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Pleural effusion: laboratory tests in 300 cases

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ABSTRACT The cause of pleural effusion was studied in 300 consecutive patients by clinical examination and laboratory tests. The three most common causes were found to be cancer 117 cases (metastatic 65, bronchogenic 34, mesothelioma 10, lymphoma 7, other 1); tuberculous infection 53; and bacterial infection 38. The cause was not found in 62 patients. Cancer diagnosis was established by cytological examination of pleural fluid (63), closed pleural biopsy (37), and open pleural biopsy (11). Tuberculosis was diagnosed by culture of pleural fluid (12), closed pleural biopsy (38), and open pleural biopsy (3). In cases of empyema 12 Gram-positive and two Gram-negative cocci and two anaerobes were identified. The various causes and the usefulness of the different investigative procedures are discussed, and the data evaluated in the light of current knowledge about mechanisms of transfer through the pleural space.

Pleural effusion represents a very common diagnostic problem. In all studies on the causes of this condition, apart from those that are evident, such as congestive heart failure and cirrhosis, the percentage of undetermined causes is still around 20%, even after complete diagnostic evaluation.

We determined the origin of pleural effusion in patients with subacute or chronic conditions admitted to a department of thoracic diseases. The purpose of this study was to determine the specific cause—malignancy or tuberculous or bacterial infection—and to evaluate the laboratory tests.

Methods

This study was based on a prospective survey of 300 patients admitted between October 1972 and October 1976. Each patient found to have fluid after thoracentesis was included in the study and was followed in the thoracic outpatient clinic. The following points were recorded systematically: chest or extrathoracic disease in the past; occupational exposure (mainly to asbestos); tobacco use; length of evolution of disease and previous treatment; clinical examination; characteristics of the pleural fluid obtained at first thoracentesis (macroscopic appearance; cell counts, regarded as lymphocytic if more than 75% lymphocytes, eosinophilic if more than 10% eosinophils; presence of lysed leucocytes, of mesothelial cells, or of malignant cells; protein value regarded as a transudate if less than 3 g/100 ml and an exudate if more than 3 g/100 ml; glucose content; amylase content; routine and Mycobacterial cultures); chest radiographs (frontal and lateral upright, and a lateral decubitus film in order to visualise slight effusion and to differentiate free from fixed fluid); technetium lung scan; functional tests; closed pleural biopsy with Abrams's needle; and purified protein derivative (PPD) skin reaction. Evolution of the condition with or without treatment was recorded, and cases of chronic (more than two months) and acute or subacute pleural effusion were separated.

The study group included 215 men and 85 women. The cause of the pleural effusion was found in 238 of the 300 patients by laboratory tests; but in 62 patients it remained undiagnosed even after complete evaluation, including open pleural biopsies in 15 patients.

Results

The most frequent causes of pleural effusion were cancer (39%), tuberculous infection (17·6%), and bacterial infection (12·6%): 20·6% were undiagnosed, and other causes represented 10% (table 1). The characteristics of effusions due to these principal causes and the usefulness of various laboratory tests in their diagnosis are described.

CHARACTERISTICS OF PLEURAL EFFUSIONS ACCORDING TO CAUSE

No specific characteristics were observed for the

Table 1 *Causes of pleural effusion in 300 patients*

Cause	*No of patients*		
	Men (215)	*Women (85)*	*Total*
Cancer (total)	75	42	117
Metastasis (total)	29	36	65
from Adenocarcinoma (unknown primary)	22	19	41
Breast carcinoma		12	12
Uterine cervical carcinoma		3	3
Epithelial carcinoma (unknown primary)	2		2
Undifferentiated carcinoma (unknown primary)	2		2
Pancreatic carcinoma		1	1
Laryngeal carcinoma	1		1
Oesophageal carcinoma	1		1
Stomach carcinoma	1		1
Vulvar carcinoma		1	1
Lung carcinoma (total)	33	1	34
Epithelial	31	1	32
Oat-cell	2		2
Mesothelioma	9 (+ asbestosis, 7)	1	10
Post-radiation lymphoma	3	2	5
Lymphoma	1	1	2
Other		1	1
Undiagnosed	45	17	62
Tuberculous infection	35	18	53
Bacterial infection	32	6	38
Others (total)	26	4	30
Asbestosis	8		8
Trauma	5	1	6
Congestive heart failure	4	1	5
Cirrhosis	2	1	3
Embolism	1	1	2
Subphrenic abscess	2		2
Rheumatoid arthritis	1		1
Systemic lupus	1		1
Virus	1		1
Chylothorax	1		1

