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Etiologic Considerations of Nonspecific Pleuritis

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Twenty-three patients with nonspecific pleuritis were studied to determine clinical outcome. After a mean follow-up period of 6 months (1 to 36 months), a diagnosis was reached in 17 patinets, while 6 patients remained unknown.

The causes of the nonspecific pleuritis diagnosed on initial pleural biopsy were tuberculosis (11 patients, 48%), neoplasm (2 patients, 8.7%), parapneumonic effusion (1 patient), subphrenic abscess (1 patient), congestive heart failure (1 patients), and nephrotic syndrome (1 patient).

The diagnosis was made by therapeutic trials (tuberculosis: 11 patients, parapneumonic effusion: 1 patient, congestive heart failure: 1 patient), by repeat pleural biopsy in 1 hepatoma, by open thoractomy in 1 lung cancer, by exploratory laparotomy in 1 subphrenic abscess, and by kidney biopsy in 1 nephrotic syndrome.

The WBC counts (more than 2,000/mm^3) and lymphocyte percentage (more than 60%) in the pleural fluid were significantly elevated in the patients with tuberculosis compared to those with malignant pleurisy, and other laboratory data were meaningless.

As a result of this investigation, we suggest that tuberculous pleurisy is the most common cause of nonspecific pleuritis in Korea and that therapeutic trial with antituberculous medication for patients with high WBC count and lymphocyte percent in pleural fluid can help to locate the nonspecific pleuritis.

Key Words: *Nonspecific pleuritis*

INTRODUCTION

Exudative pleural effusions are common manifestations, but sometimes its causes remain unknown. In Korea, the most common causes of exudative pleural effusion are tuberculosis in 59 ~64% and malignant neoplasms in 15~31%. However, 10~18% remain unknown[1~3].

In western counties, the most common causes of exudative pleural effusion are malignant neoplasm in 35~68% and tuberculosis in 1~30% (mean 14 %), where 12 ~ 24 % remain unknown[4~6,8,9].

The identification of the causes of exudate is necessary because treatment and prognosis are determined according to etiologies, but some cases remained unknown despite extensive diagnostic studies (chest X-ray, biochemical assay of fluid, bacterial smear and culture, cytology, pleural biopsy and thoracoscopy). In these cases, repeated pleural biopsies and cytology increase the diagnostic yield in patients[6~8] but add to the expense and morbidity of those patients.

The purpose of this investigation was to determine the causes of nonspecific pleuritis on initial pleural biopsies and to determine if individuals with nonspecific pleuritis could be distinguished from those with malignant or tuberculous pleural effusion by routine laboratory data.

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MATERIALS AND METHODS

1. Subjects

All patients who had closed pleural biopsies performed from August 1985 to December 1989 at

the Chungnam National University Hospital and who were diagnosed as having nonspecific pleuritis were included in this investigation.

Patients selected for the study met the following criteria: 1) exudative pleural effusion, 2) nondiagnostic biochemical, cultural, and cytologic studies of the fluid, and 3) nonspecific pleuritis diagnosed by closed needle biopsy of the pleura. Nonspecific pleuritis was characterized by the presence of one or several of the following: acute, subacute or chronic inflammation, fibrosis, or mesothelial cell hyperplasia.

There were 23 patients who met these criteria and were classified into 3 groups according to their ultimate diagnosis. Group I consisted of patients who were not diagnosed despite a variety of studies. Group II consisted of those who were ultimately diagnosed as having tuberculous pleurisy. Group III included those who were ultimately diagnosed as having malignant pleural effusion.

The controls were tuberculous pleurisy (15 cases) and malignant pleural effusion (11 cases, lung cancer) proven by initial pleural biopsy.

The ages of the patients in the nonspecific pleuritis group were 46±13 years, and for the control group it was 43±20 years in tuberculosis (15 cases) and 55±12 years in malignant pleural effusion (11 cases). The mean duration of follow-up in patients with nonspecific pleuritis, between the initial pleural biopsy and ultimete diagnosis, was 6(1~36) months (Table 1).

2. Methods

More than one biopsy was performed with a Cope needle. Three pieces of tissue were obtained and submitted for histologic study. Pleural fluid obtained at the time of the biopsy was routinely sent for cell count with differential, protein, glucose, bacterial and mycobacterial culture and cytologic examination. The chemotherapy criteria included : 1) strongly positive intermediate strength tuberculin test, 2) pleural fluid lymphocyte greater than 50% and a protein level greater than 5.0 g/dl. But in this study, the tuberculin test did not apply.

