ETIOLOGY AND CLINICAL IMPLICATIONS OF EOSINOPHILIC PLEURAL EFFUSIONS

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Abstract. This prospective study examined the etiology of eosinophilic pleural effusions investigated at a Thai thoracic center from January 1996 to February 1998. Among the 405 eligible pleural effusions, 31 were eosinophilic (EoPF) and 374 were noneosinophilic (NEoPF). Malignant effusions were established in 159 of the 405 patients, yielding a prevalence of 0.39. Malignant effusions were responsible in 24 of the 31 EoPF (77.4 %), and 135 of the 374 NEoPF (36 %)($p = 0.01$). Bayesian analysis showed the post-test probability of malignancy in eosinophilic pleural effusions among our patient population to be 0.76. Tuberculous pleuritis was the etiology in 155 patients with NEoPF (41.4 %) but in none of the patients with EoPF ($p < 0.001$). There was no significant difference between EoPF and NEoPF in miscellaneous causes including paragonimiasis, amebiasis, lupus pleuritis, chylothorax, and yellow nail syndrome. It is concluded that eosinophilic pleural effusions are at least as likely to be malignant as noneosinophilic effusions. The finding of eosinophilic pleural effusions should not be regarded as suggestive of benign conditions.

INTRODUCTION

Eosinophilic pleural effusions (EoPF), defined as the presence of 10 % or more eosinophils in the pleural fluid, are relatively rare and account for 5 to 8 % of exudative pleural effusions (Light, 1995a; Sahn, 1988a). Previous studies held that EoPF was frequently related to benign diseases and denoted a favorable prognosis (Sahn, 1982; Kokkola and Valta, 1974; Veress *et al,* 1979). EoPF is con-sidered to be rarely associated with malignant pleural disease and carry a low probability for malignancy (Adelman *et al,* 1984).

However, these notions almost entirely originated from retrospective data and did not take into account the prevalence of malignancy among the studied patients (Sahn, 1982; Kokkola and Valta, 1974; Veress *et al,* 1979). Malignancy may be found more commonly in EoPF among population with high prevalence of malignancy (Kuhn *et al,* 1989).

The present study was prospectively conducted in an attempt to : 1) examine the etiology of eosinophilic pleural effusions, 2) assess its malignant potential by utilising Bayes' theorem, and 3) explore its clinical implications.

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MATERIALS AND METHODS

From January 1996 to February 1998, consecutive patients with a pleural effusion attending the Central Chest Hospital, Thailand, were studied. A detailed history, a thorough physical examination, and a chest radiograph were taken. Thoracentesis was performed in a standard manner. Closed pleural biopsy was carried out, using an Abrams' needle (Abrams, 1958). At least 3 pieces of pleural tissues were taken. Patients with pneumothorax or previous thoracentesis were excluded since pneumothorax and prior pleural puncture are known to produce pleural eosinophilia (Spriggs, 1979; Light, 1995).

The pleural fluid was examined macroscopically, cytologically, biochemically, and microbiologically including acid-fast bacilli staining and cultures for M tuberculosis. The fluid aliquots were analysed for erythrocyte count, leukocyte count and differential subsets, protein, glucose, and lactate dehydrogenase (LDH).

Diagnostic classification

For the purposes of this study, malignant effusion was diagnosed when neoplastic pleural tissue and/ or fluid cytology were identified (Sahn, 1988b). A diagnosis tuberculous pleuritis required one of the following : A) the pleural tissue exhibited

granulomas in the absence of clinical evidence of sarcoidosis, tularemia, and fungal infection; B) pleural tissue or pleural fluid stained acidfast bacilli or grew M tuberculosis (Light, 1995c).

Parapneumonic effusions were diagnosed when the effusion was associated with pneumonia, pulmonary abscess or bronchiectasis, and empyema if the pleural fluid cultures were positive (Light, 1995a). All the patients were followed up for at least 6 months.

