Eur Respir J 2003; 21: 952–955
DOI: 10.1183/09031936.03.00099502
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European Respiratory Journal
ISSN 0903-1936

Prognostic features of residual pleural thickening in parapneumonic pleural effusions

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Prognostic features of residual pleural thickening in parapneumonic pleural effusions. D. Jiménez Castro, G. Díaz, E. Pérez-Rodríguez, R.W. Light. ©ERS Journals Ltd 2003.

ABSTRACT: The objective of the study was the identification of predictive factors for the development of residual pleural thickening (RPT) in patients with parapneumonic effusion.

The design of the prospective study involved investigating patients with parapneumonic pleural effusions diagnosed between March 1991 and December 2000 in the respiratory department of Hospital Ramón y Cajal (Madrid, Spain) which is a 1,500 tertiary-care hospital.

The clinical and radiological characteristics and measurements of microbiological and biochemical variables in the pleural fluid taken from the patients were studied. RPT was defined in a posteroanterior chest radiograph as pleural thickening of $\geqslant$10 mm measured at the lateral chest wall at the level of an imaginary line, tangent to the diaphragmatic dome.

A total of 48 of the 348 patients studied (13.79%) were found to have RPT. Among the factors studied, only presence of pus in the pleural space, Fine classes IV and V, temperature $\geqslant$38°C and delayed resolution of pleural effusions after diagnosis (>15 days) were independently associated with the risk of RPT.

This study showed that significant residual pleural thickening was not a common complication of parapneumonic pleural effusions. There are certain risk factors for the development of residual pleural thickening. However, this complication was not associated with long-term functional repercussions in the series of patients involved in this study.

Eur Respir J 2003; 21: 952–955.

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Keywords: Drainage
empyema
loculations
microbiology
parapneumonic effusion
thoracoscopy

Received: October 30 2002
Accepted after revision: January 3 2003

Despite the advent of potent antibiotics, bacterial pneumonia still results in morbidity and mortality. The annual incidence of bacterial pneumonia is estimated to range from 1.8–8 cases per 1,000, with ~20% requiring hospitalisation [1]. It has been reported that 57% of hospitalised patients with bacterial pneumonia have an accompanying pleural effusion [2–4]. The morbidity and mortality rates in patients with pneumonia and pleural effusions are higher than in patients with pneumonia alone [5]. Most pleural effusions associated with pneumonia resolve without any specific therapy directed toward the pleural fluid [2], however ~10% require operative intervention for their resolution. Delay in implementing proper therapy for these effusions is responsible for much of the morbidity, which can be substantial. This delay can lead to characteristic changes in the pleural space, including loculations and pleural thickening [6].

Previous studies have assessed what features predict pleural thickening in tuberculous pleural effusions [7, 8], however only one study has retrospectively analysed predictive factors for the development of residual pleural thickening (RPT) in parapneumonic pleural effusions (PPE) [9]. Moreover, there are no studies addressing if RPT is associated with long-term functional consequences in this group of patients.

The purpose of the present study was to prospectively evaluate the prognostic features of RPT and its functional repercussions in a consecutive series of patients with PPE. The authors therefore hypothesise that RPT is an uncommon complication of PPE and is not associated with long-term functional repercussions.

Materials and methods

All patients diagnosed as having PPE in the Respiratory Dept of Ramón y Cajal Hospital (Madrid, Spain) between March 1991–December 2000 were candidates for the study. The authors prospectively included all patients with positive microbiological cultures in the pleural fluid, gross pus in the pleural space or pleural exudates associated with pneumonia who had undergone diagnostic thoracentesis. Patients with previous pleural disease were excluded from the study. All patients included in the present study signed an informed consent form that had been approved by the institutional review board.

