Pleural Mesothelioma: Experience With 62 Cases in 9 Years

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OBJECTIVES: To describe the diagnostic approach, clinical and radiological characteristics, and survival of patients with pleural mesothelioma treated in our hospital over a 9-year period.

PATIENTS AND METHOD: All patients with a diagnosis of pleural mesothelioma diagnosed in our hospital from January 1992 through December 2000 were studied.

RESULTS: Sixty-two patients (49 men) with a mean age of 65 years (range, 45-85) were diagnosed. Probable or known contact with asbestos was established for 41 patients (66%). Ninety-four percent of the patients had chest pain or dyspnea at the onset of clinical assessment. The tumor was situated in the right hemithorax in 33 patients; 59 patients had pleural effusion, and 3 only had pleural thickening. The pleural fluid was bloody in 19% of patients, glucose levels were less than 60 mg/dL in 44%, and the pH of pleural fluid was less than 7.20 in 19%. The diagnosis was established by pleural biopsy for 52%, and by thoracoscopy or thoracotomy for 44%. The median survival was 11 months (95% confidence interval, 8-15); the probability of survival was 0.22 after 2 years, and 0.09 after 5. For the subgroup of patients with epithelial tumors the probability of survival was 0.31 after 2 years and 0.16 after 5 years. In the univariate analysis the predictors of survival were general clinical status (Karnofsky scale), platelet count, serum albumin level, pleural pH, glucose and lactate dehydrogenase levels, and histological type.

CONCLUSIONS: The clinical, radiological, and biochemical characteristics of the pleural fluid from patients with pleural mesothelioma and their survival rate were described.

Key words: *Mesothelioma. Malignant pleural effusion. Pleural biopsy. Survival.*

Mesotelioma pleural: experiencia durante 9 años y descripción de 62 casos

OBJETIVO: Describir las características clínicas, radiológicas, el método diagnóstico y la evolución de los pacientes con mesotelioma pleural estudiados en nuestro hospital durante 9 años.

PACIENTES Y MÉTODO: Se ha incluido a todos los pacientes diagnosticados de mesotelioma pleural en nuestro hospital entre enero de 1992 y diciembre de 2000.

RESULTADOS: Se ha incluido a 62 pacientes (49 varones), con una edad media de 65 años (rango: 45-85). De ellos, 41 (66%) tenían antecedentes de contacto con asbesto seguro o probable. El 94% presentaba dolor torácico o disnea al comenzar el estudio; el tumor era derecho en 33 pacientes, en 59 había derrame pleural y en 3 sólo engrosamiento pleural. El líquido pleural era hemático en el 19% de los pacientes. El 44% tenía concentraciones de glucosa inferiores a 60 mg/dl, y en el 19% el pH pleural era inferior a 7,20. El diagnóstico se realizó en el 52% de los pacientes mediante biopsia pleural, y en el 44% mediante toracoscopia o toracotomía. La mediana de supervivencia fue de 11 meses (intervalo de confianza del 95%, 8-15); la probabilidad de supervivencia fue de 0,22 a los 2 años, y del 0,09 a los 5 años. Para los tumores epiteliales la probabilidad de supervivencia era de 0,31 a los 2 años y de 0,16 a los 5 años. En el análisis univariante se asociaron al pronóstico de supervivencia el estado clínico general (escala de Karnofsky), el número de plaquetas, la albúmina sérica, así como el pH, la glucosa y la lactatodeshidrogenasa pleurales y el tipo histológico.

CONCLUSIONES: Se describen las características clínicas, radiológicas, del líquido pleural y la supervivencia de los pacientes con mesotelioma pleural.

