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Assessment of Pleural fluid cholesterol & Protein in analysing Exudates & Transudates

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ABSTRACT

Introduction : Pleural effusion is defined as an abnormal and excessive collection of fluid in the pleural space. The most common cause in the West and India are infections followed by malignancy. In India, tubercular effusion is the most common cause followed by malignant effusion and a very few due to parapneumonic effusion. Aims and Objectives- To study the role of pleural fluid cholesterol in differentiating transudative and exudative pleural effusion and comparison of pleural fluid cholesterol to Light's criteria. **Methods:** This prospective study was carried out in hundred randomly selected adult patients of both sexes suffering from pleural effusion, where thoracocentesis yield a sufficient good quantity of pleural fluid for examination, were included. The patients were divided into three groups clinically according to expected nature of the fluid on aetiological grounds. **Results:** The aetiological classification of the 100 effusions is shown in table 1. According to the causal disease, 22 pleural fluid samples were labelled as transudates and 78 were labelled as exudates. The commonest type of effusion was found to be Tuberculous followed by Malignancy, Para-pneumonic, Congestive heart failure, Chronic liver disease. Results show that an increased concentration of cholesterol greater than 60 mg/dL and/or total protein levels greater than 3 g/dL in pleural fluid constitute useful measurements for separating exudates from transudates.**Conclusion:** Combined pleural fluid cholesterol and total protein are simple, cost effective, and useful parameters for differentiation of transudates from exudates. Simultaneous measurement of total protein and cholesterol in pleural fluid permits the identification of exudates through the elevation of either one or both of these indicators, with an accuracy superior to the best that has been reported with the criteria of Light *et al*. The proposed combination has the advantages that a simultaneous blood sample is not required and that chemical tests are reduced from four to two, thereby, lowering the cost of the diagnostic procedure.

Keywords: pleural effusion, exudate, transudate, Light's criteria, cholesterol .

Introduction

Pleural effusion is defined as an abnormal collection of fluid in the pleural space. Two types of effusions can develop (transudative and exudative). Transudative pleural effusions are caused by fluid leaking into the pleural space and increased hydrostatic pressure or decreased osmotic pressure. Exudative effusions are caused by blocked blood vessels, inflammation, lung injury and drug reactions which causes damage or disruption of pleural membranes or vasculature[1,2]

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Pleural effusion is a manifestation of several diseases, both pulmonary and extra-pulmonary, often isolated[1]. Based on the underlying pathological abnormality and mechanism of formation, effusions may be either transudates or exudates[2]. Analysis of pleural effusions is an important diagnostic step to guide further investigations and treatment. The most commonly accepted criteria for differentiating exudates from transudates in pleural effusions is through the measurement of total protein and lactate dehydrogenase (LDH) levels in serum and pleural fluid. These were established by Light et al[3] in 1972. Sensitivity and specificity, calculated from their data, were 99% and 98%, respectively. However, many workers have found Light's criteria as unsatisfactory[1,2,4,5].

In 1987, Hamm *et al* [6] showed that cholesterol concentration increases in exudative pleural effusions and, by using a cut-off point of 60 mg/dL, these correctly labeled 95% of 62 pleural fluid samples. Exudative pleural effusions are a common diagnostic problem in clinical practice as the list of causes is

quite exhaustive,[1-6] although sometimes they can be inferred from the clinical picture. The aetiological distribution of pleural effusions in various series depends on the geographical area, patient's age and advances in the diagnostic methods and treatment of the underlying causes. The difficulty in determining the cause of pleural effusion is shown by the fact that in many series "unknown aetiology" constitutes nearly 15%.[1-4] Exudative effusions require to be separated into infectious causes, non-infectious causes and malignancy.

Since the criteria of Light *et al* [3] require both pleural and blood samples, and four bio-chemical measurements, we examined whether a similar result could be obtained by combining cholesterol estimation with only one of the individual components of Light *et al*,[3] thus, simplifying the diagnostic procedure and lowering the cost.

Methedology

This prospective study was carried out in hundred randomly selected adult patients of both sexes suffering from pleural effusion, where thoracocentesis yield a sufficient good quantity of pleural fluid for examination, were included. Study involved Prior Consent from Hospital Authorities / Medical Superintendents of the Local Randomly selected Tertiary care hospitals including ours having Chest Medicine Ward & ICU with well equipped BioChemistry / Pathology Labs. The study was conducted within ethical standards.

All patients underwent a detailed history and a complete clinical examination. Blood investigations (complete haemogram, total protein, glucose, cholesterol and LDH), urine examination, chest radiograph (postero-anterior view), sputum smear examination for acid-fact bacilli (AFB) were done in all patients. Additional investigations including a lateral chest radiograph, fluoroscopy, ultrasonography, computed tomography chest, pleural biopsy, bronchoscopy, 2-D echocardiogram, standard renal, liver, and thyroid profiles and other tests were done wherever indicated. Pleural fluid analysis was done for total protein, glucose, LDH, cholesterol, total cell count, differential cell count, gram stain for bacteria, Ziehl-Neelsen stain for AFB and cytology in all patients. Pleural and serum collected at the same time.

The patients were divided into three groups clinically according to expected nature of the fluid on aetiological grounds.

Group I. Patients with congestive heart failure (CHF), cirrhosis of liver and pericardial effusion. CHF was diagnosed by an enlarged heart, radiological signs of congested lungs, peripheral oedema, and response to treatment of CHF. Liver cirrhosis was diagnosed by evidence of liver cirrhosis on liver sonogram. Pericardial effusion was diagnosed by 2-D echocardiogram.