The routine study of the pleural fluid included: pH, determined by a blood gas analyser (model 995-Hb; AVL Medical Instruments, Roswell, GA, USA), biochemical testing of pleura/serum (proteins, lactate dehydrogenase (LDH), glucose, cholesterol, triglycerides, albumin and adenosine deaminase), haemogram, cytology and microbiological testing of pleura (Gram stain, Ziehl stain, aerobic, anaerobic and mycobacterial cultures). The following variables were collected through chart review and patient interviews: age, sex, abnormalities on

chest radiographs, indication for thoracentesis (diagnostic, therapeutic), number of thoracenteses, pleural effusion volume (as a percentage of the entire hemithorax, subjectively visually assessed), side affected and Fine classes [10] (a five classes prediction rule which accurately identifies the patients with community-acquired pneumonia who are at low risk for death and other adverse outcomes; prospectively used from 1997 in the present study). The authors also recorded: antibiotic therapy, pleural drainage (thoracentesis, chest tube, fibrinolytics, thoracoscopy or thoracotomy), length of stay in hospital, complications, in-hospital deaths, 6 month deaths, 6 month re-admissions and RPT at discharge and at 6 months. Pulmonary function tests and Borg scale were performed at discharge and at 6 months to evaluate the functional impact of RPT in this group of patients. Patients were divided into two groups based on the presence or absence of RPT at the 6 month radiograph. RPT was measured at the lateral chest wall of a posteroanterior chest radiograph at the level of an imaginary line tangent to the diaphragmatic dome. RPT was defined as a pleural thickness of $\geqslant$10 mm because this thickness may have important clinical repercussions.

Statistical analyses were performed using computer software. Results were expressed as mean±SD unless otherwise stated. Variable distributions were compared with a normal distribution using the Kolmogorov-Smirnov test. The characteristics of the patients with and without RPT were compared using the Chi-squared test with Yates correction or Fisher's exact test for noncontinuous variables, the nonparametric Mann-Whitney U-test for continuous variables with non-normal distribution and unpaired t-test for those with normal distribution.

Crude odds ratios (ORs) and their 95% confidence intervals (CI) were used to describe the association between RPT and potential risk factors. Subsequently, a multiple logistic regression analysis was performed to adjust for the confounding effects of other factors and a logistic regression model was built by a stepwise forward method. Factors were selected from those that were statistically associated with RPT in the univariate analysis and from those that were thought to influence the model. Adjusted ORs, in the multivariable logistic regression, were estimated by the method of maximum likelihood and 95% CIs were based on the SD coefficient estimates and normal approximation. Two-tailed p-values of $\leqslant$0.05 were considered statistically significant.

Table 1. – General characteristics in patients with or without residual pleural thickening (RPT)

Variable	RPT	No RPT	p-value
Subjects n	48	300	
Age yrs	61±18	64±14	0.35
Males n	20	164	0.12
Volume[#]	64±26	52±26	<0.01
pH	7.15±0.15	7.19±0.11	0.02
Glucose mg·dL^{-1}	48±27	54±28	0.14
LDH IU·L^{-1}	625±543	488±315	0.01
Pleural leukocyte count per mm^3	5309±1593	3488±1657	<0.01
Time from symptoms to treatment days	6±4	6±5	0.52

[#]: per cent of entire hemithorax; LDH: lactate dehydrogenase; IU: international units.

Results

During the study 387 potentially eligible outpatients with PPE were evaluated. From these 387 patients, 21 patients were excluded because of their refusal to give informed consent, a further 15 were excluded because of previous pleural disease and three patients died during hospital admission. The final analysis included 348 patients, 184 males (52.9%) and 164 females (47.1%) with an average age of 63.16± 14.50 yrs. A total of 48 patients (13.79%) had RPT $\geqslant$10 mm 6 months after discharge.

The clinical, radiological and microbiological characteristics of patients with or without RPT are shown in table 1. The patients with RPT had significantly larger effusions, lower pleural fluid pH and higher pleural fluid LDH and leukocyte levels.

Pleural leukocyte counts had the highest diagnostic accuracy for separating patients with and without RPT as measured by the area under the receiver-operating characteristic curve (AUC= 0.78) compared with the volume of the effusion (AUC=0.63), pleural fluid glucose (AUC=0.47), pleural fluid LDH (AUC=0.39) or pleural fluid pH (AUC=0.61).

