Cholesterol in Pleural Effusions*
A Diagnostic Aid
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In this prospective study of 70 patients with pleural effusion, the underlying disease could be identified in 62 cases. By predefined criteria, 31 of these effusions were classified as transudates and 31 as exudates. Pleural fluid protein content, LDH activity and cholesterol level were measured to investigate their utility in differentiating the exudates from the transudates. Protein and LDH levels, and their pleural fluid-to-serum ratios, resulted in erroneous classification of 11 to 15 percent of the effusions. Mean cholesterol level in malignant effusions was 94 mg/dl, 76 mg/dl in inflammatory effusions and 30 mg/dl in the transudates. Using a dividing line of 60 mg/dl to separate the exudates from the transudates, only 5 percent were incorrectly classified. Elevated cholesterol levels in exudates seem to be independent of the serum levels. Our findings indicate that the pleural fluid cholesterol level is a simple and cost-effective aid in differentiating exudative from transudative pleural effusions.

Pleural effusions evolve in the course of a variety of diseases. They represent a common diagnostic task to the clinician. A correct diagnosis of the underlying disease is essential to rational management. In many cases, a diagnosis may be established without difficulty. However, despite employment of extensive diagnostic procedures, the cause remains elusive in 10 to 20 percent of all cases.1–3

A primary diagnostic step is the identification of a pleural effusion as either a transude or an exudate. Transudates are secondary to diseases elevating hydrostatic pressures in the systemic or pulmonary circulation, or diseases decreasing plasma colloid-osmotic pressure. Exudates develop when the permeability of the pleural surface is altered or lymphatic drainage is impaired.4

Levels of pleural fluid protein and lactic dehydrogenase (LDH) are commonly analyzed to classify an effusion as an exudate or a transude. A protein level of 3.0 g/100 ml and an LDH level of 200 IU are used as dividing lines separating transudates from exudates. Results have not always been satisfying.5

Light et al6 demonstrated improvement of diagnostic accuracy by establishing the following criteria for exudates: pleural fluid protein-to-serum protein ratio greater than 0.5, pleural fluid LDH-to-serum LDH ratio greater than 0.6, and/or pleural fluid LDH greater than 200 IU.

In their series of 150 patients, exudates usually fulfilled at least one of these criteria, and all but one transude had none of these characteristics.

The purpose of this study is to investigate the utility of the pleural fluid cholesterol level in separating exudates from transudates. The results are compared with the pleural fluid protein level, LDH level and the three criteria of Light et al.

**Patients and Methods**

Seventy pleural effusions from 70 consecutive patients admitted to our hospital were studied prospectively between August, 1984 and May, 1985.

Diagnosis of pleural effusion was established by physical examination, chest x-ray film and in several cases by ultrasound study. In small effusions, an ultrasound-guided thoracentesis was performed.

The patients were placed in four different diagnostic groups: 1) transudates in congestive heart failure/other transudates (CHF/OTH TRANS), 2) exudates of malignant origin (MALIG), 3) other exudates (OTH EXUD), or 4) effusions of mixed origin or undetectable cause.

Patients were individually classified after careful evaluation of all data and results at the end of hospitalization. Sixty-six pleural fluid cytology samples from 66 patients, 12 pleuroscopic and 18 autopsy reports were available for interpretation. The following main criteria were considered to establish a correct diagnosis.

**Group 1**

Congestive heart failure was determined by an enlarged heart, x-ray signs of congested lungs, peripheral edema, response to treatment of CHF, and/or absence of malignancy or pulmonary infiltrates.

Liver cirrhosis was diagnosed by clear evidence of liver cirrhosis in the absence of heart failure, malignancy or pulmonary infiltrates, and responsiveness to diuretic treatment.

Nephrosis, hypalbuminemia and other causes of transudates were not observed.

**Group 2**

Exudates of a malignant origin fit the following criteria: histologic proof of a malignant tumor; cytologic and/or histologic evidence of a malignant pleural effusion; absence of diseases causing transudates; and no pulmonary infiltrates.

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pleural effusions of obscure origin fell into the fourth diagnostic group.

No chylous or traumatic effusions were observed.

Samples of venous blood and pleural fluid were usually obtained on the same day shortly after hospital admission. Only the results of the first thoracentesis were considered.

