Eur Respir J 1999; 15: 166–169
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Diagnostic utility of eosinophils in the pleural fluid

M.A. Martínez-García, E. Cases-Viedma, P.J. Cordero-Rodríguez, M. Hidalgo-Ramírez, M. Perpiñá-Tordera, F. Sanchis-Moret, J.L. Sanchis-Aldás

Diagnostic utility of eosinophils in the pleural fluid. M.A. Martńez-Garcá, E. Cases-Viedma, P.J. Cordero-Rodŕguez, M. Hidalgo-Ramŕez, M. Perpiñá-Tordera, F. Sanchis-Moret, J.L. Sanchis-Aldás. ©ERS Journals Ltd 2000.

ABSTRACT: This study was conducted to assess the prevalence of eosinophilia in 358 consecutive samples of pleural fluid (all cases corresponded to first thoracentesis), to review the cause of eosinophilic pleural effusions, and to determine whether the presence of eosinophils increases the likelihood of nonmalignant underlying disorders.

Eosinophilic pleural effusions were identified in 45 patients (12.6%): malignant underlying conditions were diagnosed in 11 patients (24.4% with eosinophilic effusions) and benign aetiologies were found in 27 patients. Benign aetiologies included uncomplicated paraneumonic effusion in 10 patients, tuberculosis in seven, complicated paraneumonic in five, liver cirrhosis in three, hydronephrosis in one and pulmonary thromboembolism in one. Seven pleural effusions were idiopathic. There was no difference in the prevalence between eosinophilic and noneosinophilic effusions according to the different diagnoses. With parameters of sensitivity, specificity, pretest and post-test probability and positive and negative predictive values for any prevalence figure using the Bayes′ theorem and for any value of eosinophils (both in percentage or absolute numbers) in the pleural fluid (receiver operating characteristic curve) an adequate predictor of benign disease was not found.

It is concluded that pleural eosinophilia at the initial thoracentesis cannot be considered as a predictor of an underlying benign disorder.

Eur Respir J 2000; 15: 166–169.

The Service of Pneumology, Hospital Universitario La Fe, Valencia, Spain.

Correspondence: E. Cases-Viedma, Servicio de Neumologá, Hospital Universitario La Fe, Avenida Campanar 21, E46009 Valencia, Spain. Fax: 34 963987397

Keywords: Benign diseases
malignancy
pleural effusion
pleural fluid eosinophilia
tuberculosis

Received: December 16 1998
Accepted after revision September 30 1999

Eosinophilic effusions, defined as ≥10% eosinophils of the white blood cells [1, 2], account for 5–8% of exudative pleural effusions [1, 3]. Despite many decades of observation and discussion, the clinical significance and prognostic value of this finding remain controversial. As eosinophilia is a rare finding in malignant pleural effusion, it has been used as an indicator of good prognosis [3, 4]. Recent studies, however, have not confirmed a lower prevalence of eosinophilic pleural effusion in malignancies [1, 2]. On the other hand, certain conditions are known to frequently produce pleural fluid eosinophilia, such as bloody effusion, pneumothorax, chest trauma, or repeated thoracentesis [5–10]. Also, a high proportion of idiopathic effusions are characterized by pleural fluid eosinophilia, although in most cases data are based on relatively small series of patients [2, 3, 6, 9, 11].

The aim of this study was to estimate the prevalence of eosinophilia in a large series of pleural effusions, to review the spectrum and frequency of disorders associated with eosinophilic pleural effusions, and to determine whether the presence of eosinophils increases the probability of benign disorder and reduces the likelihood of malignancy.

Patients and methods

A retrospective study was made of 385 consecutive samples of pleural fluid collected at the hospital Universitario La Fe, Valencia, Spain (a tertiary care centre with 1,200 beds serving a population of 500,000 inhabitants) between January 1994 and April 1997. All data are from the first thoracentesis. Bloody effusions (resulting from thoracic trauma or surgical operations) and effusions associated with air in the pleural space were excluded, as well as cases in which more than one cause of pleural effusion was identified and there were doubts regarding the causative underlying disorder. A total of 27 samples were excluded for the following reasons: blood effusions (n=23), pneumothorax (n=3), and doubtful aetiology (n=7). A total of 358 samples of pleural fluid were finally included in the study.