The results of the univariate analyses are depicted in table 2. Only the results that were statistically significant, or close to significance, are presented. Temperature $\geqslant$38°C, total leukocyte count $\geqslant 10^4$·mm^{-3} and Fine classes IV and V

Table 2. – Univariate analysis of variables associated with residual pleural thickening

Variable	Characteristics				
	Unfavourable	Favourable	Crude OR	95% CI	p-value
Fine classes	IV, V	I, II, III	12.86	5.78–28.61	<0.01
Temperature °C	$\geqslant$38	<38	8	4.12–15.53	<0.01
Leukocytes per mm^3	$\geqslant 10^4$	$<10^4$	14.31	6.97–29.35	<0.01
Volume %	$\geqslant$50	<50	1.79	0.89–3.58	<0.01
LDH IU·L^{-1}	$\geqslant$1000	<1000	0.76	0.26–2.26	0.01
pH	$\leqslant$7.20	>7.20	0.94	0.49–1.80	0.02
Pus	Yes	No	8.64	3.03–24.66	<0.01
Pleural leukocytes per mm^3	$\geqslant 6\times10^3$	$<6\times10^3$	2.75	1.30–5.82	<0.01
Pathogen	Yes	No	0.20	0.10–0.40	<0.01
Fibrinolisis	Yes	No	2.17	1.04–4.51	0.05
Thoracoscopy	Yes	No	6.73	1.62–27.88	0.01
Thoracotomy	Yes	No			
In-hospital stay days	>7	$\leqslant$7	1.36	0.60–3.04	0.01
Resolution of pleural effusions days	>15	$\leqslant$15	26.25	11.57–59.57	<0.01
Time from symptoms to treatment days	>3	$\leqslant$3	4.28	1.49–12.27	0.28

OR: odds ratio; CI: confidence interval; LDH: lactate dehydrogenase; IU: international units.

were associated with RPT. Of the pleural fluid characteristics, presence of pus or pathogens in the pleural space, pleural fluid volume $\geq$50%, LDH $\geq$1,000 IU·L^{-1}, pH$\leq$7.20 and leukocyte count $\geq 6\times10^{3}\cdot mm^{-3}$ were statistically associated with RPT. Finally, the need for fibrinolisis or thoracoscopy, and a hospital stay >7 days or a resolution of the pleural effusion >15 days were associated with RPT. There was no association between the delay in instituting proper therapy and the development of RPT.

The final model of the multivariable logistic regression analysis is presented in table 3. The risk indicators for RPT, expressed as estimated ORs, were temperature (13.90 for temperature $\geq$38°C *versus* temperature <38°C), resolution of the pleural effusion (1.22 for resolution >15 days *versus* resolution $\leq$15 days), presence of pus in the pleural space (9.91 for presence of pus *versus* absence of pus) and Fine classes IV and V (1.08 for classes IV and V *versus* classes I, II and III).

There were no statistically significant differences between the forced vital capacity (FVC) values at discharge and at 6 months, nor in the Borg dyspnoea index (a measure of perceived breathlessness on a scale of 0–10, with higher values indicating more severe dyspnoea [11]) between patients who developed RPT and those who did not (table 4). However, the authors did demonstrate a marked reduction in the pleural thickening with regard to time (6.89±5.07 mm at discharge *versus* 4.55±4.89 mm at 6 months, p<0.01).

Discussion

The prevalence of RPT was 13.79% in the series of patients incorporated in this study with PPE 6 months after the hospital discharge. MARTINEZ *et al.* [9], in a study of 126 patients 3 months postdischarge, reported that the prevalence of RPT was 62%, however 21.5% of their patients had been lost in follow-up. There are two possible explanations for the higher prevalence of RPT reported by MARTINEZ *et al.* [9]: 1) the patients had more severe illness compared with the present study; and 2) the patients were studied, for a second time, 3 rather than 6 months (as in the present study) after discharge. WAITE *et al.* [12] evaluated the chest tomography scans in 35 patients with empyema within 2 weeks of a thoracentesis demonstrating an empyema. They reported only two from a total of 35 patients with RPT >5 mm. A possible bias in their group of patients was that measurements of RPT were taken too early in the course of the disease and the prevalence could be greater when pleural fibrosis is definitively established.