Protein level was measured by the biuret method (Boehringer-Mannheim). Lactic dehydrogenase (LDH) was measured with the Boehringer-Mannheim kit at 0°C. Results are given in international units (IU); the upper normal limit (serum) is defined at 40 IU.

Cholesterol was measured by the cholesterol-oxidase-PAP method (kinetic colorimetric test at 25°C, Boehringer-Mannheim). Results are expressed in mg/dl.

RESULTS

Classification of the 70 effusions is shown in Table 1. Group 4 includes patients with CHF and carcinoma (two cases), CHF and pleuropneumonia (two cases), probable carcinoma and pleuropneumonia (one case), non-Hodgkin lymphoma and CHF (one case), uremia and CHF (one case), and probable pulmonary infarction (one case).

Table 2 summarizes cytopathologic and histologic

frac{\text{PLEURAL FLUID PROTEIN}}{\text{gms/100 ml}}}

\begin{align*}
8 & \quad \bullet \\
7 & \quad \bullet \\
6 & \quad \bullet \\
5 & \quad \bullet \\
4 & \quad \bullet \\
3 & \quad \bullet \\
2 & \quad \bullet \\
1 & \quad \bullet \\
\end{align*}

\text{CHF/ OTH TRANS} \quad \text{MALIG} \quad \text{OTH EXUD}

\text{FIGURE 1. Pleural fluid protein content in patients with congestive heart failure (CHF) or other transudates (OTH TRANS), malignant disease (MALIG) and exudates of other origin (OTH EXUD).}
findings in the group with exudates of malignant origin. Case 10 was a patient with advanced metastatic lung cancer with extensive mediastinal involvement. Clinical criteria left the malignancy as the only probable cause of the pleural effusion. Case 16 was a patient with advanced metastatic ovarian cancer with proven malignant ascites and probable malignant pleural effusions.

Figure 1 shows protein concentrations of pleural fluid in the first three diagnostic groups. Patients with CHF or transudates of other origin clearly show lower protein values (mean 2.1 ± 0.9 g/100 ml, range 0.4 to 3.8) than patients with malignant effusions (mean 4.4 ± 0.7 g/100 ml, range 3.4 to 6.3) or other exudates (mean 4.3 ± 1.7 g/100 ml, range 1.9 to 7.8). Using a dividing line at 3.0 g/100 ml to separate transudates from exudates, five of 31 patients (16 percent) with CHF/other transudates are incorrectly classified as having an exudate. All patients with effusions of malignant origin are correctly classified. Two of eight patients with pleuropneumonia or tuberculosis (group 3) are misclassified as having transudates.

Figure 2 demonstrates ratios of pleural fluid protein to serum protein in the first three diagnostic groups. In patients with CHF or other transudates, the ratio is lower (mean 0.34, range 0.06 to 0.56) than in patients suffering from malignant effusions (mean 0.64, range 0.49 to 0.82) or other exudates (mean 0.60, range 0.32 to 0.84). Using a dividing line of 0.5 to separate transudates from exudates, five of 31 patients (16 percent) with CHF/other transudates are falsely classified as having exudates. One of 23 malignant effusions (4 percent) is incorrectly classified as a transudate. Two of eight patients with exudates of other origin were mistakenly classified as having transudates.

Figure 3 depicts LDH activities in the pleural fluids of each diagnostic group. In CHF/other transudates, mean LDH is 110 IU (range 25 to 426); in malignant effusions, 366 IU (range 119 to 1631). Other exudates have a mean value of 887 (range 84 to 2632). A
considerable overlap between the different groups is obvious. Using a dividing line of 200 IU, three of 30 effusions (10 percent) in the group of CHF/other transudates are falsely classified as exudates (>200 IU). In one patient in this group, LDH was not measured. Twelve of 23 patients (52 percent) with malignant effusions would be interpreted as having transudates. Two of eight patients with other exudates are misclassified as having transudates. Using a dividing line at 160 IU (two-thirds of normal upper limit for serum as suggested by Petermann and Speicher7), four patients (13 percent) in group 1 are misclassified. Three patients (13 percent) in group 2 and two patients in group 3 are not correctly classified.