Palabras clave: *Mesotelioma. Derrame pleural maligno. Biopsia pleural. Supervivencia.*

Introduction

Reports of pleural mesothelioma cases began to increase in number in the first decades of the twentieth century. Epidemiological studies have linked pleural mesothelioma mainly to contact with asbestos, a material known to the Egyptians but that began to be used increasingly in manufacturing processes only in the late nineteenth century. The incidence of the disease is forecast to increase in Europe in the first 2 decades of the present century[1,2] although the rate of new cases may already have peaked in the United States of America.[3] Spain has no asbestos mines, such that industrial applications have relied on imports. Bearing in mind that asbestos imports to Spain peaked in the

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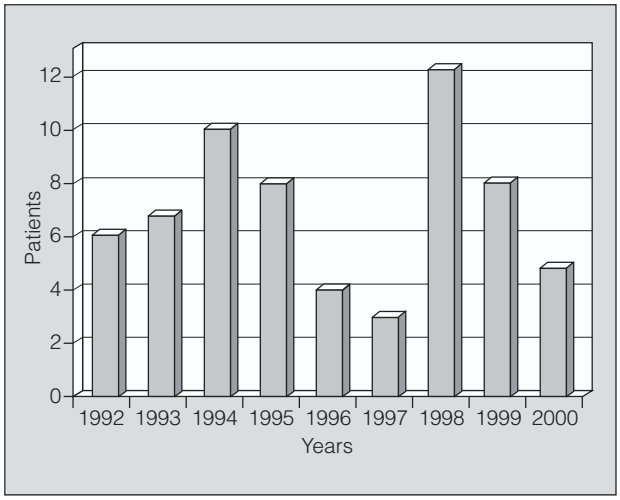

Figure 1. Distribution of patients diagnosed with pleural mesothelioma by year.

1970s[4] and that the latency period between contact with the material and the development of mesothelioma ranges from 20 to 40 years, it is likely that the incidence of pleural mesothelioma in this country will increase in the coming years. Until now, few reports of experience with series of patients diagnosed with this tumor have been published in Spanish journals.[5-10]

In the present paper we will describe the clinical and radiologic characteristics of pleural mesothelioma diagnosed in our hospital over a period of 9 years and discuss the diagnostic process and course of disease in our patients.

Patients and Methods

All patients diagnosed with pleural mesothelioma in our hospital from January 1992 through December 2000 were included in the study. The patients presenting with pleural effusion were tested according to our department's diagnostic protocol.[11] Tests were performed to determine biochemical parameters, including interferon gamma levels, and Löwenstein or bacterial cultures were ordered in some cases. During the period of time covered by the present study, tumor markers in pleural fluid began to be studied, and therefore the results of those tests were available for some patients in the series.

Asbestos exposure was classified in 4 categories:[12] group 1, ascertained, if exposure was reported by the patient; group 2, probable, if the patient's profession or other activities were associated with situations that normally led to asbestos exposure[13]; group 3, unlikely, based on information given by the patient; and group 4, uncertain, if no information about the patient's activities was available.

To reach a histologic diagnosis of mesothelioma the fragments of 10% formalin-fixed tissue were embedded in paraffin (Autotecnicon-Shandon, Cheshire, UK). Thin serial sections were cut from the paraffin block and mounted on pairs of slides to be stained with hematoxylin and eosin and in some cases other stains (e.g. Masson, periodic acid-Schiff [PAS] or PAS-diastase). A diagnosis of pleural mesothelioma was suspected if inspection under an optical microscope indicated the presence of one of the following criteria: *a)* mesothelial cells infiltrating fibrous tissue, forming nests or tubules in the pleura; *b)* evident cell atypia; and *c)* the presence of papillary mesotheliomas of the epithelial subtype.

