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USE OF CHOLESTEROL IN THE DIFFERENTIATION OF EXUDATIVE AND TRANSUDATIVE PLEURAL EFFUSION

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ABSTRACT

Light's criteria (protein and LDH) have been used to the present to differentiate exudative pleural effusion from transudative. This is both time consuming and relatively more expensive as compared to measuring cholesterol.

During 1992-1993, a prospective study on 70 patients with effusion was carried out measuring fasting LDH, protein, cholesterol, alkaline phosphatase and glucose. All patients had their underlying disease diagnosed; then Light's criteria was compared to cholesterol using Wilcoxon's test and Student's t-test.

Our findings showed taking a value of pleural cholesterol>55 mg/dL and pleural/serum cholesterol > 0.3 to define exudative effusion resulted in less erroneous classification with a sensitivity of 93%, a specificity of 100%, a positive predictive value (PPV) of 100% and an accuracy of 95.2%. Using Light's criteria gave a sensitivity of 95%, a specificity of 95%, a PPV of 97.6% and an accuracy of 95.2%. Using cholesterol in differentiating exudate from transudate was especially useful in patients with C.H.F. who received diuretics. Therefore, using cholesterol to differentiate exudative from transudative pleural effusion is more cost-effective and just as useful as Light's criteria.

Keywords: Effusion, pleural, exudative, transudative

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INTRODUCTION

Pleural effusion develops in a variety of illnesses. Chemical analysis of this fluid can often help in arriving at a diagnosis.[1] Nevertheless, even in the best settings, we are unable to make a diagnosis in 20% of the cases.[2] The first approach in diagnosis is to establish if the effusion is an exudate or a transudate. Up to the present, Light's criteria using LDH and protein have been used.[2,3] LDH>200 I.U., protein>3g/100mL, pleural LDH/serum LDH>0.6, and pleural protein/serum protein >0.5 has been defined as exudative.[2,4] Because of the cost of these tests in our country, we evaluated cholesterol, triglyceride and alkaline phosphatase (ALP) levels to help differentiate exudate from transudate.

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MATERIALS AND METHODS

During 1992-1993, a prospective study on 70 patients with pleural effusion was carried out. In a fasting state, each patient had 20 mL of pleural fluid drained to which 0.5 mL (2500 units) of heparin was added and at the same time 5

Table I. Mean values ($\bar{X}$), SDs, and ranges of the parameters studied in the different types of effusions.

		Trans. N= 20	Neoplastic N=17	TB N= 21	Misc. N= 5
P/S Prot	$\bar{X}$	0.31	0.63*	0.65*	0.74*
	SD	0.13	0.11	0.13	0.32
	Range	0.1-0.46	0.48-0.9	0.4-1	0.47-103
P LDH	$\bar{X}$	88	309*	243*	171*
	SD	30	204	127	84
	Range	45-173	75-848	65-636	69-288
P/S LDH	$\bar{X}$	0.34	0.98*	0.96*	0.72*
	SD	0.11	0.71	0.42	0.35
	Range	0.1-0.5	0.3-2.9	0.4-2.2	0.2-1.2
P Chol	$\bar{X}$	29	72*	92*	60*
	SD	10	19	27	42
	Range	18-58	44-116	54-157	20-119
P/S Chol	$\bar{X}$	0.18	0.45*	0.51*	0.39*
	SD	0.08	0.12	0.07	0.21
	Range	0.1-0.4	0.2-0.7	0.4-0.7	0.1-0.6
P Tri	$\bar{X}$	20	46*	46*	108*
	SD	4.7	24	20	17
	Range	15-32	20-88	20-100	17-429
P/S Tri	$\bar{X}$	0.22	0.37*	0.37*	0.55*
	SD	0.09	0.17	0.15	0.58
	Range	0.05-0.4	0.2-0.8	0.08-0.8	0.06-1.5
P ALP	$\bar{X}$	24	51*	59*	49*
	SD	11	36	14	24
	Range	11-60	21-167	31-80	21-85
P/S ALP	$\bar{X}$	0.34	0.47*	0.53*	0.44*
	SD	0.12	0.14	0.14	0.23
	Range	0.1-0.6	0.2-0.7	0.3-0.9	0.2-0.8

