commonest causes of pleural effusion include tuberculosis, neoplasia, congestive cardiac failure and pneumonia [2]. Many studies have reported that relatively large numbers of patients with pleural effusion in whom a definite diagnosis could not be made, despite extensive investigations [3,4]. Even though thoracoscopy is used to determine the diagnosis in this group of patients, this facility is not available in most government hospitals in Eastern India. Therefore, primary objective of our study is to find out the number of cases remained undiagnosed after commonly available investigations and to evaluate their role in the diagnosis of exudative effusions.

MATERIAL AND METHODS

A single centered, prospective, cross-sectional, observational study was conducted with special reference to aetiological diagnosis of

exudative pleural effusions in the Department of Chest Medicine of NRS Medical College, Kolkata, India from February 2008 to February 2013. We included 568 patients above the age of 11 years irrespective of sex attending out-patient department within the study period. The diagnosis of pleural effusion was made by clinical and radiological examination and ultimately confirmed by aspiration of fluid from pleural spaces. Subsequently the fluid has been sent for a series of biochemical, cytological, histopathological and microbiological tests for determination of nature of the effusion.

Following tests of pleural fluid had been performed:

1. Physical – Color, turbidity, viscosity, specific gravity.
2. Biochemical – Sugar, Protein, Albumin, Lactate Dehydrogenase (LDH).
3. Cytological examination of pleural fluid.
4. Microbiological – Gram stain, culture for pyogenic organism, ZN (Zeihl-Neelsen) stain, AFB (acid-fast bacilli) culture.
5. Special tests – ADA (adenosine deaminase), cholesterol, triglyceride, amylase, lipase.

The amount of pleural fluid sent for different investigations included:

1. Biochemical examination – 5 ml.

2. Haematological examination – 5 ml. (Total RBC count, WBC count, haematocrit).
3. Microbiological examination – Gram stain and culture – 10 ml. Zeihl-Neelsen stain for M. tuberculosis – 5 ml.
4. Cytological examination – 5-25 ml. (EDTA or 0.3 ml. of heparin as preservative).

A sample of serum, obtained within 24 hours of thoracentesis was used to measure glucose total protein, albumin, LDH, LFT, urea and the creatinine label. Effusions were considered as exudates if at least one of the following criteria was met or considered as transudates if none of the following criteria is met (Light's criteria).

1. Pleural fluid protein to serum protein ratio > 0.5.
2. Pleural fluid LDH to serum LDH ratio > 0.6.
3. Pleural fluid LDH greater than 2/3rd of the upper limit of normal for the serum LDH / or pleural fluid LDH > 200 IU/L.

Then based on the light's criteria we divided them into transudative and exudative effusions. We excluded transudative effusion cases from our study and also those who refused to give written consent for the study. Patients with minimal effusion noted on CT (computed tomography) scan of the thorax but not on chest radiograph and/or coagulopathy (prothrombin time greater than 2.0 by international normalised ratio, [INR]) and/or platelet count less than 20000/L were also excluded from the study. Demographical data, characteristics of the pleural effusion, clinical presentation, investigation results, and the final diagnoses were obtained. Pleural biopsy was performed by using the Abram's needle. Other investigations that might contribute to the diagnosis were carried out. These sputum direct smear for AFB, sputum AFB culture, CT scan of the thorax, and bronchoscopic examination for suspected lung carcinoma and pulmonary tuberculosis. Tuberculous pleural effusions were diagnosed when one or more of the following criteria were satisfied: sputum or pleural fluid AFB smear or Mycobacterial culture positivity; presence of epithelioid granulomas with or without caseating necrosis and/or presence of AFB on histological examination of pleural biopsy or lymph node biopsy specimen; cytological evidence of tubercular inflammation and/or AFB staining positivity of fine-needle aspiration sample from lymph nodes. A neoplastic pleural effusion was defined as a effusion due to an underlying malignancy. It can be a malignant or paramalignant effusion. Malignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimens were conclusively positive for malignancy. Paramalignant effusions were diagnosed when pleural biopsy specimens or pleural fluid cytology specimens were negative and other known causes of the pleural effusions were also excluded in patients with a histologically-proven malignancy elsewhere, for example, by per-cutaneous or image (CT) guided lung biopsy or trans-bronchial lung biopsy. Parapneumonic effusions were defined as pleural effusions associated with an acute febrile illness and cough, in which the chest radiographs revealed pulmonary infiltrates and the patient responded to antibiotic treatment. Empyema was diagnosed when pus was present or microorganisms isolated from the pleural aspirate. Effusions associated with rheumatoid arthritis cases were diagnosed by excluding other possible causes, anti-CCP positivity and pleural biopsy report suggestive of rheumatoid aetiology. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 10.0. A p-value of <0.05 was taken as being statistically significant.

