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CLINICAL UTILITY OF PLEURAL FLUID CHOLESTROL IN DIFFERENTIATING TRANSUDATES FROM EXUDATES PLEURAL EFFUSION.

Pulmonary Medicine

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ABSTRACT

OBJECTIVES: To assess the significance of pleural fluid cholesterol levels in differenting transudative and exudative pleural effusion as compared with light's criterion.

MATERIAL AND METHODS: 100 patients of pleural effusion from wards of TB and chest Hospital, Patiala, Punjab were studied. A detailed clinical history, a thorough physical examination and routine radiological and laboratory investigations were carried out in all the patients. Patients were clinically divided into exudative and transudative groups.The value of protein, LDH and cholesterol were estimated in pleural fluid along with serum cholesterol and protein. Sensitivity, specificity, PPV, NPV and accuracy of all parameters were calculated with the cut off of cholesterol as 60 mg/dl.

RESULTS: Pleural cholesterol has sensitivity and specificity of 92.6% and 100% respectively to differentiate between exudative and transudative pleural effusion.

CONCLUSION: Pleural cholesterol as a parameter to separate exudative pleural effusion from transudative is easier, efficient, cost effective and there is no need of blood sample.

KEYWORDS

INTRODUCTION

Pleural cholesterol is thought to be derived from degenerating cells and vascular leakage from increased permeability. Though the cause of the rise in cholesterol levels in pleural exudates is unknown, two possible explanations have been put forward. According to the first, the cholesterol is synthesized by pleural cells themselves for their own needs[1](extrahepatic synthesis of cholesterol is now known to be much greater than was once thought, depends on the metabolic needs of cells, and is in dynamic equilibrium with cholesterol supply by low density lipoprotein and cholesterol removal by high density lipoprotein),[2] and the concentration of cholesterol in pleural cavity is increased by the degeneration of leukocytes and erythrocytes, which contain large quantities. The second possible explanation is that pleural cholesterol derives from plasma; some 70 percent of plasma cholesterol is bound to low density, high molecular weight lipoproteins, and the rest to high density lipoprotein or very low density lipoproteins and the increased permeability of pleural capillaries in pleural exudate patients would allow plasma cholesterol to enter the pleural cavity.[3]

The classification of pleural effusion as transudative or exudative is the primary diagnostic step because, if the effusion is a transudate, no further diagnostic procedures are necessary and therapy is directed towards the underlying disease process. However, if the effusion is exudative, a more extensive diagnostic work-up is required to distinguish between the many possible causes of exudative effusion. Many criteria have been established but none has a 100% sensitivity and specificity. The aim of the present study is to assess the value of the pleural cholesterol level to differentiate between exudate and transudate and to establish its utility as compared with light's criterion.

MATERIAL AND METHODS

This prospective study was conducted on patients of either sex presenting to the department of TB and Chest, Government Medical College and Rajindra hospital, Patiala with sign and symptoms of pleural effusion. The sample size was 100. Out of which 75 were exudative and 25 transudative pleural effusion based on light's criterion and clinical ground.

Two gold standards were used for classifying a pleural effusion as transudative or exudative. One was Light's criteria, i.e. pleural fluid LDH (Lactate Dehydrogenase) >200 IU/L, pleural fluid to serum LDH ratio >0.6 and pleural fluid protein to serum protein ratio >0.5.[4] The presence of any one of the three criteria established that the pleural fluid was exudative while the diagnosis of transudative effusion was made in the absence of all three criteria.

The other gold standard was clinical criteria by which a patient was classified as having a transudative effusion if he had a clinical condition that could give rise to a transudative effusion such as congestive heart failure, cirrhosis of the liver or nephrotic syndrome, with a response to treatment of the underlying condition and absence of any other condition which could give rise to a pleural effusion. Patients were classified as having an exudative effusion if they fulfilled the criteria for diagnosis of tubercular, malignant or parapneumonic effusion.