*$p<0.001$ with respect to the group of transudates; Trans.= transudative; Misc.= miscellaneous; P= protein; S= serum; Prot= protein; Chol= cholesterol; Tri= triglyceride; ALP= alkaline phosphatase.

mL of blood drawn. These were analyzed for glucose, total protein, LDH, ALP, cholesterol and triglyceride. These tests were done using an enzymatic analyzer with an Echniqone kit and Technicon RA 1000, except for protein which was manually analyzed. Using clinical, radiological, microbiological, chemical and pathological evaluation, a firm diagnosis was established in 63 patients.

Light's criteria as mentioned in the introduction was applied to these patients to check the specificity and sensitivity compared to the established diagnosis.

Pleural cholesterol levels above 55 mg/dL and/or a pleural cholesterol/serum cholesterol level above 0.3 were defined as exudative.[2] Again, these criteria were compared to the established diagnosis to give us the specificity, sensitivity, predictive values and efficiency.

Statistical analysis

The usefulness of each parameter was established using the Bayessian method to measure:

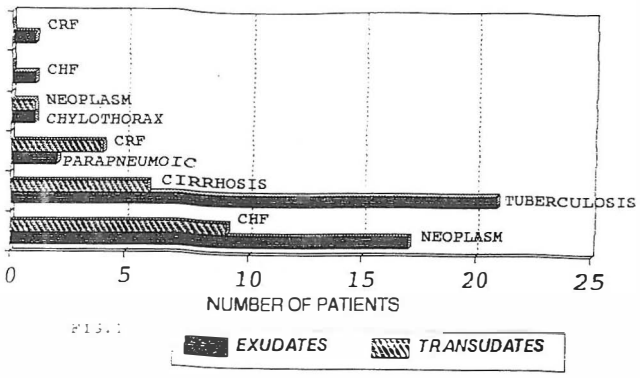

Fig. 1. Transudates and exudates based on Light's criteria. As noted, tuberculosis and neoplasms are the most common cause of exudation, while CHF and cirrhosis are the main causes for transudation.

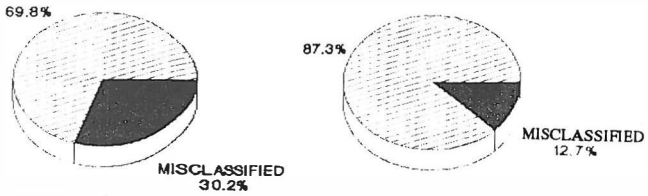

Fig. 2. Using the criterion of LDH>200 IU alone or LDH ratio>0.6 gave poor results with 30% and 12% misclassification, respectively.

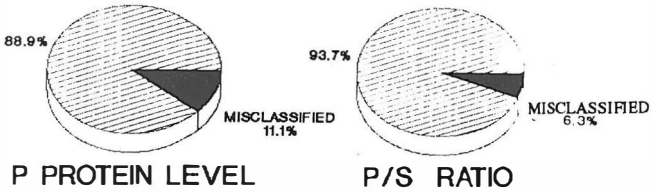

Fig. 3. Using the criterion of pleural protein level>3 g/dL or a ratio of >0.5 gives good results with only 11.1% and 6.3% misclassification, respectively.

Sensitivity= TP/TP + FN
Specificity= TN/TN + FP
Positive predictive value (PPV)= TP/TP + FP
Negative predicitive value (NPV)= TN/TN + FN
Efficiency= TP + TN/TP + TN + FP + FN

The statistical significance of differences between means was established by Student's t-test and Wilcoxon's t-test.