RESULTS

Five hundred and sixty eight patients above the age of 11 years of exudative effusions were studied from February 2008 – February 2013. There were two patients who had no obvious cause for their exudative pleural effusions despite pleural fluid analysis, pleural biopsy, CT of the thorax and abdomen and other investigations.

Among the remaining 566 patients in whom causes of effusion were identified, 410 patients were male and 156 patients were female. The mean age of patients with benign effusions was 44 years (standard deviation 9) and with the malignant effusion was 63 years (standard deviation 12). Among the benign effusions 185 were right sided, 161 were left sided and 60 were bilateral effusions. Among the malignant effusions 95 were right sided, 64 were left sided and only 1 effusion was bilateral effusion. Exudative effusions were most commonly due to tuberculosis (54.57%) followed by malignancy (28.17%) [Table/Fig-1]. 120 patients had primary lung cancer, namely: adenocarcinoma (65), squamous cell cancer (30), small cell carcinoma (22), large cell cancer (3) and 40 patients had other malignancies, such as breast cancer (10), cervical cancer (6), ovarian cancer (4), colon cancer (8), gastric cancer (2), oesophageal cancer (1), testicular malignancy (4) and lymphoma (5). Lymphocytic pleural effusion was commonly associated with malignancy and tuberculosis [Table/Fig-2]. 98.7% of tuberculous effusions were lymphocyte-predominant (i.e., lymphocyte constituted more than 50% of the white cell count in pleural fluid) as compared to only 16.67% of patients with parapneumonic effusion and of empyema each (p<0.0001). There was no significant difference seen in the proportions of malignant effusions which were lymphocyte-predominant (p = 0.89).

The diagnostic yield of sputum smear for AFB in diagnosing tubercular effusion was 27.4%. Yields of pleural biopsy, lymph node FNAC, pleural fluid AFB staining, pleural fluid BACTEC culture and BAL fluid AFB staining were 62%, 81.5%, 3.2%, 31.25% and 13.15% respectively [Table/Fig-3]. Diagnostic yields of different investigations in the diagnosis of malignant effusions are also seen in [Table/Fig-3] with highest yield being seen in FOB guided biopsy (84.6%) followed by CT guided FNAC (77.6%).

Distribution of pleural fluid ADA (adenosine deaminase) value in various aetiologies is shown in [Table/Fig-4]. 77.4% of tubercular pleural effusion cases and 25% of empyema cases had pleural fluid ADA value of more than 70 IU/L. We found sensitivity of pleural fluid ADA in the diagnosis of tubercular effusion was 97.74% and specificity was 72.26% using 40IU/L as a cut-off value.

Complications arises due to the diagnostic procedures are summarized in [Table/Fig-5]. Iatrogenic pneumothorax due to pleural biopsy and CT-guided FNAC occurred in only 0.9% and 1.7% cases respectively. Haemoptysis was the only complication after bronchoscopic procedures and it occurred in 3.9% cases.