All thoracentesis procedures were carried out by the same medical team. All cytological examinations were performed by manual cell count. A pleural effusion was defined as eosinophilic when ≥10% of the leukocytes were eosinophils. The diagnostic procedure was performed by the department where the patient was being treated and the causative disorders were established by clinical, bacteriological, analytical and/or histological data. Pleural tuberculosis was diagnosed by the findings of caseous granulomata in the pleural biopsy and/or positive culture for *Mycobacterium tuberculosis* in pleural fluid, respiratory samples or biopsy material. Parapneumonic effusion was defined by synchronous occurrence with acute febrile illness, purulent sputum and infiltrate on the chest radiographic film. The diagnosis of complicated paraneumonic

effusion was made by the presence of a pleural fluid with a pH <7, a glucose level <40 mg·dL^{-1} and a positive Gram's stain or culture. The empyemas, diagnosed by the presence of purulent liquid and consistent clinical/radiological signs of infection, were included in complicated paraneumonic effusion. Effusions were classified as malignant when pleural fluid cytological findings and/or pleural biopsy were diagnostic for malignancy. In these patients the authors checked whether they had previously been treated with drugs that may have induced effusion eosinophilic pleural effusions (especially chemotherapy drugs). Pulmonary thromboembolism was diagnosed by ventilation/perfusion lung scans and/or pulmonary angiography. Effusions secondary to congestive heart failure, nephrotic syndrome, and liver cirrhosis were diagnosed by clinical and laboratory criteria. Effusions were classified as idiopathic if no aetiology could be assigned at the initial or subsequent evaluations. These patients were followed for at least 18 months after the first thoracentesis. Effusions were classified as transudates or exudates using the criteria of LIGHT *et al.* [12]. Patients with transudate pleural effusions were followed for at least 3 months to confirm the aetiology.

Statistical analysis

The prevalence of diagnoses among eosinophilic and noneosinophilic pleural effusions was compared using the Chi-squares test with Yates' correction when necessary. Statistical significance was set at $p<0.05$. The diagnostic utility of eosinophilic pleural effusion for the prediction of underlying benign disorders was assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value and pretest and post-test probability. The Bayes' rule was applied to estimate the positive and negative predictive values for a prevalence figure of a benign condition in a given patient. A receiver operator characteristic (ROC) curve was plotted to define the cut-off point with the highest diagnostic value for the presence of eosinophils in the pleural fluid. Finally, the prevalence of a benign disorder (PB) before and after the diagnosis of eosinophilic pleural effusions was determined by the estimate of pretest and post-test probability.

Results

The study sample consisted of 358 pleural effusions from 212 males and 146 females, with a mean±SD age of 53.4±11.2) yrs; (range: 14–93 yrs). Eosinophilic pleural effusions were identified in 45 patients (12.6%). Malignant underlying conditions were diagnosed in 11 patients (lung carcinoma in nine cases and metastatic disease in two). Benign aetiologies included uncomplicated parapneumonic effusions in 10 patients, tuberculosis in seven, complicated paraneumonic effusions in five, liver cirrhosis in three, hydronephrosis in one, and pulmonary thromboembolism in one. In the remaining seven patients the pleural effusions were idiopathic. When eosinophilic and noneosinophilic effusions were compared, there were no differences in the prevalence of malignancy (24.4% *versus* 26.8%, p=0.87) or idiopathic effusions (15.5% *versus* 8.9%, p=0.17) (table 1).