individual causes, but, when the most and the least frequent findings were examined for the four aetiological groups defined, certain trends could be ascertained (table 2).

Cancerous effusion was observed in 41 of the 85 women in the study. Exudate (92%), large effusion (82%), mesothelial cells (62%), chronic condition (57%), bloody fluid (36%), and fluid containing fewer than 1000 cells/ml (35%) findings were found more often than in the other three groups, while fluid containing more than 1000 cells/ml (28%), encysted fluid (26%), purulent fluid (≃0%) and lysed leucocytes in fluid (≃0%) were found less frequently.

Tuberculous effusion was observed in 21% of non-whites and 17% of alcoholics. The most frequent findings compared to the other groups were positive PPD (92%), clear fluid (75%), lymphocytic fluid (65%), fluid containing more than 1000 cells/ml (51%), loss of weight (46%), and free fluid (40%). The least frequent were negative PPD (5%) and eosinophils in fluid (0%).

Table 2 *Clinical and biological data from 270 cases of pleural effusion*

Cause	*Total cancer*	*Tuberculosis*	*Empyema*	*Undiagnosed*
Number	117	52	38	62
Men/women	75/41	34/18	32/6	45/17
Average age	53	45·5	54·7	48·8
Chronic condition	**66*** (57)	20	*10*† (26)	30
Fever	37	32	**28** (87·5)	*17* (27)
Loss of weight	52	**24** (46)	*7* (18)	15
Clear fluid	62	**39** (75)	*3* (7)	36
Purulent fluid	*6* (≃0)	7	**32** (84)	*1* (≃0)
Bloody fluid	**42** (36)	6	*3* (7)	19
>1000 cells/ml	*33* (28)	**27** (51)	15	23
<1000 cells/ml	**41** (35)	11	*4* (10)	15
Lymphocytic	22	**34** (65)	*0* (0)	17
Lysed leucocytes	*5* (≃0)	5	**32** (84)	*1* (≃0)
Eosinophilic	8	*0* (0)	3	**12** (19)
Mesothelial cells	73 (62)	19	*11* (29)	33
Glucose <30 mg/100 ml	3	*0* (0)	**6** (15)	1
Exudate	**107** (92)	46	31	*47* (75)
Transudate	3	*0* (0)	*0* (0)	**4** (6)
Large effusion	**95** (82)	38	21	*38* (51)
Free fluid	46	**21** (40)	*3* (7)	17
Encysted fluid	*31* (26)	22	**24** (63)	25
PPD+	61	**48** (92)	*18* (47)	47
PPD−	49	*3* (5)	**11** (47)	11

*Bold numbers are the most frequent among the four aetiological groups; figures in parentheses are percentages.
†Numbers in italics are the least frequent among the four aetiological groups; figures in parentheses are percentages.

Empyema was observed in 36% of alcoholics. The most frequent findings were fever (87·5%), purulent fluid with lysed leucocytes (84%), encysted fluid (63%), negative PPD (47%), and less than 30 mg glucose/100 ml pleural fluid (15%). The least frequent were positive PPD (47%), mesothelial cells (29%), chronic condition (26%), loss of weight (18%), fewer than 1000 cells/ml of pleural fluid (10%), free fluid (7%), clear fluid (7%), bloody fluid (7%), and transudate or lymphocytic (0%).