The paraffin block remaining after optical microscopic inspection was then studied using immunohistochemical techniques with peroxidase-avidin-streptavidin complex and an automatic staining system (Tech-Mate 500, Dako, Glostrup, DK). Positive controls and negative ones (replacing the primary antibody with nonimmune serum) were established in all cases. A battery of antibodies was used to differentiate adenocarcinoma from mesothelioma:[14,15] *a)* the adenocarcinoma markers were Ber-EP4 (Dako), Moc 32 (Dako), monoclonal carcinoembryonic antigen (Dako), B72.3 (Biogenex, San Ramon, CA, USA), and Leu M1 (Becton-Dickinson, San Jose, CA, USA); and *b)* markers for mesothelioma were keratin 5/6 (Dako), mesothelioma antibody clone HBME–1 (Dako), thrombomodulin (Dako), calretinin (Novocastra, Newcastle-upon-Tyne, UK), and vimentin (Dako). Although broad-spectrum keratin (AE1/AE3, Dako) does not allow mesothelioma to be differentiated from carcinoma, it was used to check the antigenicity of the material.

Since 1999 our department has been collaborating in carrying out a randomized controlled trial of treatments for mesothelioma that include chemotherapy. Samples from the patients enrolled in this study (n=11) were sent for review by a panel of pathologists. In all cases the diagnosis was confirmed.

Statistical Analysis

The Kaplan-Meier method was used for the analysis of survival and log-rank testing was used for comparisons. Survival was calculated from the date of thoracocentesis or needle biopsy of the mass or pleural thickening. Cox stepwise regression analysis was used for the multivariate study of survival. Because of the number of patients for whom it was not possible to establish the histological diagnosis for type of mesothelioma, probably because of the small amount of the transparietal pleural biopsy material, it was decided not to include that variable in the Cox regression model.

Results

Sixty-two patients (49 men and 13 women), with a mean (SD) age of 65 (9) years (range, 45-85 years). Figure 1 shows the distribution of patients over the years of study. Twenty-five patients had group 1 contact with asbestos, 16 were in group 2, 9 in group 3, and 12 in group 4. Table 1 indicates the source of asbestos

TABLE 1
Types of Asbestos Exposure of the 41 Patients for Whom Contact Was Ascertained or Probable

Type of Contact	No. of Patients (%)
Industry	10 (24.4)
Asbestos fiber cements and tubing	8 (19.5)
Railway	7 (17.1)
Automobile	5 (12.2)
Building construction and maintenance	5 (12.2)
Stevedores	3 (7.3)
Fire fighters	1 (2.4)
Unspecified contact	2 (4.9)

contact for the 41 patients in groups 1 and 2. None of the 62 patients had ever received chest radiotherapy.

Table 2 lists the presenting symptoms for all patients. Chest pain and/or shortness of breath were experienced by 94%. Only 1 patient was asymptomatic, such that investigation began with a fortuitous finding in a chest radiograph. The first symptom was pain for 19 patients, shortness of breath for 19, and both for 5. Two patients had experienced pneumothorax before tests began. One had occurred a year earlier; the other was the reason for initiating tests. One patient had been treated by our department 5 years earlier for pleural effusion and analysis of 2 biopsies had been nondiagnostic; the effusion and the symptoms disappeared and recurred on the same side in the presenting episode. One patient had suffered deep vein thrombosis 3 weeks before diagnosis. Acropachy was not detected in any patient. Eleven of the 62 patients had platelet counts exceeding 400 000 cells/μL. The Karnofsky index at the time of diagnosis was equal to or greater than 80 in 38 patients (61%).

Pleural involvement was on the right side at the time of study in 33 patients and on the left side in 29. Fifty-nine presented with pleural effusion and 3 patients only had pleural thickening. The pleural effusion was large in 32 patients (massive in 9 of them), medium in 24, and small in 3. Observations made in the first chest radiographs and computed tomography (CT) scans are shown in Table 3. Because the pleural effusions were drained from some patients before the scans were performed, the CT findings were not always consistent with those of the simple radiographs. CT scans from near the time of diagnosis were not available for the 10 patients who are not included in Table 3.

