EOSINOPHILIC PLEURAL EFFUSION IN ADULTS AT SRINAGARIND HOSPITAL

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Abstract. The presence of pleural eosinophilia remains a controversy in etiology and prognosis. We conducted this study to evaluate the etiology of eosinophilic pleural effusion and to define the factors that determine malignancy in eosinophilic pleural effusion. Between 1 August 1994 and 1 July 2000, 50 patients were diagnosed with eosinophilic pleural effusion; 35 men and 15 women averaging 56.4 years of age. Most (96%) had exudative pleural effusion. Malignancy was the most common (46%) established cause followed by tuberculosis (10%), parapneumonic effusion (8%), and empyema thoracis (2%). We encountered only one case of pneumothorax and parasitic pleural effusion (from *Strongyloides stercoralis*). Unknown causes constituted 22% of cases. The etiology of those who had previously undergone thoracocentesis did not differ from those having their first thoracocentesis.

Patients with malignant pleural effusion had significant longer duration of clinical symptoms ($\geq$1 month) and weight loss than benign pleural effusion. The median duration of symptoms in benign pleural effusion was 14 days. Fever was more characteristic in patients with benign than in those with malignant pleural effusion. The percentage of eosinophils in pleural fluid and blood did not differ between the two groups. Pleural fluid eosinophils in malignant *vs* benign pleural effusion were 26.6% (range 10% to 63%), and 30.6% (range 10% to 93%), respectively.

We concluded that, pleural eosinophilia did not indicate benign conditions which would spontaneously resolve. Malignant pleural effusion should be considered especially in areas malignancy is prevalent.

INTRODUCTION

Eosinophilic pleural effusion is confirmed by the presence of 10 or more percent eosinophils among the leukocytes in the pleural fluid (Light, 1995). This occurs in 5% to 8% of exudative pleural effusion (Sahn, 1988), but its diagnostic significance is controversial. Light *et al* (1973) argued that the presence of pleural fluid eosinophilia militates greatly against tuberculosis and malignant neoplasm, and emphasized that it frequently occurs in association with a pneumothorax. Similarly, Veress *et al* (1979) reported 30 eosinophilic pleural effusions with self-limiting diseases and favorable outcome. So it would seem that the presence of pleural fluid eosinophilia considerably reduces the probability of malignancy or tuberculosis and increases the likelihood of an underlying benign disorder such as pneumothorax, previous thoracocentesis, benign asbestosis effusions, parasitic diseases, and idiopathic effusions (Adelman *et al*, 1984).

Notwithstanding, Rubins and Rubins (1996) conducted a prospective cohort study to determine the diagnostic and prognostic significance of eosinophilic pleural effusion and found that malignancy was as prevalent among eosinophilic as noneosinophilic pleural effusions. However, patients with eosinophilic pleural effusion had better survival. A high percentage of malignancy in eosinophilic pleural effusion was also reported by Riantawan *et al* (1998). Consequently, malignancies may be common in eosinophilic pleural effusion where malignancy is prevalent (Kuhn *et al*, 1989).

The objective of our study was to define : 1) the etiology of eosinophilic pleural effusion, and 2) the factors that determine malignancy in eosinophilic pleural effusion.

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MATERIALS AND METHODS

A cross sectional study was conducted between August 1, 1994 and July 31, 2000 at Srinagarind Hospital, Khon Kaen University, Thailand. Patients 15 years or older with pleural fluid eosinophils ≥ 10% were included. Patient's charts and laboratory finding were reviewed. Data collection included: demographic data, initial clinical symptoms and signs, history of previous thoracocentesis, pleural fluid analyses, pleural biopsy, abnormal chest radiographs, blood eosinophilia, and final diagnosis.

Diagnostic criteria

Transudative or exudative pleural effusion was defined by Light's criteria (1995). A malignancy was diagnosed when neoplastic pleural tissue and/or fluid cytology were confirmed. A diagnosis of tuberculous pleural effusion was defined by positivity of any one of the following : 1) *Mycobacterium tuberculosis* identified in a culture of the pleural fluid and/or sputum; 2) Caseating granulomas in the absence of any clinical evidence of sarcoidosis, tularemia, or fungal infection in the pleural tissue; 3) A response to antituberculous drugs revealved by an improvement of clinical symptoms and clearing of chest radiographs.

The diagnostic criteria for other diseases were: 1) Pneumothorax - air in pleural space, 2) Parapneumonic effusion - any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis, 3) Empyema thoracis - pus in pleural space or Gram stain and/or bacterial pathogen cultured from the pleural fluid, 4) Chylous pleural effusion - milky appearance of the pleural fluid due to a high level of cholesterol, 5) Meigs' syndrome - a presence of ascitis and pleural effusion in patients with benign ovarian or uterine tumor resolved after removal of the ovarian or uterine tumor, 6) Unknown etiology - investigation revealed no definite diagnosis or final investigation could not be done because of the patient lost to follow-up.

Ethics

The Ethics Committee of the Faculty of Medicine, Khon Kaen University, Thailand, approved this research.