In undiagnosed effusion eosinophils (19%) and transudate (6%) were the most frequent findings, and exudate (75%), large size (51%), fever (27%), and purulence with lysed leucocytes (≃0%) were the least frequent.

LABORATORY TESTS IN THE DIAGNOSIS OF THE CAUSE OF PLEURAL EFFUSION (table 3)

In cancerous effusion cytological examination of pleural fluid was positive in 54%, closed pleural biopsy in 40%, and open pleural biopsy in 78%. Other pathological tests (biopsies of bronchi, liver, and lymph nodes; and cytology of bronchial aspiration or sputum) were positive in 42%.

In tuberculous effusion closed pleural biopsy was positive in 88%, open pleural biopsy in 100%,

Table 3 *Laboratory tests in the diagnosis of 300 cases of pleural effusion (percentages in parentheses)*

Cause	*Cancer (117)*		*Tuberculous (52)*		*Empyema (38)*		*Undiagnosed (62)*		*Others (30)*	
	Performed	*Positive*	*Performed*	*Positive*	*Performed*	*Positive*	*Performed*	*Positive*	*Performed*	*Positive*
Laboratory test										
Cytology of pleural fluid	117	63 (54)	52	0	38	0	62	0	30	0
Closed pleural biopsy	92	37 (40)	43	38 (88)	10	0	46	0	20	0
Open pleural biopsy	14*	11 (78)	3	3 (100)	0	0	15	0	5	0
Bronchial biopsy	83	49 (42)	17	0	17	0	27	0	13	0
Other biopsies	49		2	0	0	0	8	0	2	0
Cytology of sputum	24		11	0	7	0	9	0	8	0
Cytology of bronchial aspiration	18		6	0	11	0	10	0	3	0
Bacteriology of pleural fluid	117	0	52	2 (3)	38	15 (39)†	62	0	30	0
Mycobacterial culture of pleural fluid	117	0	52	12 (23)	38	0	62	0	30	0
Mycobacteriology of pleural fluid	117	0	52	10 (19)	38	0	62	0	30	0

*Seven mesothelioma, four metastases, three post-radiation.
†Six streptococcus, five pneumococcus, one staphylococcus aureus, one proteus, one pyocyaneus, two anaerobes.

and Mycobacterial culture in 23%; two species of bacteria were found to be associated with this condition.

In empyema bacterial culture results were positive in 39%.

For all cases, closed pleural biopsy was positive in 30%, open pleural biopsy in 37%, routine bacterial culture in 5%, and Mycobacterial culture in 4%.

The usefulness of lateral decubitus chest radiographs was principally to see slight effusion. The number of cells/ml of pleural fluid had no influence on its mobility; when fluid was encysted, it seldom contained less than 30 mg/100 ml of protein, and the mobility of the liquid was found also to be independent of protein concentration.

The usefulness of functional tests was slight. Restriction and hypoxia, depending on the abundance of fluid, were the abnormalities most often observed with such tests.

Lung scan perfusion was performed in 148 cases, but was of no use in diagnosis, since in 145 cases it showed only abnormalities in relation to fluid.

Discussion

The fact that many patients in this study came from a department of internal medicine explains the observation of so many chronic pleural effusions and so few that were due to congestive heart failure or to cirrhosis. This fact also explains the differences in causes from those seen in other studies (Storey *et al,* 1976), although the number due to indeterminate causes was the same (about 20%).

The value of radiology in recognising the cause lies principally in seeing lung changes in tuberculosis, heart enlargement in congestive heart failure, etc. The lateral decubitus view (Vix, 1974) that gives an unobstructed tangential view of the recumbent chest by lowering the head end of the table 15–20°, centring the *x*-ray beam on the recumbent lateral chest wall and exposing the film during expiration is useful for seeing as little as 5 ml of fluid in the pleural space (Moskowitz *et al,* 1973), for determining whether the fluid is free or encapsulated, and for discerning subpulmonary effusion. The ultrasonic technique (Gryminski *et al,* 1976) is particularly useful in detecting and evacuating small amounts of loculated fluid and in differentiating between loculated fluid and pleural thickening. The usefulness of computed tomography has yet to be established, but it is of great value in recognising pleural plaques associated with asbestosis (Kree, 1976).