In the 59 patients who had pleural effusion, the fluid was serous in 21 (34%), serosanguineous in 18 (29%), bloody in 12 (19%), and cloudy in 3 (5%). Information about the appearance of the effusion was unavailable for 5 patients. The effusion was drained from all patients following the criteria of Light.[16] Two patients had a ratio of pleural fluid to serum protein levels less than 0.5 and a ratio of pleural fluid to serum lactate dehydrogenase levels greater than 0.6. The pleural fluid glucose concentration was available for 57 patients: in 25 it was less than 60 mg/dL. The pleural fluid pH was known for 53 patients: in 10 the pH was less than 7.20. In 27 patients one of those 2 parameters was less than the reference limit. The interferon gamma concentration in pleural fluid was less than the cut points used in our hospital (3.5 pg/mL) in the 48 patients for whom that parameter was known. Carcinoembryonic antigen and carbohydrate antigen 72.4 (CA-72.4) concentrations were under the established cut points (20 ng/mL and 16 IU/mL, respectively) in all patients in whom those determinations were made: 35 patients for the carcinoembryonic antigen and 33 for CA-72.4. However, the CA-15.3 concentration was greater than 45 IU/mL in 19 out of 33 patients (58%), and CA-549 was greater than 24 IU/mL in 11 out of 18 patients (61%).

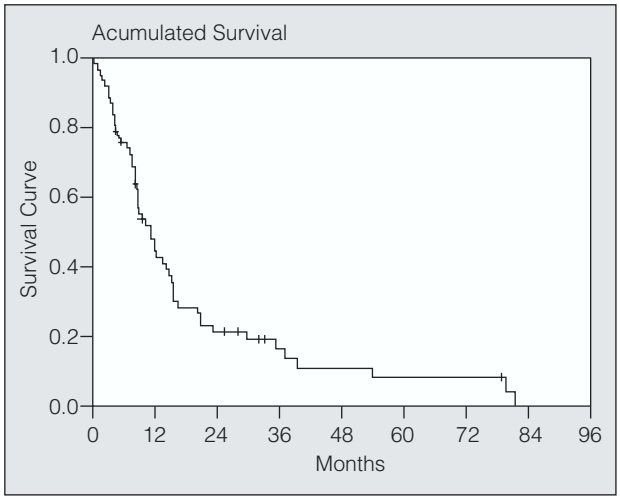

Figure 2. Survival curve for the 62 patients with pleural mesothelioma.

Table 4 lists the diagnostic methods employed. Transparietal pleural biopsy was the test that gave the diagnosis for 52% of the patients. More than 6 months passed between initial testing and diagnosis for 5

TABLE 2
Symptoms at the Time of Diagnostic Testing

Symptoms	No. of Patients (%)
Shortness of breath	49 (79)
Chest pain	40 (64.5)
Weakness	16 (25.8)
Nonproductive cough	14 (22.6)
Low-grade fever	14 (22.6)
Anorexia	12 (19.4)
Productive cough	11 (17.7)
Weight loss*	6 (9.7)
Abdominal discomfort	3 (4.8)
Night sweats	2 (3.2)
Hemoptysis	2 (3.2)
Asymptomatic	1 (1.6)

*Weight loss was recorded as a finding if greater than 5 kg.

TABLE 3
Findings at Presentation on a Simple Chest Radiograph and on the First Computed Tomography Scan

Radiological Findings	Simple Chest Radiograph
Pleural effusion	59 (95.2%)
Loss of volume	24 (38.7%)
Ipsilateral mediastinal shift	7 (11.3%)
Contralateral mediastinal shift	7 (11.3%)
Pleural thickening	3 (4.8%)
Pleural calcifications	2 (3.2%)
Radiological Findings	**Computed Tomography Scan of the Chest**
Pleural effusion	37 (59.7%)
Pleural thickening	36 (58.1%)
Diseased mediastinal lymph nodes	6 (9.7%)
Pleural calcifications	1 (1.6%)

TABLE 4
Test That Established the Diagnosis in the 62 Patients in the Series. Diagnostic Yield for the Biopsy Techniques Used