In cases of tuberculous pleurisy, the prevalence of RPT varies from one study to another. LEE *et al.* [13] reported 10%, SOLER *et al.* [14] reported 72% and DE PABLO *et al.* [7] and BARBAS *et al.* [8] reported intermediate values of 43% and 52%, respectively. These variations can be attributed to the lack of a uniform concept for RPT. In some instances a pleural thickness of >2 mm is defined as abnormal in other cases a thickness of $\geq$10 mm is required to be defined as abnormal. In the present study the authors used an upper limit of 10 mm, because functional disturbances could be found in this group of patients.

The evolution of empyema occurs through three overlapping stages (exudative, fibrinopurulent and organising phases) [15]. During these phases, the pleural fluid leukocytes and LDH levels increase with a simultaneous decline in glucose and pH levels. The time required for the progression to the organising stage has been cited as ~2–3 weeks [16]. The results from the present study, in the univariate analysis, concur with others [17–19] and suggest that patients who eventually developed intense RPT had enhanced inflammatory activity in the pleural space. In patients with RPT $\geq$10 mm, the volume of the pleural fluid, pleural leukocyte counts and LDH levels were significantly higher than in those with lower levels of RPT. However, pH levels were significantly lower in patients with RPT measured at 6 months. The authors found that pus and pathogen isolation were more frequent in the group of patients with RPT, as was the need for fibrinolysis and thoracoscopy, these findings support the inflammatory mechanism. Fine's prediction rule identifies patients who are at high risk of death, however this is the first study, to date, that has assessed its value in identifying pleural complications such as RPT. It can be speculated that the severity of illness at presentation predisposes the patient to more severe pleural disease and RPT. The results from the present study cannot confirm a relationship between the delay in initiating proper therapy and a risk for developing pleural thickening. Most patients were treated early in the course of the disease and this could explain the results found from this study.

With multivariable analysis, the present study suggests that fever, delayed resolution of the pleural effusion, presence of pus in the pleural space and higher Fine scores are independently associated with the risk of developing RPT. To the best of the authors' knowledge, this is the first study in which an association between RPT and clinical conditions (mentioned above) have been demonstrated in a study designed such that confounding risk factors could be eliminated. If this subgroup of patients may benefit from earlier therapeutic interventions or steroid treatment, this has to be addressed in a well-designed, prospective study.

The authors decided to measure FVC at discharge and at 6 months, as well as the Borg dyspnoea index, to investigate whether RPT was associated with long-term functional sequelae. The authors could not find differences in these values between patients who developed RPT and those who did not. Patients without RPT experienced significantly higher improvement in FVC between discharge and 6 months when compared with patients who developed RPT. Moreover, the authors could demonstrate a marked reduction in pleural thickening measured at discharge and at 6 months.

In conclusion, in the present study of patients with parapneumonic pleural effusion, 13.79% had residual pleural thickening $\geq$10 mm at 6 months. Patients who developed residual pleural thickening $\geq$10 mm at 6 months had higher

Table 3. – Multivariable analysis of risk factors for residual pleural thickening

Variable	Adjusted OR (95% CI)	p-value
Temperature $\geq$38°C	13.90 (4.03–47.99)	<0.001
Resolution >15 days	1.22 (1.13–1.30)	<0.001
Pus	9.91 (1.12–87.91)	0.04
Fine classes IV and V	1.08 (1.04–1.12)	<0.001

OR: odds ratio; CI: confidence interval.