Diagnosis	No. of patients / Total no. of patients (%)
Tubercular pleural effusion	310/568 (54.57%)
Malignant pleural effusion	160/568 (28.17%)
Empyema	60/568 (10.56%)
Parapneumonic effusion	30/568 (5.28%)
Rheumatoid pleural effusion	5/568 (0.9%)
Pancreatitis	1/568 (0.17%)
Unidentified	2/568 (0.34%)

[Table/Fig-1]: Distribution of patients in different aetiologies

Cause of effusion	n	n (%)
Tubercular effusion	310	306 (98.7%)
Malignant effusion	160	116 (72.5%)
Empyema	60	10 (16.67%)
Parapneumonic effusion	30	5 (16.67%)
Rheumatoid effusion	5	1 (20%)
Pancreatitis	1	0 (0%)

[Table/Fig-2]: Causes of pleural effusion and percentage which were lymphocyte-predominant

Group	Procedures	n/n [no. of patients showing positive results/no. of patients in whom test was performed](%)
Malignant pleural effusions	Positive malignant cells in pleural fluid	88/160(55%)
	Pleural biopsy	39/86(45.34%)
	CT guided FNAC	45/58(77.6%)
	Lymphnode FNAC	29/60(48.34%)
	FOB guided biopsy	11/13(84.6%)
Tubercular pleural effusion	Sputum smear for AFB	85/310 (27.4%)
	Pleural biopsy	90/145(62%)
	Lymph node FNAC	110/135(81.5%)
	Pleural fluid AFB staining	10/310(3.2%)
	Pleural fluid BACTEC culture	10/32(31.25%)
	BAL fluid AFB staining	5/38(13.15%)

[Table/Fig-3]: Investigations contributing to diagnosis of malignant and tubercular effusions

	Total case (566)	Range of ADA (IU/L)					
		<40		40-70		>70	
		No	%	No	%	No	%
Tubercular effusion	310	7	2.3%	63	20.3%	240	77.4%
Malignant effusion	160	150	93.7%	10	6.2%	-	-
Empyema	60	15	25%	30	50%	15	25%
Para-pneumonic effusion	30	15	50%	15	50%	-	-
Rheumatoid arthritis	5	4	80%	-	-	1	20%
Pancreatitis	1	1	100%	-	-	-	-

[Table/Fig-4]: Pleural fluid ADA level in relation to diagnoses

Procedures	Complications	Percentage (%)
Blind pleural biopsy	Pneumothorax	2 (0.9%)
	Hemorrhage	3 (1.3%)
	Vaso-vagal attack	1 (0.4%)
CT guided FNAC and true-cut biopsy	Pneumothorax	1 (1.7%)
Fibre-optic bronchoscopy	Hemoptysis	2 (3.9%)

[Table/Fig-5]: Complications arising due to diagnostic procedures

DISCUSSION

In comparison to most previous studies which showed that upto 20% of patients with pleural effusions had no definite aetiology despite extensive investigations, our study has shown that only two cases (only 0.345%) of exudative effusions remain undiagnosed by using commonly available investigations like pleural fluid analysis, blind pleural biopsy, lymphnode FNAC, image and bronchoscopy guided FNAC and biopsy [2,3,4]. This difference may be attributed to the efficiency of pathologists, proper technique of pleural fluid collection and transport to the laboratory, appropriate application of the diagnostic procedures in proper clinical set up. To obtain a definite diagnosis was not only important for providing appropriate management but also because one-fifth of patients with no definite diagnoses continue to have recurrent effusions and was more likely to be associated with an occult malignancy as per literature [5,6].

In this study we found tuberculosis as the most common cause of exudative effusions like some of the earlier studies [2,7,8]. They found tuberculosis as the most common cause because they excluded referral cases from non-medical wards as the majority of these patients had malignancy as cause of the effusion. But in one recent study from Singapore How SH et al., found malignancy as the most common cause of exudative effusion in their study [9]. This difference may be attributed to the local difference of incidence of tuberculosis. India is the highest TB burden country

with World Health Organisation (WHO) statistics for 2011 giving an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 8.7 million cases [10].