Analysis and statistical methods

Data are expressed as mean (SE). Group comparisons were made by one-way analysis of variance or unpaired student' s *t*-test as appropriate (Armitage and Berry, 1994). Chi-squared test was used for comparison of categorical variables (Altman, 1993). Data analyses were made by SPSS program. Statistical significance was assessed at 5% level.

The probability of malignancy after the finding of pleural eosinophilia is estimated by Bayes's theorem, which states that :

$$P(\text{disease/test result}) = \frac{P(\text{test result/disease}) \times P(\text{disease})}{P(\text{test result})}$$

where P(disease/test result) represents the probability of malignancy after the finding of pleural eosinophilia, P(test result/disease) is the probability of eosinophilia in malignant pleural effusions, P(disease) is the likelihood of malignancy in the population studied, and P (test result) is the probability of eosinophilia in all exudates (Pauker and Kassirer, 1987).

RESULTS

Clinical and pleural fluid profiles

A total of 426 patients with pleural effusions attended the hospital during the study period. Nineteen patients underwent thoracentesis prior to this admission and the effusions in two patients were associated with pneumothorax and were excluded from the study. Thus, 405 patients were eligible for the study (Table 1). Among these 405 pleural effusions, 31 (7.6 %) were eosinophilic (EoPF) and 374 (92.4 %) were noneosinophilic (NEoPF).

The mean age among patients with EoPF was older than those with NEoPF (57 *vs* 46 years, p = 0.003). The mean pleural fluid erythrocyte count was higher in the EoPF group than in the NEoPF group (86,315 *vs* 24,000, p = 0.001). The mean pleural fluid eosinophil percentage was 34 among patients with EoPF.

Etiology of pleural effusions

Overall, the pleural effusions in 39.2 % of the 405 patients were caused by malignancy (Table 2). A diagnosis of tuberculous pleuritis was reached in 38.3 % of the patients. Empyema and parapneumonic effusions were responsible in 7.6% and 4.6%, respectively. Despite all the investigations, the effusions were idiopathic in 4.4 % of the patients. Anecdotal cases comprised pancreatitis (2), pulmonary embolus (2), chylothorax (2), atelectasis (2), paragonimiasis (1), amebiasis : (1), lupus pleuritis (1), and yellow nail syndrome (1).

Etiologic differences between EoPF and NEoPF

Malignant pleural effusion was the established cause in 77.4 % among the EoPF as compared with 36 % among the NeoPF (p = 0.01) (Table 2). Tuberculous pleuritis was responsible in none of the 31 patients with EoPF in contrast with 41.4 % of the patients with NEoPF ($p < 0.001$). There was no significant difference in the other causes of pleural effusions between the two groups.

Probability of malignancy in EoPF

Applying the data arising from the present study, the probability of malignancy after the finding of EoPF could be described as following :

$$P(\text{disease/test result}) = \frac{24/159 \times 159/405}{31/405} = 0.76$$

DISCUSSION

The present study has prospectively examined the etiology of eosinophilic pleural effusions and

Table 1

Clinical and pleural fluid profiles of 405 patients classified into eosinophilic and noneosinophilic pleural effusions.

	Eosinophilic (n = 31)	Noneosinophilic (n = 374)	p value
Age, yrs	57 (2.6)	46 (1.7)	0.003
Male : Female	14 : 17	195 : 179	> 0.05
Erythrocytes, cells/ mm^3	86,315 (16,770)	24,000 (10,540)	0.001
Leukocytes, cells/ mm^3	7,535 (3,556)	8,209 (3,374)	> 0.05
Lymphocytes, (%)	48 (6.5)	82 (3.4)	< 0.001
Neutrophils, (%)	18 (4.9)	13 (2.9)	> 0.05
Eosinophils, (%)	34 (6.7)	3 (1.8)	< 0.001
LDH, IU/l	612 (98.5)	578 (44.3)	> 0.05
Protein, g/dl	4.1 (0.3)	4.9 (0.1)	0.01
Glucose, mg/dl	96 (12.4)	88 (4.3)	> 0.05

* Values in mean (SE)

Table 2

Etiology of pleural effusions.