Table 4. – Comparison between forced vital capacity (FVC) values and dyspnoea perception (Borg scale) at discharge and at 6 months in patients with and without residual pleural thickening (RPT)

Variable	RPT	No RPT	p-value
Borg at discharge	2.00±0.92	1.72±1.12	0.10
Borg at 6 months	1.92±1.20	1.61±1.08	0.07
Change Borg scale	0.08±0.28	0.11±0.04	0.08
FVC % at discharge	88.50±8.40	89.12±5.98	0.53
FVC % at 6 months	89.17±8.85	90.93±6.64	0.11
Change FVC %	0.67±0.45	1.81±0.66	<0.0001

peak temperatures, longer times for resolution of pleural effusion, higher likelihood of the presence of pus in the pleural space and higher Fine scores than the patients without residual pleural thickening. However, patients with residual pleural thickening did not have significantly lower pulmonary functions 6 months postdischarge than those without residual pleural thickening, suggesting that this complication has limited functional impact.

References

1. Neiderman MS, Bass JB, Campbell GD, *et al.* Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am Rev Respir Dis* 1993; 148: 1418–1426.
2. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. *Am J Med* 1980; 69: 507–511.
3. Taryle DA, Potts DE, Sahn SA. The incidence and clinical correlates of parapneumonic effusions in pneumococcal pneumonia. *Chest* 1978; 74: 170–173.
4. Heffner JE, McDonald J, Barbieri C, Klein J. Management of parapneumonic effusion. *Arch Surg* 1995; 130: 433–438.
5. Brewin A, Arango L, Hadley WK, Murray JF. High-dose penicillin therapy and pneumococcal pneumonia. *JAMA* 1974; 230: 409–413.
6. Sahn SA. Management of complicated parapneumonic effusions. *Am Rev Respir Dis* 1993; 148: 813–817.
7. De Pablo A, Villena V, Echave J, López Encuentra A. Are pleural fluid parameters related to the development of residual pleural thickening in tuberculosis? *Chest* 1997; 112: 1293–1297.
8. Barbas CS, Cukier A, Varvalho CR, Barbas JV, Light RW. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. *Chest* 1991; 100: 1264–1267.
9. Martínez MA, Cordero PJ, Cases E, *et al.* Factores predictivos del engrosamiento pleural residual en el derrame pleural metaneumónico [Prognostic features of residual pleural thickening in metapneumonic pleural effusion]. *Arch Bronconeumol* 1999; 35: 108–112.
10. Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
11. Borg GA. Psycophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
12. Waite RJ, Carbonneau RJ, Balikian JP, Umali CR, Pezzella AT, Nash G. Parietal pleural changes in empyema: appearances at CT. *Radiology* 1990; 175: 145–150.
13. Lee CH, Wang WJ, Lan RS, *et al.* Corticosteroids in the treatment of tuberculous pleurisy: a double-blind, placebo-controlled, randomized study. *Chest* 1988; 94: 1256–1259.
14. Soler JJ, Gil Suay V, Cordero P, *et al.* Corticoides en la tuberculosis pleural. Reducen el engrosamiento pleural residual? [Corticosteroids in tuberculous pleurisy. Do they diminish residual pleural thickening?] *Arch Bronconeumol* 1994; 30: Suppl. 1, 43.
15. American Thoracic Society. ATS Statement. Management of nontuberculous empyema. *Am Rev Respir Dis* 1962; 85: 935–936.
16. Landreneau RJ, Keenan RJ, Hazelrigg SR, Mack MJ, Naunheim KS. Thoracoscopy for empyema and hemothorax. *Chest* 1995; 109: 18–24.
17. Soler JJ, Gil Suay V, Cordero P, Perpiñá M, Martínez E, Sanchís J. Engrosamiento pleural en el derrame pleural tuberculoso. Factores asociados. [Pleural thickening in tuberculous pleural effusion. The associated factors.] *Arch Bronconeumol* 1995; 31: 157–161.
18. Heffner JE, Brown LE, Barbieri C, DeLeo JM. Pleural fluid chemical analysis in parapneumonic effusions. *Am J Respir Crit Care Med* 1995; 151: 1700–1708.
19. Colice GL, Curtis A, Deslauriers J, *et al.* Medical and surgical treatment of parapneumonic effusions. *Chest* 2000; 118: 1158–1171.