A univariate analysis was done with Student's t-test and analysis of variance (ANOVA).

RESULTS

1. Causes of Nonspecific Pleuritis

The final diagnosis explaining the pleural effusion and the diagnostic study or procedure that eventually established the cause are shown in Table 2. Tuberculosis was the most frequent cause, occurring in (47.8%) of the 23 patients. Other causes were malignancy in 2 (8.7%) patients, parapneumonic effusion, subphrenic abscess, congestive heart failure. and nephrotic syndrome in 1 patient, respectively. Six patients were placed in the indeterminate group (26.1%).

2. Diagnostic Procedures

Eleven cases were diagnosed as having tuberculous pleurisy empirically, i.e., they were cleared and had no recurrence after antituberculous chemotherapy.

Even though the initial clinical impression was malignancy in 2 patients with neoplastic disease, the diagnosis was not made early because the specimens from multiple biopsies were not diagnostic. Repeat pleural biopsies established that 1 patient had hepatoma which metastacized to the right pleural cavity 2 months later. Repeat pleural biopsies (5) were nondiagnostic in another patient who was subsequently diagnosed as lung cancer (adenocarcinoma) by open thoracotomy.

In parapenumonic effusion, sputum and pleural fluid culture were negative, but parenchymal infil-

Table 1. The Distribution and Follow-up Duration of Subjects

Subjects	Mean Age (yr.)	Sex (M/F)	Follow-up Duration (mo.)
Nonspecific pleuritis (n=23)	46 (20–64)	12/11	6 (1–36)
Controls			
Tbc. pleurisy (n=15)	43 (20–81)	10/ 5	13 (7–18)
Malignancy (n=11)	55 (25–74)	8/ 3	8 (3–19)

Controls : Tuberculous or malignant pleurise diagnosed on initial pleural biopse
Follow-up duration : Nonspecific pleuritis – between initial pleural biopsy and ultimate diagnosis ; Tbc. pleurisy and malignancy – between diagnosis and end point of treatment

Table 2. Causes of Nonspecific Pleuritis (N=23)

Final Diagnosis	Diagnostic Procedure or Study					Numbers (%)
	Clinical Trial	Pleural Biopsy	Open Thoracotomy	Explo-laparotomy	Kidney Biopsy	
Tuberculous	11					11 (48%)
Malignant						2 (8.7%)
Lung cancer			1			1
Hepatoma		1				1
Miscellaneous						4 (17%)
Parapneumonic effusion	1					1
Subphrenic abscess				1		1
Congestive heart failure	1					1
Nephrotic syndrome					1	1
Indeterminate						6 (26%)
Total	13	1	1	1	1	23 (100%)

Table 3. Comparision of Parameters Between Nonspecific Pleuritis and Controls

Diagnosis	WBC's (/mm³)	Lymph. (%)	Chol. (mg/dl)	Glucose (mg/dl)
Nonspecific pleuritis (n=23)	2,386 ± 643	67 ± 5	97 ± 29	95 ± 39
Controls				
Tbc. pleurisy (n=15)	1,961 ± 555*	75 ± 5*	117 ± 32	91 ± 17
Malignant pleurisy (n=11)	583 ± 531	50 ± 10	93 ± 22	75 ± 29

Lymph. (%) : percent of lymphocyte Chol. : Cholesterol

* : P-value < 0.005 between tuberculous pleuritis and malignant effusion

tration and pleural effusion disappeared after a therapeutic trial of antibiotics. Subphrenic abscess was diagnosed by exploratory laparatomy. In 1 patinet, congestive heart failure subsequently developed (neck vein engorgement, ventricular gallop sound, cardiomegaly and compatible echocardiographic findings to heart failure), so it was concluded that the initial effusion was directly or indirectly related to the heart failure. Then, the pleural effusion disappeared after digitalis therapy and the pleural fluid protein level had been 4.1 g/dl. One patient was recognized 3 months later as mesangiocapillary glomerulonephritis (MCGN) after closed pleural biopsy, and the pleural fluid protein level had been 3.5 g/dl.

The remaining 6 patients were ultimately classified as an indeterminate group and had received chemotherapy (INH, RFP, EMB, mean 4 months) for tuberculosis, but there was no response to chemotherapy.

3. Comparision of Parameters between Nonspecific Pleuritis and Controls

Table 3 shows the mean±SD value of WBC, lymphocyte percentage, cholesterol and glucose in the pleural fluid of the patients with nonspecific pleuritis and controls (tuberculous and malignant pleurisy).