The lung perfusion scan is difficult to interpretate (Mishkin and Brashear, 1970; Tow and Wagner, 1970). This depends on the amount of fluid, the degree of absorption of gamma photons—particularly when using technetium, and, principally, on the posture (in the upright lung compression by fluid reduces perfusion of the lung bases; in the supine posture all the blood vessels are compressed). When radioactive xenon is used (Davidson and Glazier, 1972), ventilation is decreased to a greater extent than perfusion, and in unilateral pleurisy, mechanical lung function is abnormal in both lungs.

The functional effect of pleural effusion is restriction, with a decrease in dynamic lung compliance. In distinguishing between pulmonary and pleural restriction measurement of the maximum static pulmonary recoil pressure may be useful (Colp *et al,* 1975).

Tests on pleural fluid are very useful in the diagnosis of cause. It is important, however, to note the conditions under which thoracentesis is carried out, since pleural fluid is heterogeneous. In fact, important variations were noted in macroscopic features, in total and differential leucocyte counts, and in protein content, in relation to the duration of evolution of the pleural effusion, to previous thoracentesis, to the posture and movement of the thorax before collection of fluid, and to the site of puncture (at the top or at the base). It is essential that the conditions of thoracentesis be standardised, so that the initial fluid obtained is examined and it is carried out when the thorax is in the upright position and at the lowest point at which a fluid rich in cells can be obtained. Apart from the macroscopic appearance, it is also important to make total and differential cell counts, cytological examinations, and analyses of the chemical constitution and bacteriology of the fluid.

Total and differential cells counts are of no value in defining cause (Leuallen and Carr, 1955; Dines *et al,* 1975). On the other hand, lymphocytic fluid suggests either cancer or tuberculosis (Yam, 1967; Light *et al,* 1973), although the absence or scarcity of mesothelial cells is a more constant characteristic than lymphocytosis in tuberculosis (Spriggs and Boddington, 1960). We confirmed the following characteristics: in tuberculous effusion the fluid contained the greatest number of cells, was the most lymphocytic, and had only a few mesothelial cells; whereas in cancerous effusion the fluid contained the smallest number of cells, was rarely lymphocytic, and contained the greatest number of mesothelial cells. The determination of T and B lymphocytes in pleural effusions (Petterson *et al,* 1978) could also

be useful since more T lymphocytes are found in pleural fluid than in blood in tuberculosis, and fewer B lymphocytes are found in fluid than in blood in tuberculosis, malignancy, and non-specific pleurisy.

Cytological examination has given a positive indication of malignancy in from 50% (Leuallen and Carr, 1955) to 60% (Dines *et al*, 1975) of cases. The combination of standard cytological and chromosomal examinations identified 83% of tumours, a result significantly better than that with either method used alone (Dewald *et al*, 1976).

Distribution of exudate from transudate depends principally on the pleural fluid protein (Leuallen and Carr, 1955) and on certain other characteristics (Ayvazian, 1977):

	Transudate	*Exudate*
Protein	< 3 g/100 ml	> 3 g/100 ml
Specific gravity	< 1014	> 1016
Lactic dehydrogenase	< 200 units	> 200 units
Cells	Round cells	Predominantly white and red blood cells

The total protein concentration depends mainly on the permeability of the mesothelium to pleural fluid and on lymphatic drainage. Analysis of pleural fluid immunoglobulins showed that all three, IgA, IgG, and IgM, are present; and their distribution suggests that transudation of serum proteins rather than local synthesis was their source (Shallenberger and Daniel, 1972). This is in keeping with the finding that their concentration is lower in pleural fluid than in serum (Hirsch *et al*, 1971). On the other hand, the level of complement in pleural fluid was reduced in cases of rheumatoid arthritis and lupus erythematosus; this may be due to complement conversion by immune complex (Hunder *et al*, 1977).