The following clinical evidences were used to include or exclude the cases :-

(1) Congestive heart failure: presence of clinical features (increased jugular venous pulse, pedal edema, tachycardia and ventricular gallop) with cardiomegaly or echocardiac evidence of cardiac dysfunction.
(2) Renal diseases: elevated urea (>20 mmol/L) or creatinine > 167 µmol/L with or without signs or symptoms of fluid overload.
(3) Malignancy: confirmed by cytology or histological proof of malignant tumor and in absence of all other conditions associated with pleural effusion.
(4) Liver cirrhosis: sign and symptoms of chronic liver disease and positive ultrasonography or computed tomography findings with lab evidence of hepatic derangements and portal hypertension.
(5) Tuberculosis: signs and symptoms like evening rise of temperature, loss of weight and appetite, cough with expectoration were supported by raised erythrocyte sedimentation rate(ESR), sputum for acid fast bacilli(AFB), chest X-ray, biopsy or fine needle aspiration cytology of lymph node.
(6) Infective effusion: clear evidence of infection (positive microbiologic culture), elevated CRP or leukocytosis, or positive sputum stain.
(7) Hypoalbuminemia: serum albumin < 20 gm/L.[16]

Pleural effusions associated with congestive cardiac failure, renal diseases, hypoalbuminemia and liver cirrhosis were classified as transudates and all others as exudates.

Inclusion criteria:

1. Age >15 years.
2. Clinically and radiologically demonstrable moderate to large pleural effusion.
3. Willingness to participate in the study.

Exclusion criteria:

1. **History of previous thoracocentesis .**
2. **A bleeding diathesis.**

Patients with hypercholesterolemia were also excluded from the study. Patients on diuretics for their underlying disease in the group of transudative effusion were not excluded from the study.

Work-up:

A detailed history, physical examination and chest X-ray was done. Investigations were as follows :-

- Haemoglobin, total leucocyte count, differential leucocyte count, ESR, mantoux test, sputum for AFB
- Pleural fluid of the patient was tested for- Total proteins, LDH level, cholesterol level, sugar, cytology, ZN stain, malignant cells.
- Serum proteins and LDH level were also measured for Light's criterion.
- Samples were processed immediately without any delay. The fluids were centrifuged for 5 min at 1500/rpm. The supernatant fluid and serum were analyzed for protein, LDH and cholesterol levels by Biuret method, DGKC method, and CHOD–PAP method respectively.[5] Senstivity, specificity, positive predictive value(PPV), negative predictive value(NPV) and accuracy of all parameters were calculated and the cut off for cholesterol was taken as 60 mg/dl, below that was transudate and above that was exudate.

RESULTS

Exudative pleural effusion is more common than transudative effusion. Maximum number of patients were in the age group of 30-60 years. Male preponderance was seen in pleural effusion, twice more common in males.Breathlessness was the most common presenting symptom in both the groups. Cough, chest pain and fever were more common in exudative group while extrapulmonary manifestations were much more common in transudative group. Majority of the effusions were medium sized . Right sided effusions were more common in both groups than left .However, bilateral was the most common type in transudative effusions. Most of the patients had duration of symptoms for 1-3 months in both the groups. Straw coloured effusions were the most common along with lymphocytic predominance on cytology.

1. With a cut off value of pleural fluid protein of 3 gm%, it was observed that the sensitivity and specificity of this parameter to differentiate between exudative and transudative pleural effusions is 96%.
2. The sensitivity of pleural fluid to serum protein ratio was 89% and specificity was 92% with a reference value of 0.5.
3. With a cut off value of pleural fluid LDH of 200 IU/L, it was observed that the sensitivity and specificity of this parameter to differentiate between exudative and transudative pleural effusions is 93% and 96% respectively.
4. The sensitivity of pleural fluid to serum LDH ratio was 98.7% and specificity was 84% with a reference value of 0.6.
5. Mean pleural fluid cholesterol values were found to be higher in exudates than transudates and the increase is statistically highly significant.
6. With the reference limit of 60 mg/dl, the sensitivity obtained from pleural fluid cholesterol was 92% and the specificity was 100% in differentiating exudative from transudative pleural effusion.
7. Light's criteria was found to be 84% sensitive and 76% specific in differentiating exudative from transudative pleural effusion. It misclassified 12 out of 75 exudative and 6 out of 25 transudative effusion.
8. Pleural cholesterol has a better sensitivity, specificity, and PPV in differentiating transudates and exudates than the parameters of Light's criteria. This also avoids the plasma protein, serum LDH and pleural fluid protein, and LDH measurement. Therefore, it is a more efficient, easier, and a more cost effective method to differentiate exudates from transudates. This study also suggests that determination of pleural cholestrol should be in routine practice in all cases of pleural effusion.