Figure 4 demonstrates ratios of pleural fluid LDH to serum LDH. In CHF/other transudates mean LDH ratio is 0.43 (range 0.09 to 1.39). Malignant effusions show a mean ratio of 1.45 (range 0.59 to 3.62). In exudates of other origin, mean ratio is 5.52 (range 0.48 to 19.94). There still is an appreciable overlap between groups.

Using a ratio of 0.6 to demarcate transudates from exudates, five of 30 patients (17 percent) with CHF/other transudates are incorrectly classified. One of 23 patients (4 percent) with malignant effusion is falsely classified as having a transudate. One of eight exudates of other origin would be misinterpreted as a transudate.

Figure 5 summarizes the concentrations of cholesterol in pleural effusions grouped by diagnostic category. Effusions associated with CHF/other transudates have a mean cholesterol concentration of 30 ± 12 mg/dl (range 5 to 55). In effusions of malignant origin, mean cholesterol is 94 ± 25 mg/dl (range 62 to 155). Between these groups, no overlap occurs. In other exudative effusions, mean cholesterol level is 76 mg/dl (range 28 to 124). Drawing the dividing line at a cholesterol level of 60 mg/dl, the first two groups are completely separated. In the group of other exudates, three of eight patients have pleural fluid cholesterol levels below 60 mg/dl, suggesting false classification as transudates.
Applying the method of Light et al., all exudates (groups 2 and 3) in our study are correctly classified. Of 31 patients, only two fulfill less than two of the three characteristics. The transudates in our patients cannot be identified nearly as well by this method. Of 30 effusions (group 1), nine (30 percent) fulfill Light's criteria for exudates (six cases with one characteristic, three cases with two characteristics). Thus, nine of 61 effusions (15 percent) are misclassified by this method.

Using a dividing line for the pleural fluid LDH at 160 IU, ten of 61 effusions (16 percent) are incorrectly classified by these adjusted criteria of Light et al. Again, all misclassified effusions are transudates.

Using two rather than one of Light's criteria for exudates, the results improve: five of 61 effusions (8 percent) are incorrectly classified using a dividing line for the LDH at 200 IU. A dividing line at 160 IU leads to four of 61 (7 percent) incorrectly classified effusions.

The combined numbers of incorrectly classified effusions in groups 1 through 3 (n = 62) for each single parameter are: protein, seven of 62 (11 percent); protein ratio, eight of 62 (13 percent); LDH (dividing line 200 IU), 17 of 61 (28 percent) (one value missing); LDH (dividing line 160 IU), nine of 61 (15 percent); LDH ratio, seven of 61 (11 percent); cholesterol, three of 62 (5 percent); cholesterol ratio, four of 62 (6 percent).

Thus, cholesterol and cholesterol ratio are the two parameters which best separate transudates from exudates in this series.

**Discussion**

Early and decisive evidence of the transudative or exudative nature of a pleural effusion may be of considerable clinical value and is often used as a basis for further diagnostic procedures and therapeutic considerations. No single chemical test or series of tests has yet proved to be completely reliable. Hence, the search for diagnostic improvements is kept alive.

It has long been known that cholesterol is constantly found in all pleural fluids. Nevertheless, we were not able to find systematic studies of pleural fluid cholesterol levels in transudative or exudative effusions.

In this study, we found a mean cholesterol level of 30 mg/dl in the transudates and a mean level of 94 mg/dl in malignant effusions. Effusions of inflammatory origin had a mean cholesterol level of 76 mg/dl. Using a value of 60 mg/dl as a dividing line, malignant effusions were completely separated from the transudates. Three of eight effusions of inflammatory origin had a cholesterol level below this line, suggesting erroneous classification as transudates. Of 62 pleural fluids investigated, only 5 percent were incorrectly classified by this method.

The pleural fluid-to-serum cholesterol ratio resulted in erroneous classification of 6 percent of our cases,
using a dividing line of ≥0.3 to characterize exudates. This ratio did not substantially change the results determined by pleural fluid cholesterol level. Thus, we conclude that the cholesterol level in pleural effusion is a result of the underlying disease rather than a reflection of the serum cholesterol level.

This finding is in agreement with observations in the rare condition of a chyliform pleural effusion (cholesterol effusion). In these effusions, accumulation of extraordinarily high cholesterol levels has been reported to be independent of the serum cholesterol level. These effusions have a history of years to decades and are usually tuberculous in origin. Our findings demonstrate that the cholesterol level is already elevated in exudative effusions of much shorter duration.