Statistical analysis

Mean and standard deviation were calculated for continuous data, and number and percentage for the categorical data. Group comparisons were made using the unpaired Student's *t*-test for continuous variables, and χ^2 or Fisher's test for categorical one. P-values < 0.05 were considered significant.

RESULTS

During the study period, 50 patients (35 men and 15 women) averaging 56.4 years (range, 16 to 87 years) were diagnosed with eosinophilic pleural effusion. Nearly half of them (46%) had an underlying disease such as diabetes mellitus (14%), malignancy (8%), or old pulmonary tuberculosis (6%). Over half (54%) smoked cigarettes (Table 1). The mean duration of symptoms was 40.8 days (range, 1 to 210 days). The most common clinical symptoms were cough (76%), dyspnea (68%), fever (48%), weight loss (46%), and pleuritic chest pain (34%) (Table 2).

Exudative pleural effusion was found in 48 patients (96%). Only two presented with transudative pleural effusion caused by nephrotic syndrome secondary to systemic lupus erythrematosus and volume overload from acute post streptococcal glomerulonephritis. Half (48%) of the patients developed right-sided pleural effusion, 42% left-sided, and 10% bilateral.

Malignancy was the most common established cause of eosinophilic pleural effusion (46%) (Table 3). Among our 50 subjects with eosinophilic pleural effusions, 24 (48%) had a history of previous thoracocentesis, whereas for 26 (52%) it was their first time of thoracocentesis. Notwithstanding, there was not any significant difference in the etiology of the two groups. The four common causes of eosinophilic pleural effusion were: malignancy, unknown, tuberculous pleural effusion, and parapneumonic effusion. The 23 malignancies included: 11 adenocarcinoma of unknown origin, 6 bronchogenic carcinoma (4 adenocarcinoma and 2 squamous cell carcinoma cell type), 1 cervical carcinoma, 1 osteosarcoma, 1 cholangiocarcinoma, 1 medullary thyroid carcinoma, and 2 of an unknown cell type. Parasitic pleural effusion accounted for 1 case which was

Table 1
Patient's characteristics.

Patient's characteristics	n = 50
Age, years (mean, SD)	56.4 (16.4)
Male : female ratio	35:15
Underlying diseases (%)	
None	54
Present[a]	46
Diabetes mellitus	14
Malignancy :	8
Hepatoma	2
CA cervix	2
Osteosarcoma	2
Medullary thyroid carcinoma	2
Old pulmonary TB	6
Coronary heart disease	6
Chronic obstructive pulmonary disease	4
Valvular heart disease	4
Chronic renal failure	4
Others	14
Smoking (%)	
Present	54
Absent	18
Undetermine	28

[a]Some patients had more than 1 underlying diseases.

Table 2
Clinical symptoms of 50 patients.

Clinical symptoms[a]	%
Cough	76
Dyspnea	68
Fever	48
Weight loss	46
Pleuritic chest pain	34
Anorexia	32
Chest discomfort	30
Fatique	18
Hemoptysis	14
Edema	4
Abdominal distention	4
Shoulder pain	2
Neck mass	2
Sore throat	2
Low back pain	2
Alteration of conscious	2
LUQ abdominal pain	2
DVT right lower extremity	2
Hoarseness and dysphagia	2

[a]Every patients had more than 1 clinical symptoms.

caused by *Strongyloides stercoralis*. One case in the unknown group presented with chylous pleural effusion - the final investigation of which could not be done because the patient did not return for follow-up.

A comparison of patients with malignant *vs* benign pleural effusion was presented in Table 4. There was no statistically significant difference between the groups in age, sex, or smoking. Patients with malignant pleural effusion had a significantly longer duration of clinical symptoms (≥ 1 month). Weight loss was the only clinical symptom found more often in sufferers of malignant pleural effusion than benign pleural effusion. Patients with fever preferred benign more than malignant pleural effusion, eventhough it was not statistically significant. There was no difference in the history of previous thoracocentesis found between groups. The percentage of eosinophils in the pleural fluid of those with malignant pleural effusion was 26.6% (range, 10% to 63%), not statistically different from those with benign pleural effusion (30.6%, range 10% to 93%). The pleural fluid profile, abnormal chest radiographs, and blood eosinophilia could not be used to differentiate these two conditions.

DISCUSSION

Almost all cases (96%) of eosinophilic pleural effusion were exudative. In this study, we found malignancy was the most frequent cause of eosinophilic pleural effusion. This high figure may be explained by the high prevalence of malignancy in our study population, as observed in other reports (Kuhn *et al*, 1989; Rubins and Rubins, 1996; Riantawan *et al*, 1998; Martinez-Garcia *et al*, 2000). Eventhough a previous thoracocentesis or previously introduced of air or blood into the pleural space, can be the primary cause or a concomitant finding, there was no difference in the etiology of our who had a previous thoracocentesis and those who had thoracocentesis for the first time. Tuberculosis was the most common cause of benign eosinophilic pleural effusion (Kamel *et al*, 1989; Bassiri *et al*, 1997). Our finding indicated malignancy and tuberculosis were the two most common causes of eosinophilic pleural effusions (combined 56%). This strongly contrasts with the conception that pleu-

Table 3
Etiology of eosinophilic pleural effusion.