Table 1. – Different diagnoses in patients with eosinophilic and noneosinophilic pleural effusion

Diagnosis	Pleural effusion		p-value
	Noneosinophilic (n=313)	Eosinophilic (n=45)	
Heart failure	25 (8.0)	0	NS
Benign kidney disease	16 (5.1)	1 (2.2)	NS
Liver cirrhosis	18 (5.7)	3 (6.7)	NS
Uncomplicated parapneumonic	49 (15.7)	10 (22.2)	NS
Complicated parapneumonic and empyema	9 (2.9)	5 (11.1)	NS
Pulmonary tuberculosis	65 (20.8)	7 (15.6)	NS
Malignancy	84 (26.8)	11 (24.4)	NS
Pulmonary embolism	3 (1.0)	1 (2.2)	NS
Idiopathic	28 (9.0)	7 (15.6)	NS
Other*	16 (5.1)	0	NS

Data are presented as absolute numbers with percentage in parentheses. *: three pancreatitis; two subphrenic abscess; three hydatid disease; three rheumatoid arthritis; one Wegener's granulomatosis; one systemic mastocytosis; two Dressler's syndrome; and one pericardial disease. NS: nonsignificant.

The predictive value of eosinophilic pleural effusion for a benign aetiology was considered at a cut-off point of 10% eosinophils in the pleural fluid. The sensitivity, specificity, positive predictive value and negative predictive value for a prevalence of 75.6% of benign disease were 52%, 47%, 75.1% and 28.1%, respectively. The post-test probability, the probability of an eosinophilic pleural effusion being benign assuming the pretest probability or PB mentioned before, was calculated by the formula:

$$\frac{\text{Probability quotient} \times \text{odds pretest}}{(\text{Probability quotient} \times \text{odds pretest}) + 1}$$

Where the probability quotient is defined as: sensitivity/(1 - specificity) and odds pretest is defined as: PB/(PB+1). The result of post-test probability was 75.1%. Table 2 shows the positive and negative predictive values for any pretest probability or prevalence figure of benign disease. Figure 1 shows that the optimal value for both the positive and

Table 2. – Different positive and negative predictive values in relation to the prevalence of benign disorders

Prevalence	Positive predictive value	Negative predictive value
0.1	0.10	0.90
0.2	0.20	0.79
0.3	0.29	0.69
0.4	0.39	0.59
0.5	0.49	0.49
0.6	0.59	0.39
0.7	0.69	0.29
0.8	0.80	0.19
0.9	0.90	0.10

Positive predictive value: true positive test results from malignant pleural effusions/all positive test results; Negative predictive value: true negative test rsults from benign pleural effusions/all patients with negative results. Both calculated according to the prevalence of benign disorders.

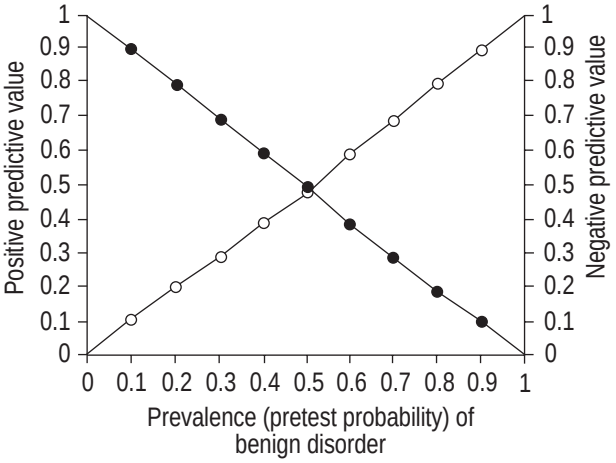

Fig. 1. – Pretest probability curve for the prediction of a underlying benign disease. Both curves cross in the point where the relation between positive and negative predictive values is optimal. In this cross point none of predictive values are >50%, which means that eosinophilic pleural effusion is not useful for predicting an underlying benign disorder for any prevalence (pretest probability) of benignity. ○: positive predictive value; ●: negative predictive value.