The pleural fluid WBC count of the patients with nonspecific pleuritis and controls (tuberculous and malignant pleurisy) were 2,389 mm³, 1,961 mm³, and 583/mm³, respectively, There were statistically significant differences in pleural fluid WBC counts between tuberculous and malignant pleurisy ($p < 0.005$).

The percentages of cells in the pleural fluid which were lymphocytes were 67%, 75% and 50%, respectively. There were statistically significant differences in the pleural fluid lymphocyte percentage between tuberculous and malignant pleurisy

Table 4. Comparision of Parameters Among the Nonspecific Pleuritis

Diagnosis	WBC's (/mm³)	Lymph. (%)	Chol. (mg/dl)	Glucose (mg/dl)
Tuberculous (n=11)	3,513 ± 974*	77 ± 12**	106 ± 44	86 ± 16
Malignant (n=2)	588 ± 95	50 ± 30	111 ± 12	140 ± 15
Indeterminate (n=6)	921 ± 370	55 ± 32	91 ± 24	99 ± 27

* : P-value < 0.005 between tuberculous pleuritis and malignant effusion
** : P-value < 0.05 between tuberculous pleuritis and malignant effusion

($p<0.005$). Cholesterol levels were 97 mg/dl, 117 mg/dl and 75 mg/dl, respectively, but there were no significant differences between these 3 groups. The lowest concentration of glucose was found in the malignant pleurisy group, but there was no statistically significant difference between these groups.

4. Comparision of Parameters among the Nonspecific Pleuritis Group

The laboratory data of nonspecific pleuritis along its etiologies are shown in Table 4. The pleural fluid WBC count of the patients with ultimately diagnosed tuberculous pleurisy, ultimately diagnosed malignant pleurisy, and the indeterminate group were $3,513\pm974/mm^3$, $588\pm95/mm^3$ and $921\pm370/mm^3$, respectively. There were statistically significant differences between the ultimately diagnosed tuberculous and malignant pleurisy groups ($p<0.005$).

The pleural fluid lymphocyte percentage was significantly higher ($p<0.05$) in the patients with ultimately diagnosed tuberculous pleurisy (77%) than those with ultimately diagnosed malignant pleurisy (50%) and intermediate in the indeterminate group (55%), but the overlap was considerable. There were no statistically significant differences between these 3 groups in pleural cholesterol and glucose.

DISCUSSION

Pleural effusion is an important and common clinical finding, but diagnosis of the causes of effusion is often difficult. The diagnosis of pleural effusion is most often established by chemistries of fluid, bacterial smear and culture, cytology for malignancy and closed pleural biopsy.

Diagnostic yield in patients with tuberculous pleurisy had been reported to 20~25% by pleural fluid culture, 60~80% by closed pleural biopsy, 76% by pleural biopsy culture and 95% by combined pleural biopsy with pleural biopsy culture in the same patients[10~12].

The yield of diagnosis of malignant pleurisy was 35~70% based on cytologic finding only and 40~70% on closed pleural biopsy findings only. When these 2 procedures are combined in the same patient, the yield approachs 90%[8,13].

Reasons for the negative results of closed pleural biopsies in those patients who were ultimately diagnosed as having either malignant or tuberculous pleurisy are: 1) early lesion, 2) focal seeding with malignant nodule or granuloma or 3) absence of parietal pleural involvement[34,35].

Salyer et al.[18] reports that the causes of exudative pleural effusion in 271 patients were malignancy in 35%, tuberculosis in 20%, and parapneumonic effusion in 16%. Scerbo et al.[6] notes that out of 163 patients, 40% were malignancy 30% were tuberculosis and 12% were parapneumonic effusion. Prakash et al.[7] found that the causes of exudate in 414 patients were malignancy in 67.9% and tuberculosis in 1.4%, and Storey et al.[4] found malignancy in 48% and tuberculosis in 1%.

In summary, the above literature reports that the most common cause of exudate is malignancy in 35~68%, then tuberculosis in 1~30%. Other causes were empyema, connective tissue disease and pulmonary infartion etc. In Korea, the causes of exudative pleural effusion were tuberculosis in 59~64% and variable malignancy in 15~31%[1~3].