The diagnosis of tubercular pleural effusion depends on the demonstration of tubercle bacilli in the sputum, pleural fluid or pleural biopsy specimen or the demonstration of granulomas in the pleura. Mycobacterial culture of the pleural fluid had a higher sensitivity than direct smear for AFB because direct examination requires bacilli concentration of 10,000/ml but the culture only requires the presence of ten to 100 organisms per ml. The sensitivity of pleural biopsy for diagnosing the tuberculous pleural effusion is higher than these two tests [4,7,11]. These studies demonstrated the sensitivity of pleural biopsy in tubercular effusion in the range between 50%-74%. In our study we found the sensitivity of mycobacterial culture, AFB smear and pleural biopsy were 3.2%, 31.25% and 62% respectively. The diagnosis can also be established with reasonable certainty by demonstrating elevated levels of ADA or interferon-gamma in the pleural fluid [10,12]. Because of poor economic status of most of our patients we could not estimate interferon-gamma level in pleural fluid. We found that 98.7% of our tubercular effusion cases were lymphocytic predominant and 97.7% of tubercular cases had ADA level above 40 IU/L. Though there was no statistically significant difference in the proportion of lymphocyte predominance between tubercular and malignant effusion but we found a significant difference between tubercular and malignant effusion in respect to ADA value. When we decide the cut-off to 70 IU/L then the term "high ADA value" is restricted to Tubercular Pleural Effusion (TBPE), empyema and rheumatoid arthritis. When we mark cut-off to 100 IU/L then only diagnosis is TBPE. It clearly shows that the higher the level of ADA, more likely the diagnosis was tuberculosis. So the pleural fluid ADA level could be used to exclude the diagnosis of tuberculous pleural effusions in patients with undiagnosed lymphocytic pleural effusions. Our finding in this respect was similar to some of the earlier studies [13,14]. Verma et al., also concluded that ADA > 100IU/L was observed in TB only in their recent study [14].

Cytological examination of pleural fluid specimens was the most specific method for identifying malignant effusions but it has a sensitivity of only 56% to 75% [7,11,15-18]. A previous study had shown that one sample of pleural fluid cytology has a sensitivity of 48.5% in identifying a malignant effusion and this may increase to 56.3% when diagnostic thoracentesis is repeated two or three times [17]. In our study sensitivity of one sample cytology was 40.6% which increased upto 55% after repetition for two or three times. Pleural biopsy in our study had a diagnostic yield of 45.34% which is consistent with that of 43% to 57% reported in other studies [7,11,16-19]. We did not repeat pleural cytology or biopsy in each and every suspected cases of malignant effusion in order to reduce complications of these invasive procedures. Another drawback of our approach was that we did not go for thoracoscopic pleural biopsy due to unavailability of the procedure. So we had to depend upon blind pleural biopsy. It is still value as a diagnostic procedure because of simplicity of the procedure and acceptable results.

The most frequent complication after a closed pleural biopsy is pneumothorax. However, the incidence of pneumothorax and the requirement for tube thoracostomy are comparable after thoracentesis and pleural biopsy [20]. This is probably because more experienced individuals usually perform the pleural biopsy. In the literature second most complication is bleeding causing haemothorax [21]. In our study hemorrhage was the most common complications followed by pneumothorax. This discrepancy may be due to technical expertise of the more trained technician in performing these biopsies. The rate of these complications are also much less compared to the existing literature [20]. There is also one case report of an arteriovenous fistula from an inter-costal

artery to an intercostal vein developing after pleural biopsy [22]. In our study we did not find any such complication.

We could not make diagnosis in 2 cases (0.34%). These two cases also had not attended to us for follow-up. Diagnosis would have been established by repetitions of the procedures in the follow-up visits. The figure “0.34%” is not as such a big issue especially when we studied such a large sample size.

CONCLUSION

Routine investigations are useful as well as safe options especially in the resource-poor set-up to reach the aetiological diagnosis of exudative pleural effusions.

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