Etiology	Previous thoracocentesis n (%)	First thoracocentesis n (%)	Total n (%)
1. Malignancy	11 (22)	12 (24)	23 (46)
2. Unknown	6 (12)	5 (10)	11 (22)
3. Tuberculous pleural effusion	2 (4)	3 (6)	5 (10)
4. Parapneumonic effusion	1 (2)	3 (6)	4 (8)
5. Empyema	1 (2)	0	1 (2)
6. Pneumothorax	0	1 (2)	1 (2)
7. Meigs' syndrome	1 (2)	0	1 (2)
8. Nephrotic syndrome secondary to SLE	1 (2)	0	1 (2)
9. APSGN	0	1 (2)	1 (2)
10. Subphrenic collection	1 (2)	0	1 (2)
11. *Strongyloides stercoralis*	0	1 (2)	1 (2)
Total	24 (48)	26 (52)	50 (100)

SLE = Systemic lupus erythrematosus; APSGN = Acute post streptococcal glomerulonephritis.

Table 4
Clinical and laboratory finding of patients with malignant and benign pleural effusions.

	Malignancy (n=23)	Benign (n = 16)	p-value
Age, yrs (mean, SD)	56.5 (16.3)	52.5 (16.2)	0.23
Male : female	15:8	12:4	0.52
Smoking (%)	47.8	50.0	0.42
Duration of symptoms			
Median (days)	30	14	
≥ 1 month (%)	78.3	42.9	0.04[a]
Symptoms and signs (%)			
Fever	34.8	62.5	0.17
Weight loss	65.2	12.5	0.003[a]
Pleuritic chest pain	34.8	37.5	0.87
Hemoptysis	17.4	6.3	0.63
Lymphadenopathy	30.4	18.8	0.48
Hepatomegaly	30.4	6.3	0.11
Previous thoracocentesis (%)	47.8	43.8	0.93
Pleural fluid profiles			
Color (%)			
Bloody	13.0	6.3	0.63
Serosanguinous	47.8	12.5	0.05
Cells			
WBC, cells/mm^3 (mean, SD)	1,759 (1,843)	2,760 (2,132)	0.94
RBC > 100,000 cells/ mm^3 (%)	30.4	25.0	1.00
% Eosinophils (mean, SD)	26.6 (16.2)	30.6 (24.6)	0.73
% Eosinophils in first thoracocentesis (mean, SD)	24.5 (16.3)	30.3 (22.5)	0.75
Protein, g/dl (mean, SD)	4.9 (1.2)	4.6 (1.6)	0.23
Abnormal chest radiographs other than pleural effusion (%)	52.2	37.5	0.56
Blood eosinophils > 700 cells/ mm^3	30.4	18.8	0.48

[a]p-value < 0.05 (Student's *t*-test for continuous variables, chi-square or Fisher's test for categorical variables).

ral eosinophilia reduces the probability of malignancy and tuberculosis (Veress *et al*, 1979; Adelman *et al*, 1984).

Parapneumonic effusion and empyema thoracis were the second most common causes of benign eosinophilic pleural effusion. These benign conditions were also found in other studies (Wysenbeek *et al*, 1985; Kuhn *et al*, 1989; Rubins and Rubins, 1996). Pneumothorax was found in only one case, in contrast to comments that pleural eosinophilia was a normal reaction of the pleura to the introduction of air (Spriggs, 1979). Despite our being in an area endemic for parasitic infestations, parasitic pleural effusion was encountered only once from *Strongyloides stercoralis*, which is a rare cause of eosinophilic pleural effusion (Goyal, 1998; Emad, 1999). Other parasites that cause eosinophilic pleural effusion but not found in our study include paragonimiasis (Riantawan *et al*, 1998; Ashitani *et al*, 2000), sparganosis (Ishii *et al*, 2001), hydatid disease, amebiasis, or ascariasis (Light, 1995). Unknown etiologies in our study accounted for 22%, similar to other studies (Adelman *et al*, 1984; Rubins and Rubins, 1996).

A longer duration (≥ 1 month) of clinical symptoms and weight loss were significantly found in patients with malignant pleural effusion. On the other hand, patients with benign pleural effusion had median duration of clinical symptoms 14 days. Fever was experienced more commonly among sufferers of benign diseases. The amount of eosinophils in pleural fluid and blood could not be used to differentiate malignant and benign diseases. Characteristics of the pleural fluid and pleural fluid profile also did not exhibit significant differences. A long duration of clinical symptoms in malignant eosinophilic pleural effusion may favor a better prognosis in malignant eosinophilic than noneosinophilic pleural effusion. Rubins and Rubins (1996) reported the median survival in noneosinophilic effusion 7.7 months compared to 16.8 months for those with eosinophilic pleural effusion.

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