DISCUSSION

Pleural effusion occurs in a number of pathological conditions and even exhaustive diagnostic tests fail to reveal the aetiology in as many as 15%–20% of cases.[6-8] The classification of pleural effusion as transudative or exudative is the primary diagnostic step because, if the effusion is a transudate, no further diagnostic procedures are necessary and therapy is directed towards the underlying disease process. However, if the effusion is exudative a more extensive diagnostic work-up is required to distinguish between the many possible causes of exudative effusion. In India, tubercular effusion is common and may occur in a setting where the patient is predisposed to develop an effusion due to other causes. The various criteria that have been employed include pleural fluid specific gravity, protein levels and lactic dehydrogenase (LDH) levels.[9]

The first step in determining the aetiology of a pleural effusion should be to find out whether it is a transudate or an exudate. No single test or series of tests has yet proved to be completely reliable. Several criteria have been proposed and one of these—pleural fluid cholesterol seems to have a higher diagnostic accuracy for identifying transudates. This study was designed to assess the utility of pleural fluid concentrations of cholesterol in comparison to the traditional criteria of Light et al and its individual parameters (pleural fluid LDH concentration, pleural fluid to serum LDH ratio, and pleural fluid to serum protein ratio) to distinguish between exudates and transudates .

The sensitivity, specificity of pleural fluid in present study for pleural protein to differentiate between exudative and transudative pleural effusion was 96 both. Results are not in agreement with Heffner et al[3] (1977), Guleria et al[9](2003) and Anchinmane et al[10](2011) where both sensitivity and specificity are lesser than the present study.

However, LDH is also released by neutrophils and so may be important in infections. There is no ideal biochemical marker that allows complete discrimination between transudates and exudates.[11] Our results are in partial concordance with Guleria et al [9](2003), Leers et al[12](2007) and Romero et al[13](2000). Paramothayan et al[11] (cut off value of 130 U/L) and Basran et al[14] (cut off value of 163 U/L) have tried different cut off values of fluid LDH which raised the accuracy of fluid LDH. Hence fluid LDH was found to be a better parameter than other parameters. But in the present study, we found that fluid cholesterol is a better parameter than fluid LDH .[10]

Heffner et al[3] (1977) also observed similar results which are in agreement with our study but less comparable to Guleria et al[9](2003) and Hamal et al[15](2013)who observed lesser sensitivity and specificity but still specificity was higher than sensitivity as in our study. favouring the earlier reports of various workers like Guleria et al[9] (2003),Heffner et al[3](1977) and Leers et al[12](2007) who reported that pleural/serum(p/s) LDH is more sensitive and less specific in differentiating exudative from transudative pleural effusion. Test combination increases sensitivity, improves accuracy and are the basis for Light's criteria. It includes p/s protein ratio, p/s LDH ratio and fluid LDH level. Burgess et al[16](1995) and Romero et al[14](2000) showed that Light's criteria is the best criteria to differentiate fluids into transudates and exudates than other parameters including fluid cholesterol. In the present study, we found that Light's criteria had less accuracy (82%) than fluid cholesterol (94%) which is similar to findings of Achinmane et al[10](2011). But in a study by Gazquez et al[17](1998) no parameter, including pleural cholesterol, was superior to Light's criteria.