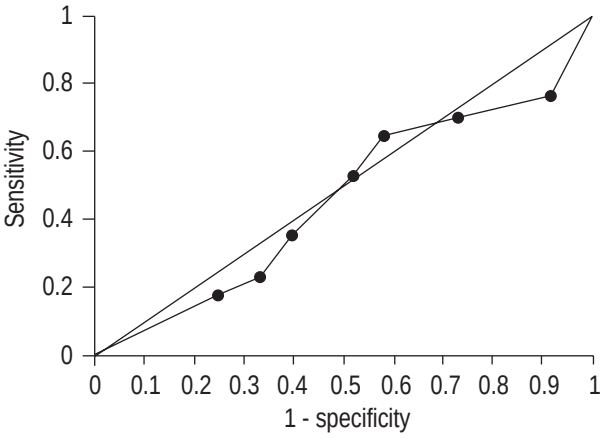

Fig. 2. – Receiver operating characteristic (ROC) curve for the diagnosis of an underlying benign disease. The resultant curve is similar to the diagonal line, which indicates that eosinophilic pleural effusion have no discriminating value.

the negative predictive values did not exceed 50%. In addition, a value of eosinophils in the pleural fluid that best differentiated malignant from benign pleural effusions, as calculated from the ROC curve, was not found (table 3 and fig. 2).

Discussion

Eosinophilia in the pleural fluid has been generally associated with a underlying benign disease. Numerous studies have shown that eosinophilic pleural effusions are less likely to be malignant [3, 4]. In a review of the literature of 343 cases of eosinophilic pleural effusion published up to 1984, ADELMAN *et al*. [3] found malignant conditions in only 8% of cases. However, KUHN *et al.* [2], in 1989, studied a series of 22 eosinophilic effusions and introducing their results into Bayes′ formula, they found that the likelihood of malignancy in the presence of eosinophilia was 47%. These authors emphasized that although pleural eosinophilia is rare in malignant effusions, it cannot be considered as indicating a good prognosis without taking into consideration the local prevalence of malignancies [2]. In the study of RUBINS and RUBINS [1] of a prospective cohort of 476 consecutive patients undergoing thoracentesis, malignancy was as frequent among eosinophilic as noneosinophilic pleural effusions (20.5% *versus* 20.1%), and the prevalence of eosinophilia among malignant effusions was low (7.8%). They concluded that pleural fluid eosinophilia is not a helpful diagnostic finding, although it does appear to be associated with improved survival independent of diagnosis.

Table 3. – Sensitivity and specificity for a benign aetiology according to the percentage of eosinophils in the pleural fluid with eosinophils

Eosinophils %	Sensitivity %	Specificity %
>4	91.6	23.5
>6	72.9	29.4
>8	58.3	35.2
>10	52.1	47.0
>12	36.9	64.7
>15	33.3	76.4
>20	25.0	82.3

Sensitivity: true positive test results/all patients with benign pleural effusions; Specificity: true negative test results/all patients with malignant pleural effusions. Both calculated according to the percentage of eosinophils n the pleural effusions.

In the current study of 358 cases of pleural effusion, the prevalence of eosinophilic effusions in patients with malignant disorders was 11.6%. It should be noted however, that the prevalence of malignancy in the population (26.5%, 95/358) was lower than that of 56% in the series of KUHN *et al.* [2], 43% in the study of LIGHT [8], and 39% in the study of HIRSCH *et al.* [11]. This may be explained by the high incidence of infections, particularly tuberculosis, in the current population′s environment. Moreover, the prevalence of malignancy was similar among eosinophilic and noneosinophilic effusions. On the other hand, the percentage of eosinophilic effusions in relation to the total number of pleural effusions (12.6%, 45/358) was similar to that found in relation to the total group of malignant effusions (11.6%, 11/95). This study also found that the positive and negative predictive values for the population and for any prevalence figure of benign disease were low. In addition, a value of eosinophils in the pleural fluid that best differentiated malignant from benign pleural effusions, as calculated from the ROC curve, was not found. To corroborate the results the authors applied the latest concepts of pretest and post-test probabilities according to the formulas introduced by SACKETT *et al.* [13], DOMÉNECH MASSONS [14] and HEFFNER [15]. Both results were very similar (75.6% and 75.1% respectively) which means that the contribution of a eosinophilic pleural effusion as a predictor of a benign pathology is almost nothing.