Diagnostic Test	Patients
Transparietal pleural biopsy	32 (51.6%)
Thoracoscopy	16 (25.8%)
Thoracotomy	11 (17.7%)
Fine-needle biopsy	3 (4.8%)
Diagnostic Test	**Diagnostic/Performed**
First pleural biopsy	23/52 (44.2%)
Second pleural biopsy	9/22 (40.9%)
Thoracoscopy	16/23 (69.6%)
Thoracotomy	11/12 (91.7%)

patients, in spite of performance of nondiagnostic thoracoscopy and thoracotomy in 1 case. The diagnosis was established in that patient by needle aspiration of a mass that had invaded the chest wall.

The histological diagnosis was epithelial mesothelioma in 32 cases, sarcomatoid mesothelioma in 9 cases, and mixed in 4 cases. The histological type could not be established in 17 cases.

Only symptomatic treatment was given to 32 patients. Pleurodesis was applied in 23 patients, with or without other treatments. An extrapleural pneumonectomy was performed in 1 patient, and 13 were enrolled in a trial of chemotherapy, which is still underway.

Fifty-three patients died during the period of follow up, 4 were living at the time of statistical analysis, and 6 were lost to follow up. Figure 2 shows the likelihood of survival in relation to time. The median survival was 11 months (95% confidence interval, 8-15). The likelihood of survival at 2 years was 0.22 and at 5 years it was 0.09. For epithelial mesotheliomas, the likelihood of survival at 2 years was 0.31 and at 5 years it was 0.16. Table 5 shows the results of the univariate analysis of survival. No relation was found between survival and age, duration of symptoms before diagnostic testing, presentation with or without pain, weight loss, presence of low-grade fever, or asbestos exposure.

Table 6 shows the combination of patient and disease parameters selected by Cox's proportional risk regression method. The variables selected for the model were general clinical status (Karnofsky index), platelet count less than or equal to 500 000/µL, and a pleural fluid lactate dehydrogenase level equal to or greater than 300 IU/L.

TABLE 5
Univariate Analysis of Survival*

Variable	No.	Median Survival (95% CI)	*P*
Sex			
Male	49	287 (197-377)	
Female	13	470 (280-660)	.1649
Karnofsky index			
<80	24	224 (81-367)	
≥80	38	457 (333-581)	.0002
Platelets, cells/µL			
<500 000	57	355 (222-488)	
≥500 000	5	95 (43-147)	.0004
Serum albumin, g/dL			
<4.5	43	262 (177-347)	
≥4.5	6	1186 (592-1780)	.0064
Pleural fluid pH			
<7.30	33	261 (232-290)	
≥7.30	20	403 (187-619)	.0218
Pleural glucose, mg/dL			
<65	28	253 (234-272)	
≥65	29	467 (297-637)	.0096
Pleural LDH, IU/L			
<300	29	443 (236-650)	
≥300	28	256 (229-283)	.0018
Histological type			
Epithelial	32	443 (267-619)	.7834†
Mixed	4	287 (0-700)	.0150‡
Sarcomatoid	9	244 (60-428)	.2821§

*Survival is expressed in days. CI indicates confidence interval; LDH, lactate dehydrogenase. †Epithelial versus mixed. ‡Epithelial versus sarcomatoid. §Mixed versus sarcomatoid.

Discussion

Pleural mesothelioma is a rare tumor that is difficult to diagnose and is susceptible to few treatment options at present. During the years encompassed by the study we found no clear trend to increasing incidence, but if we compare our findings with those reported for our hospital for the years 1974 and 1985,[5] the increase is evident. Although the rise may be an artifact of enrolling patients in a clinical trial in the last months, we know of nothing that accounts for changes in incidence in other periods of our study.