In the present study, pleural fluid cholesterol has sensitivity, specificity and accuracy of 92.6,100,94 respectively. As is evident from table (fig 1), sensitivity and specificity is maximum with cut off of 60mg/dl, especially specificity is more with 60 as cut off. Results are comparable with Guleria et al[9](2003),Hamal et al[15](2013), Valdes et al[19](1991) and Costa et al[19](1995) while there is disagreement with Hamm et al[20] (1987), Bhargava et al[21](1994), Heffner et al[10] (1997) in which sensitivity of pleural cholesterol is more than specificity. Using a dividing line of 60 mg/dl to separate exudates from transudates, only 5 percent were incorrectly classified. Elevated cholesterol levels in exudates seem to be independent of the serum levels. Pleural fluid cholesterol level is a simple and cost-effective aid in differentiating exudative from transudative pleural effusions.

LIMITATIONS

Serum cholesterol was not included in the study but Hernandez et al[22] (1994) concluded that p/s cholesterol is better than pleural chlosterol alone. Number of patients in our study were less. Lights criteria has misclassified more of transudates. Hence,our number of transudate cases should have been more for better understanding of cholesterol significance in transudates as compared to lights.

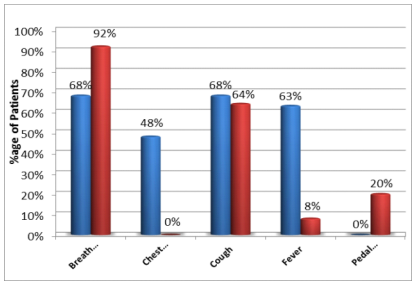

Fig 1:bar Diagram Showing Distribution Of Patients According To The Presence Of Clinical Symptoms

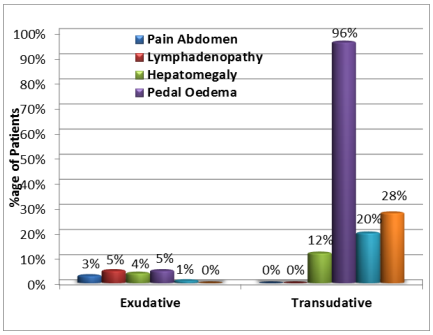

Fig 2: Bar Diagram Showing Distribution Of Patients According To The Presence Of Extrapulmonary Signs And Symptoms

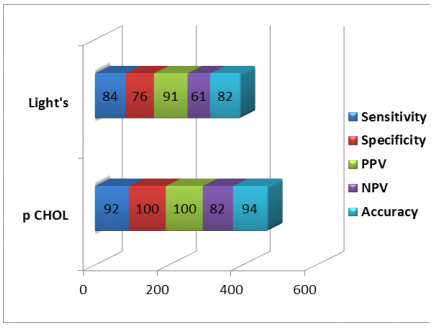

Fig 3: Diagnostic Value Of Light's Criterion And Pleural Cholestrol For Differentiation Between Exudative And Transudative Pleural Effusions.

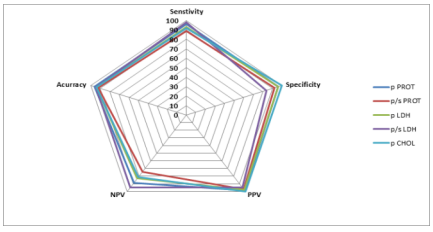

Fig 4: Diagnostic Value Of Individual Parameter For Differentiation Between Exudative And Transudative Pleural Effusions.

Parameter	Cut off	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy
p Protein	3 gm/dl	96	96	98.63	88.88	96
p/s Protein	0.5	89.3	92	97.1	74.2	92
p LDH	200 IU/L	93	96	98	83	94
p/s LDH	0.6	98.67	84	94.87	95.45	95
p CHOL	60 mg%	92	100	100	80.6	94
Light's	-	84	76	91.3	61.2	82

In FIG 5, sensitivity, specificity, PPV, NPV and accuracy of all the parameters are explained.

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