It has also been recognized that a high proportion of idiopathic effusions are characterized by pleural fluid eosinophilia [2, 3, 6, 9, 11]. In the current series, although the percentage of undiagnosed cases was higher among patients with eosinophilic pleural effusion, there were no significant differences in the percentage of idiopathic

cases among eosinophilic (15.5%, 7/45) and noneosinophilic effusions (8.4%, 28/313). It should be noted that in this series no patients were found with parasitic or asbestos-related pleural effusion. In contrast to other studies [2], the prevalence of tuberculosis among eosinophilic effusions was high (15.5%, 7/45).

In summary, eosinophilic pleural effusion is not significantly associated with underlying benign conditions for any prevalence of nonmalignancy, as well as for any absolute count or relative number of eosinophils in the pleural fluid. "Idiopathic" effusions were not significantly more frequent among eosinophilic pleural effusions, which may be due to the low proportion of this type of effusion in relation to better diagnostic procedures. The high proportion of eosinophilic effusions due to pulmonary tuberculosis is explained by the high prevalence of this infection in this population′s environment.

Acknowledgements. The authors thank M. Pulido, for editing the manuscript and editorial assistance.

References

1. Rubins JB, Rubins HB. Etiology and prognostic significance of eosinophilic pleural effusions. A prospective study. *Chest* 1996; 110: 1271–1274.
2. Kuhn M, Fitting JW, Leuenberger P. Probability of malignancy in pleural fluid eosinophilia. *Chest* 1989; 96: 992–994.
3. Adelman M, Albelda SM, Gottlieb J, Haponik EF. Diagnostic utility of pleural fluid eosinophilia. *Am J Med* 1984; 77: 915–920.
4. Wysenbeek AJ, Lahav M, Aelion JA, Kaufmann L. Eosinophilic pleural effusion: a review of 36 cases. *Respiration* 1985; 48: 73–76.
5. Varela JM, Gutiérrez-Bayard L, Calderón E. Derrame pleural eosinofilico. Dos caves de etiologá diferente. *Arch Bronconeumol* 1994; 30: 369–370.
6. Bartter T, Santarelli R, Akers S, Pratter MR. The evaluation of pleural effusion. *Chest* 1994; 106: 1209–1214.
7. Sahn SA. The pleura. *Am Rev Respir Dis* 1988; 138: 184–234.
8. Light RW. Pleural diseases. 3rd Edn. Baltimore, USA, Williams & Wilkins, 1995.
9. Light RW. Diagnostic principles in pleural disease. *Eur Respir J* 1997; 10: 476–481.
10. Fitzgerald DJ, Chaudhary BA, Davis WB. Eosinophilic pleural effusion: is it always nondiagnostic? *J Fam Pract* 1996; 42: 405–407.
11. Hirsch A, Ruffie P, Nebut M, Bignon J, Chrétien J. Pleural effusion: Laboratory tests in 300 cases. *Thorax* 1979; 34: 106–112.
12. Light RW, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; 77: 507–513.
13. Sackeff DL, Richardson WS, Rosenberg W, Haynes RB. Valoración Crtica de la Evidencia. *In*: Sackett DL, Richardson WS, Rosenberg W, Haynes RB, eds. Medicina Basada en la Evidencia. Cómo ejercer y enseñar la MBE. Madrid, Spain, Churchill Livingstone España, 1997; pp. 104–112.
14. Doménech Massons JM. Fundamentos de la teorá de la probabilidad. Pruebas diagnósticas. *In*: Doménech Massons, ed. Métodos estadśticos en Ciencias de la Salud. Barcelona, Spain, Signo, 1999; pp. 43–64.
15. Heffner JE. Evaluating diagnostic tests in the pleural space. *Clin Chest Med* 1998; 19: 277–293.