Most of our patients (41, or 66%) were classified in groups 1 or 2 for asbestos contact. The higher prevalence of exposure in our series than in others in Spain[6-10] may be owing to the fact that most patients were enrolled prospectively from among those being studied for pleural effusion, even though data was reviewed retrospectively. It is likely that the number of exposures detected was higher because clinical interviews with these patients were more thorough (including spousal interviews, and relating to environmental as well as occupational exposure, etc).

The clinical manifestations we recorded coincide with those reported by other authors Most patients had

TABLE 6
Cox Regression*

Variable	Hazard Ratio (95% CI)	*P*
General clinical status (Karnofsky index)	0.966 (0.947-0.985)	.0005
Platelets†	4.415 (1.599-12.192)	.0042
LDH‡	2.078 (1.083-3.987)	.0279

*CI indicates confidence interval; LDH, lactate dehydrogenase. †Platelet count less than 500 000 cells/µL. ‡Lactate dehydrogenase in pleural fluid less than 300 IU/L.

pleural effusion with or without pleural thickening at the time of diagnosis.

The pH and/or the glucose level in pleural fluid was low in 44% of patients in whom those biochemical parameters were analyzed, indicating a considerably higher likelihood of neoplasm in the absence of infection.[16] CA-15.3 positivity in some mesotheliomas has been described previously by our group[17] and by Miédougé et al.[18]

Pathology of a biopsy specimen is needed for reaching a diagnosis and immunohistochemical techniques must often be used additionally.[14,15,19] The yield of blind pleural biopsy is usually low. However, in our series, 51.6% of the patients were diagnosed from such a biopsy, giving a sensitivity slightly over 40%. We believe that this high diagnostic yield is partly due to the availability of an experienced pathologist to examine the pleural specimens, plus the aid of immunohistochemical techniques.[14,15] The sensitivities of thoracoscopy and thoracotomy in our study were similar to those reported by other authors.[20,21]

A possible limitation of our study is that the length of the study period meant there were changes in the technical specifications and quality of radiography, and considering that thoracoscopy and thoracotomy were not performed in many patients, we have not evaluated tumor stage, given that we did not have the means available to do so.

The treatment of pleural mesothelioma has become controversial in recent years.[22] To the traditional results obtained by chemotherapy,[23] radiotherapy and surgery, Sugarbaker et al[24] have recently added reports of longer survival with the use of extrapleural pneumonectomy, radiotherapy, and chemotherapy in highly selected, nonrandomized groups of patients. To define expected medium-term outcomes in such patients, it would probably be necessary to know if the results reported by Sugarbacker et al can be replicated in other groups of surgical patients and also to determine the usefulness of intrapleural chemotherapy, immunotherapy, or gene therapy.

Survival in our patients was similar to the rates reported for other series.[25] In studies that analyze prognostic factors, a great variety of factors have been identified. The factors that have most often been associated with a better prognosis are epithelial type,[26-33] better clinical status,[26,28,31-37] better stage,[12,27,29,30,33-35,38,] younger age,[12,26,29-31,33,36,38,39,] longer duration of symptoms prior to diagnosis,[32,34,35,39] or the absence of chest pain.[26,31,33,34] Other authors have found that the factors of good prognosis are female sex,[28,32,38] absence of weight loss,[27] normal platelet counts,[26,37] absence of elevated lactate dehydrogenase serum levels,[26] absence of leukocytosis,[28] exposure to asbestos,[12] low pleural fluid pH,[40] or absence of elevated serum concentrations of cytokeratin fragment 21.1.[37]

The prognostic factors from the univariate analysis in our study were general clinical status, histological type, serum platelet or albumin levels, pH, and glucose or lactate dehydrogenase levels in pleural fluid. We selected the Cox regression for the multivariate analysis, including general clinical status and serum platelet counts. The likelihood of 5-year survival was 0.09 for the patient series as a whole and 0.16 for patients with epithelial mesothelioma. These findings should be taken into consideration in assessing the therapeutic benefit reported from nonrandomized studies.

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