RESULTS

The etiology of 10% of the 70 patients with pleural effusion remained undiagnosed and they were thus excluded from the study. From the remaining 63 patients, 17 (11 male, 6 female) had neoplasms with exudative fluid (Fig.

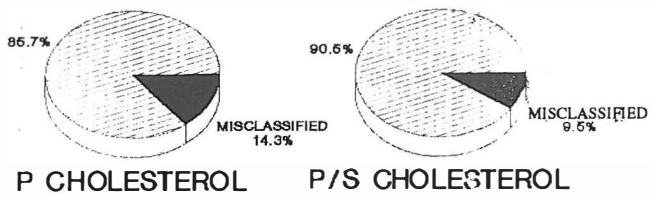

Fig. 4. Using the criterion of pleural cholesterol>55 mg/dL or a ratio of >0.3 gave good results with only 14.3% and 9.5% misclassification, respectively.

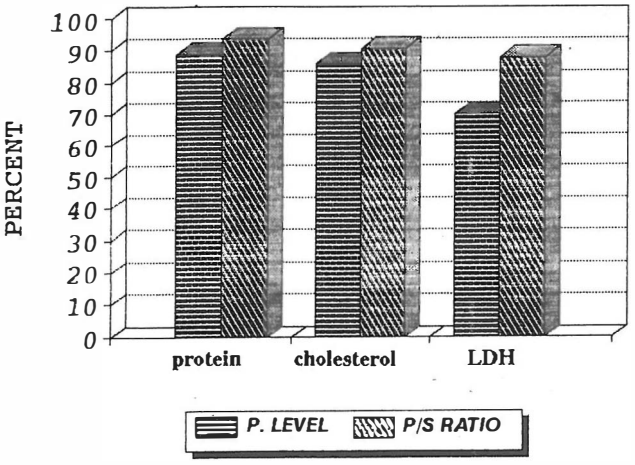

Fig. 5. The efficiency or accuracy of using protein ratio or cholesterol level is high and both are very close to each other (93.6% and 90.4%, respectively).

1.), 21 (11 male, 10 female) had tuberculosis, and 5 (4 male, 1 female) had exudate with miscellaneous causes including 2 parapneumonic effusions, 1 chylothorax, 1 CHF and 1 chronic renal failure. The remaining 20 patients had transudative effusions (11 male, 9 female); of these, 9 were due to CHF, 6 had liver cirrhosis, 4 chronic renal failure and 1 malignancy. As noted in Table I, there is a significant difference in mean values between transudate and exudate using all parameters excepts for pleural ALP/serum ALP.

In our study we used the cut off line of 55 mg/dL of pleural cholesterol (PCHOL) to differentiate exudate from transudate. With this criterion, 17% (3/17) of neoplasms, 4.7% (1/21) of tuberculosis patients, 10% (2/20) of transudative and 60% (3/5) of miscellaneous patients were misclassified (Table II). Using pleural to serum cholesterol ratios above 0.3 to define exudates gave us better results with 11.7% (2/17) of neoplasms, 10% (2/20) of transudative cases and 40% (2/5) of miscellaneous patients misclassified. The total percentage misclassified in each of the 6 parameters are shown in Figs. 2-4.

This shows that using pleural LDH>200 IU to define exudate gives a 30.2% misclassification, but LDH ratio gave better results with only 12.7% misclassification. Using pleural protein levels>3g to define exudate caused 11.1% misclassification, and using a protein ratio of >0.5 gave

Table II. Number of misclassified pleural effusion in each group for every parameter studied.