Storey et al[4,6,19] reported that 12~24% of patients with pleural effusion would remain without etiologic diagnosis despite usual diagnostic evaluations. Previous studies have shown that cases of idiopathic pleurisy which were diagnosed to nonspecific pleuritis on initial pleural biopsy, were malignancy in 25~40%. Others were connective tissue disease, pulmonary infarction, tuberculosis, systemic fungal infections, parapneumonic effusion, congestive heart failure, pancreatitis and hepatic disease. However, the indeterminate group

remained in the 12~35% range despite extensive studies[14~16]. In our investigation, tuberculosis was in 48% and malignancy in 8.7%; others were parapneumonic effusion, subphrenic abscess, congestive heart failure and nephrotic syndrome; 26% remained unknown.

Because the causes of pleural effusion often remain unsolved despite closed pleural biopsy, several biochemical parameters and tumor markers have been measured in pleural fluid to help in the differential diagnosis of various diseases. Liight et al. report that the WBC count and differential WBC count are useful diagnostically[17,18], while Leuallen et al. conclude they are of no use[5,19]. Light et al. reported that the presence of predominantly polymorphonuclear leukocytes in pleural fluid indicates that the fluid is the result of acute pleural inflammation, hence raising the possibility of pneumonia with effusion, pulmonary infartion, and pancreatitis, while tuberculous and malignant effusions frequently had more than 50% lymphocytes in the pleural fluid. In this study, the WBC counts of patients with tuberculous pleural effusion were statistically significantly higher than those of patients with malignant pleural effusion in the controls ($p<0.005$). The study showed a statistically significant ($p<0.005$) higher value of WBC count in patients ultimately diagnosed as having tuberculous pleurisy than in those ultimately diagnosed as having malignant pleural effusion. Our results are compatible with those of Light et al.[17] in tuberculous pleurisy but not in malignant pleural effution.

In has been a of controversy the glucose concentration in the pleural fluid could aid the diagnosis of the causes of effusion. Calman et al.[20] and Barber et al.[21] report that a pleural fluid glucose concentration of less than 80 mg/dl suggests a diagnosis of tuberculous pleurisy. Also, Panadero et al.[22] found that in cases with pleural glucose levels less than 60 mg/dl and pleural pH less than 7.30, there was a 90% probability of malignant effusion, while Glenert et al.[23] and Light et al.[24] have concluded they are of no use. Our results are in agreement with the latter 2 studies.

Elevated pleural fluid amylase level has been observed in pancreatitis and pancreatic tumor. Light et al.[24] in a study of 10 cases of effusion in which amylase levels were more than 160 U/dl, report 8 cases were pancreatitis. By Hamm et al's study[25], the mean cholesterol level in malignant effusions was 94 mg/dl, 76 mg/dl in inflammatory effusion and 30 mg/dl in the transudates. The above study indicated that the pleural fluid cholesterol level was an aid in differentiating exudative, especially malignant, from transudative pleural effusions, but our results were not statistically significant.

In 1974, Cortes et al.[30] proposed that measurement of the CEA level in pleural fluid suggested malignancy. Thereafter, several authors reported various arbitary levels (CEA levels>12 ng/dl with a diagnostic sensitivity of 34%, Rittger et al.[26];>10 ng/dl, 39%, Vladutiu et al.[27];20 ng/dl, 65%, Kim[29]) to separate malignant from benign effusions. But, Mckenna et al.[28] found that the CEA level increased in adenocarcinoma only. Pleural fluid adenosine deaminase (ADA) levels in the patients with tuberculous pleurisy were significantly higher than those in the patients with nontuberculous pleurisy, and sensitivity and specificity at various cut-off levels (more than 30 IU/L, Prias et al.[31]; more than 40 IU/L, Lee et al.[32]; more than 50 IU/L, Sung et al.[33]) were over 90%. In this investign-tion some tests such as amylase, CEA and ADA in the pleural fluid were not performed. Our investigation was limited by the small population of patients studied and by nonperformance of thoracoscopy, pleural biopsy culture and tuberculin skin test.

From our work, we can report the following conclusions: 1) The causes of the nonspecific pleuritis diagnosed on initial pleural biopsy were tuberculosis (11 patients, 48%) and neoplasm (2 patients, 8.7%), while others were parapneumonic effusion, subphrenic abscess, congestive heart failure and nephrotic syndrome; 6 patients (26%) remained unknown. 2) WBC counts (more than 2,000/mm^3) and lymphocyte percent (more than 60%) in pleural fluid were significantly elevated in the patients with tuberculous pleurisy compared to malignant pleurisy. 3) In view of the data obtained from our study, we suggest that therapeutic trial with antituberculous medication for patients with a high WBC count (2,000/mm^3) and lymphocyte percent (more than 60%) in pleural fluid and who have been diagnosed as having nonspecific pleuritis on initial pleural biopsy can help to locate the etiologies.

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