The cause of this increased cholesterol concentration is unknown. Cellular degeneration, mainly of white and red blood cells as assumed for chyliform effusions, may be a reasonable explanation. Another hypothesis with regard to increased pleural permeability in exudates is that the cumulation of cholesterol reflects a “serum leakage” (an analogy to the postulated mechanism for protein). Further studies of lipoprotein patterns in different pleural effusions may help clarify the underlying pathophysiology.

Chyloous pleural effusions can have cholesterol levels very similar to the exudates described here. The mere appearance of the fluid may not be sufficient to exclude a chyloous effusion. However, lymphoma or trauma represent the vast majority of the underlying diseases in this condition, causes we did not observe in our patients. In equivocal cases, elevated triglyceride values are suggestive, and demonstration of chylomicrons in the pleural fluid establishes the diagnosis of a chyloous effusion.

Pleural fluid protein level has been a well-established test to separate exudates from transudates ever since Leuallen and Carr reported its superiority to the measurement of specific gravity. In a subsequently published larger series, Carr and Power found 6 percent of their exudates and 16 percent of their transudates misclassified using a protein level of 3 g/100 ml as a dividing line. Of 230 pleural fluid samples, 8 percent were misclassified by this method.

Light et al., in a study of 150 cases of effusion, reported erroneous classification of 8 percent of the exudates and 11 percent of the transudates. Our results are in general agreement with previous findings: of 62 pleural fluids, 11 percent were incorrectly classified by protein level. Our transudates were misclassified in 16 percent of 31 cases, while all malignant effusions and six of eight inflammatory effusions were correctly classified. Light et al. found a somewhat better separation when using a pleural fluid-to-serum protein ratio. In our study, this ratio resulted in erroneous classification of 13 percent of the cases.

A raised pleural fluid LDH level was initially thought to be characteristic of malignant effusions. Later, it was shown that this test is a nonspecific but useful aid in differentiating exudates from transudates. In agreement with the results of Light et al., we found the use of LDH level to be inferior to the measurement of protein level. Our pleural fluid samples were misclassified in 15 percent of the cases by this test. The ratio of pleural fluid-to-serum LDH improved the situation but did not yield better results than the protein level.

We were not able to reproduce the excellent results of Light et al. when simultaneously applying the protein ratio, LDH ratio and LDH level. This method resulted in erroneous evaluation of 30 percent of our transudates, while all exudates were correctly classified.

It is interesting to note that the definition of an exudate by two rather than one of Light’s three criteria improved our results. Eight percent of the effusions were misclassified by this modified approach. This finding is partly due to higher protein and LDH levels in our transudates which can not be fully explained. We used the results of the first thoracocentesis as it has been reported that repeated thoracocentesis lowers cholesterol levels in chyliform effusions. In serial thoracocenteses in some of our patients we confirmed this finding, along with the observation that protein and LDH values may also decrease. Thus, diagnostic thoracocentesis after repeated therapeutic thoracocentesis may yield lower values. Possibly, Light’s results are influenced by this dilutional effect.

In this study we demonstrated that pleural fluid cholesterol level is a simple and cost-effective single test to separate exudates from transudates. It was superior to the conventional measurement of protein level, LDH and Light’s criteria. Malignant effusions were completely separated from the transudates. However, in the small group of inflammatory effusions results must hitherto be interpreted cautiously since the cholesterol level remained low in three cases.

Our study has again made evident that not all pleural effusions possess the expected biochemical characteristics of exudates or transudates. Therefore, we believe that the usefulness of the terms transudate and exudate is debatable. While laboratory tests remain as a guideline for the physician, they cannot substitute for his clinical judgment.

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REFERENCES


Centennial Celebration, Italian Society of Internal Medicine

The Centennial Celebration of the Italian Society of Internal Medicine will take place in Rome, Italy, October 19-23, at the Cavalieri Hilton Hotel. For information, contact the Society Secretariat, Corso di Francis 197, 00191 Rome, Italy.

Third International Congress on Cardiac Doppler

The International Cardiac Doppler Society will be held at the Maternushaus, Cologne, Germany, October 19-23. For information, contact: Organizing Office, Heide Harzheim, Postfach 50 14 70, 5000 Cologne 50, FRG.

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