	Trans.	Neoplastic	TB	Misc.	Total
P Prot	1/20	3/17	3/21	0/5	7/63 (11.1%)
P/S Prot	0/20	1/17	2/21	1/5	4/63 (6.3%)
P LDH	0/20	7/17	9/21	3/5	19/63 (30.1%)
P/S LDH	0/20	5/17	2/21	1/5	8/63 (12.6%)
P Chol	2/20	3/17	1/21	3/5	9/63 (14.2%)
P/S Chol	2/20	2/17	0/21	2/5	6/63 (9.5%)
P Tri	1/20	6/17	5/21	3/5	15/63 (23.8%)
P/S Tri	7/20	6/17	4/21	2/5	19/63 (30.1%)
P ALP	5/20	1/17	0/21	1/5	7/63 (11.1%)
P/S ALP	7/20	3/17	2/21	2/5	14/63 (22.2%)

Trans.= transudative; Misc.= miscellaneous; P= protein; S= serum; Prot= protein; Chol= cholesterol; Tri= triglyceride; ALP= alkaline phosphatase.

only 6.3% misclassification. Using a pleural cholesterol level>55 mg/dL gave 14.3% misclassification, and the ratio gave only 9.5% misclassification.

Concerning the specificity and sensitivity of each test, using cholesterol ratio gives us 90.6% sensitivity and 90% specificity, which is very close to the protein ratio which is 90% sensitive and 100% specific.

The efficiency of these criteria shown on graph 5 is also very close to 90.4% and 93.6%, respectively. We did not find the use of triglyceride or ALP levels helpful in this study, nor was there any significant relationship between cholesterol level and the number of leukocytes in pleural fluid, or a relationship between extent of effusion and the diagnosis.

DISCUSSION

The first step in diagnosing the etiology of pleural effusion is to establish whether it is an exudate or a transudate.[1] Light's criteria have been widely accepted so far, though some reports suggest that measuring cholesterol levels may be better or just as helpful.[2,5,6,7] Use of protein ratio in our study provided a sensitivity of 90.6%, specificity of 100%, a PPV of 100% and an efficiency of 93.6% for differentiating exudate from transudate.

There were a few patients with CRF who were misclassified as exudates. This could be due to protein loss and poor protein intake.

We noticed that the mean value of cholesterol in a transudative effusion was 29 ±10 mg/dL, in an exudate due

to malignancy 72±19 mg/dL, in tuberculosis 92±27 mg/dL and in miscellaneous causes 60±42 mg/dL. With use of a dividing line of 55 mg/dL for pleural cholesterol, we could separate transudate from exudate with 83.7% sensitivity, 90% specificity and a PPV of 94.7%. If the criterion P/S cholesterol>0.3 was used to define an exudate, we would get results with a sensitivity of 90.6%, a specificity of 90%, a PPV of 95.1% and an efficiency of 90.4%. If we used both parameters (cholesterol level and cholesterol ratio), we had less misclassification as compared to Light's criteria, and sensitivity improved to 93% with 100% specificity, 100% PPV and 95.2% efficiency. Of interest was the fact that we had 4 patients with CHF who were tapped repeatedly at prolonged intervals with the pleural cholesterol level +/- ratio remaining unchanged; whereas Light's criteria were altered. There are not enough patients to arrive at a definite conclusion regarding this point and it has to be further investigated.

The cause of the increased cholesterol concentration is unknown, but two hypotheses are available: [2,5]

A) Cholesterol production by different cells has been recognized and it is possible that destruction of white and red blood cells in pleural effusion can cause an increase in the fluid cholesterol level.

B) Increased pleural permeability causes cholesterol concentrations to increase.

We agree with the second hypothesis as we found no significant relationship between cholesterol levels and the number of WBC or RBCs in the pleural fluid.

Use of ALP as a criterion was not very helpful. Using a dividing line of 30 mg/dL for pleural ALP gave us a sensitivity of 95.3%, but specificity was only 75%. Use of triglycerides gave us even poorer results. Therefore, they are not discussed further.

In summary, P/S protein and P/S cholesterol were the most useful criteria for differentiating exudative from transudative effusion. Both are very close in accuracy, with protein being slightly more accurate; but since the cost is 1/7 that of Light's criteria, we believe that use of cholesterol to differentiate exudate from transudate may be more cost-effective.

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