Etiology	Total (n = 405)	Eosinophilic (n = 31)	Noneosinophilic (n = 374)	p value
Malignancy	159 (39.2)*	24 (77.4)	135 (36)	0.01
Tuberculosis	155 (38.3)	0	155 (41.4)	< 0.001
Empyema	31 (7.6)	1	30 (8)	> 0.05
Parapneumonic	19 (4.6)	1	18 (4.8)	> 0.05
Paragonimiasis	1	1	0	> 0.05
Amoebiasis	1	0	1	> 0.05
Pancreatitis	2	1	1	> 0.05
Pulmonary embolus	2	0	2	> 0.05
Lupus pleuritis	1	0	1	> 0.05
Chylothorax	2	0	2	> 0.05
Yellow nail syndrome	1	0	1	> 0.05
Atelectasis	2	1	1	> 0.05
Transudates	11 (2.7)	0	11 (3)	> 0.05
Idiopathic	18 (4.4)	2	16 (4.2)	> 0.05

* percent in parenthesis

evaluated the probability of malignancy in eosinophilic pleural effusions based on a sizeable series of patients attending a referral center. Several important findings arising from our study merit discussion.

The most important finding in this study is the high percentage of malignancy (77.4 %) in eosinophilic pleural effusions. The result strongly refutes the premonition that eosinophilic effusions highly suggest an underlying benign disease (Sahn, 1982; Kokkola and Valta, 1974; Veress *et al,* 1979). Our finding indicates that the underlying disease is at least as likely to be malignant in eosinophilic effusion as in noneosinophilic effusion.

The premise that eosinophilic pleural effusions carry a low probability of malignancy mostly stemmed from retrospective data and did not take into account the prevalence of malignancy among the population of interest (Sahn, 1982; Kokkola and Valta, 1974; Veress *et al,* 1979). It follows from Bayes' theorem that post-test probability, or the likelihood of the disease after the positive finding, is determined by the pre-test probability or prevalence of the disease among the population of interest (Eddy and Clanton, 1982).

From the foregoing, we applied a Bayesian analysis for our patients population and found a high probability of malignancy (0.76) after the finding of eosinophilic pleural effusions. Hence, the presence of pleural eosinophilia mandates a high index of suspicion of malignancy. This strongly contrasts with the preconception that pleural eosinophilia is mostly related to benign etiology, *eg* parasitic pleural effusions, especially in tropical countries such as Thailand. It should be mentioned that pleural effusions due to paragonimiasis and amoebiasis are indeed infrequent in the present series.

Another interesting finding from our study is that the effusions in tuberculous pleuritis in our series were always noneosinophilic. This finding is of clinical importance since tuberculosis is endemic in Thailand as reflected by the high prevalence of tuberculous pleuritis among our patients (38.3 % of the 405 patients). The result is in line with findings from countries where tuberculosis is not prevalent (Light, 1995b). A finding of pleural eosinophilia in patients with tuberculous pleuritis thus indicates a previous thoracentesis or associated pneumothorax.

Despite extensive investigations, the underlying cause of pleural effusion was unknown in 4.4 % of the cases in our study. This accords with previous finding that approximately 5 % of pleural effusions are idiopathic (Marel *et al,* 1995; Romero, 1996). Furthermore, 7.6 % of the pleural effusions in our study were eosinophilic in agreement with previous series (Light, 1995a; Sahn, 1988b). Therefore, the methodology and diagnostic accuracy in our study was not subject to any major pitfalls.

It is noteworthy that the patients with eosinophilic effusions were comparatively older that those with noneosinophilic effusions. This difference is most likely attributed to the higher proportion of underlying malignancy in the former group. The similar explanation could be made with the finding of higher pleural fluid erythrocyte count among the patients with eosinophilic effusions.

In conclusion, the present study refutes previous notion that eosinophilic pleural effusions usually indicate a benign disease. The results underscore the need for a high index of suspicion of malignancy in the presence of eosinophilic pleural effusions.

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