In rheumatoid pleurisy the glucose content of the fluid was less than 30 mg/100 ml in 70–80% of cases of effusion (Lillington *et al*, 1971). This was also true for the only case observed in this study; but this characteristic was not specific to the condition since glucose was often less than 30 mg/100 ml in empyema and in malignant pleural effusions as well.

Mycobacterial cultures have been reported to give a positive indication of cause in 24% of cases (Berger and Mejia, 1973); a similar result was obtained in this study. Positive diagnosis from cultures of pleural biopsy has been reported in 55–80% of cases of tuberculous effusion (Levine *et al*, 1970). In this study only two species of anaerobic bacteria were identified in cases of empyema, whereas anaerobes are the major cause of empyema (Bartlett and Finegold, 1974). Since this study was begun, the collection of appropriate material for anaerobic cultures, appropriate transport to the laboratory, and proper bacteriological processing have permitted improved isolation of these microbes. For other strains, particularly *Pneumococcus*, the detection of bacterial antigens by counter-immunoelectrophoresis has been found to be useful (Coonrod and Rytel, 1973).

In 60–80% of patients with tuberculosis and in 40–60% of patients with tumours definitive diagnoses have been obtained by closed pleural biopsy (Scerbo *et al*, 1971); the same percentages were found in this study. This method is safe except in cases of abnormal coagulation; even in the absence of pleural fluid the method is successful and without danger. Open pleural biopsies should be taken in cases of chronic indeterminate effusion, and fragments taken for smears and for histological, ultrastructural, and mineralogical analyses (Nebut *et al*, 1977). The taking of open pleural biopsies might well be done in association with thoracoscopy, which is well-tolerated and gives a clear view of the pleural cavity (Ash and Manfredi, 1974).

Pleural membranes are exposed to various agents and react either by accumulating pleural fluid or by cellular proliferation. In attempting to diagnose the cause of pleural effusion the mechanisms by which pleural fluid is created should be considered (Hirsch *et al*, 1976). Starling's equation for fluid movement describes the formation of pleural fluid:

Fluid movement $= k\ (HPc - HPif) - (COPc - COPif$ where k is a filtration coefficient of the pleural capillary membrane; HP is the hydrostatic pressure; COP is the colloid osmotic pressure; c is capillary; and *if* is interstitial fluid.

All these factors must be considered in the pathogenesis of pleural effusion. During the inflammatory process, alteration of the basement membrane and release of mediators could increase k: an accumulation of protein is, in fact, observed in pleural effusion during the inflammatory process. The reabsorption of pleural fluid depends on the colloid osmotic pressure: when the protein concentration in the pleural fluid reaches 4 g/100 ml, reabsorption through the visceral membrane drops to zero; and in cases of pronounced hypoalbuminaemia (for instance, in nephrotic syndrome), an increased amount of fluid will be filtered out of the parietal pleura and may also be filtered out of the visceral pleura. The role of pulmonary venous hypertension in the production

of pleural fluid is less clear than in lung oedema. In dogs pleural fluid accumulates during systemic venous hypertension and during combined systemic and pulmonary venous hypertension (Mellins *et al*, 1970).

The total movement of fluids also depends on lymphatic drainage. Diaphragmatic pleural lymphatics are more extensive on the right side than on the left, and there are potential channels for the flow of fluid from the peritoneal cavity to the pleural space. This could explain the fact that the most common pleural effusions in ascites and in asbestos pleurisy are right-sided (Chrétien *et al*, 1976). In cases in which there is obstruction of the pleural lymphatics, which drain macromolecules and protein, the protein content of the pleural effusion will be high.

At present, in the diagnosis of pleural effusion, only the factors that play a part in exchanges through the pleural membranes can be considered. A better understanding of the mechanisms of pleural effusion—such as the permeability of mesothelial cells—would permit better analysis.

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