Group II. Exudates of a malignant origin confirmed by one or more means: lung biopsy or fine needle aspiration cytology, pleural biopsy, pleural fluid cytology. A case of lymphoma was diagnosed by excisional biopsy of the lymph node.

Group III. Exudates of other origin included those patients with evidence of pneumonia or tuberculosis on radiography, leukocytosis, pleural fluid for Gram's stain, fever, and response to antibiotics or anti-tuberculosis treatment.

For the laboratory classification of pleural fluids, a cut-off point of >3 g/dL for total protein and a cut-off point of >60 mg/dL was adopted for cholesterol.

Laboratory classification was also made by using Light's criteria. According to this criteria if any one of the following is present then the fluid was classified as an exudate: (1) pleural fluid to serum total protein ratio greater than 0.5, (2) pleural fluid to serum LDH ratio greater than 0.6, and/or (3) pleural fluid LDH greater than 200 IU/L.

Data was filled in Microsoft Excel & analysed using the Statistical Package for Social Sciences (SPSS) for Windows version 17 & a computer software Epi Info version 6.2 (Atlanta, Georgia, USA). Quantitative and qualitative data were confirmed to be parametric and analyzed with student t test and Fisher exact test respectively. For paired observations (before and after treatment) paired t test was used for quantitative data and Mc Nemar's test was used for qualitative data. The sensitivities, specificities, positive predictive values and negative predictive values were obtained. The aetiological classification according to the criteria of Light *et al*[3] was used as the "Gold Standard".

Results

100 patients were finally analysed. The aetiological classification of the 100 effusions is shown in table 1. According to the causal disease, 22 pleural fluid samples were labelled as transudates and 78 were labelled as exudates. One of the 78 exudates was mis-classified as transudate (sensitivity 98%) while there was no mis-classification of the 11 transudates (specificity 100%).

Table 1:Types of pleural effusion

Transudates (Group I)	
CHF	10
Cirrhosis	9
Pericardial effusion	2
Constrictive pericarditis	1
Post operative	2
Malignant effusion (Group II)	
Lung	15
Epiglottis	3
Lymphoma	1
Other Exudates (Group III)	
Tuberculosis	40
Pneumonia	15
Liver abscess	2

CHF=Congestive heart failure

When pleural fluid cholesterol alone was used at a cut-off point of >60 mg/dL, one (tuberculous pleural effusion) of the 78 exudates was mis-classified as transudate (sensitivity 98%) while there was no mis- classification of the 11 transudates (specificity 100%). When the pleural fluid cholesterol with a cut-off point of >60 mg/dL in combination with a pleural fluid total protein with a cut-off point of >3 g/dL was used for classification, all exudates and transudates were correctly labelled (sensitivity and specificity both were 100%). The exudate that was erroneously classified by the criteria of Light *et al*[3] was correctly identified using cholesterol level, while the exudate that was mis-classified by cholesterol was correctly identified by the pleural fluid total protein level.Table 2 shows the sensitivity, specificity, PPV and NPV calculated for the criteria of Light *et al*3, for cholesterol alone, for total protein alone and for combination of cholesterol and total protein.

Table 2: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different parameters

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pleural fluid protein	98	100	100	92
Light's criteria	98	100	100	92
Pleural fluidcholesterol	98	100	100	92
Pleural fluid proteinand/or pleural fluid cholesterol	100	100	100	100

The commonest type of effusion was found to be Tuberculous followed by Malignancy , Para-pneumonic , Congestive heart failure , Chronic liver disease , as shown in Table 1. The most frequent cause of pleural exudates is tuberculosis followed by lung cancer, which is similar to the result of a study done in high tuberculosis burden countries like India.

Discussion

The initial step in the management of pleural effusions is to distinguish transudates from exudates. The criteria often used to do so are based on biochemical parameters proposed by Light *et al.*[3] Since no single test has yet proved to be completely satisfactory, the search for improved methods continues.

The cholesterol levels are elevated in exudative pleural effusions of much shorter duration.7 The cause of the increased cholesterol concentration in pleural exudates is unknown. Increased pleural permeability leading to accumulation of cholesterol in pleural exudates due to "serum leakage" may be a reasonable explanation. Cholesterol is found in all tissues and is uniformly found in all pleural effusions[8].

Our results show that an increased concentration of cholesterol greater than 60 mg/dL and/or total protein levels greater than 3 g/dL in pleural fluid constitute useful measurements for separating exudates from transudates. The diagnostic yield of this combination is superior to that obtained by Light *et* al[3] in their original investigation and to those reported by other authors2,4,5,6 and what is observed in the present study using the same diagnostic criteria in similar patients. Romero *et al*,[9] propose a modification of the cut-off points of Light *et al*3that increase specificity to 93% with a slight decrease of sensitivity to 94%. Despite the improvement, these values are lower than those obtained with the combined use of cholesterol and total protein.

Conclusion

This study is not without limitations. A sample size of convenience was taken as we could not find any suitable reference to assist calculation of sample size. Combined pleural fluid cholesterol and total protein are simple, cost effective, and useful parameters for differentiation of transudates from exudates. Simultaneous measurement of total protein and cholesterol in pleural fluid permits the identification of exudates through the elevation of either one or both of these indicators, with an accuracy superior to the best that has been reported with the criteria of Light *et al*. The proposed combination has the advantages that a simultaneous blood sample is not required and that chemical tests are reduced from four to two, thereby, lowering the cost of the diagnostic procedure.

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