Persistent Pleural Effusions in Primary Systemic Amyloidosis*

Etiology and Prognosis

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Background: **Restrictive cardiomyopathy frequently complicates primary systemic amyloidosis (AL), yet only a small number of these patients develop large pleural effusions refractory to diuretic therapy and thoracentesis. We hypothesized that disruption of pleural function by amyloid deposits underlies persistent pleural effusions (PPEs) in patients with AL disease.**
Methods: **We performed a retrospective study of AL patients with and without PPEs who had been referred to Boston University between 1994 and 2001. The presence of PPEs was defined by a failure to resolve the condition with thoracentesis and aggressive diuresis. AL cardiomyopathy patients without pleural effusions constituted the control (cardiac) group. Indexes of plasma cell dyscrasia, nephrotic syndrome, thyroid function, and echocardiographic measures of left and right ventricle performance were compared between groups. When available, closed needle biopsies and autopsy specimens of parietal pleura were examined for amyloid deposits.**
Results: **Among 636 patients with AL, 35 PPE patients underwent a median of three thoracenteses each. No statistical differences were found between the PPE and cardiac groups in echocardiographic measures of septal thickness, left ventricular systolic function, or diastolic compliance. Right ventricular (RV) hypokinesis occurred more often in PPE patients; however, nearly half of this group had normal RV systolic function. Renal function, plasma protein levels, and thyroid function were the same between groups. Nephrotic range proteinuria (*ie*, > 3 g/d) was more prevalent in the cardiac group than in the PPE group (44% vs 26%, respectively; p = 0.057). All pleural biopsies in the PPE group (six biopsies) revealed amyloid deposits. Autopsy samples of parietal pleura were negative for disease in two cardiac patients. Eighteen patients had chest tubes placed, and 11 underwent pleurodesis. PPE signaled limited survival among patients who were ineligible for treatment. Untreated PPE patients lived a median 1.8 months vs 6 months for untreated cardiac patients (p = 0.031). Survival after intensive chemotherapy and autologous stem cell transplantation was comparable in the PPE and cardiac groups (21.8 vs 15.6 months, respectively; p = 0.405).**
Conclusion: **In AL patients with cardiac amyloid, neither echocardiographic measures of ventricular function nor the degree of nephrosis distinguished those patients with PPEs. We conclude that pleural amyloid infiltration plays a central role in the creation and persistence of pleural effusions among patients with AL.** ***(CHEST 2003; 124:969–977)***

Key words: amyloid; amyloidosis; cardiomyopathy; congestive heart failure; nephrotic syndrome; pleural effusion

Abbreviations: A = late; AL = primary systemic amyloidosis; DLCO = diffusing capacity of the lung for carbon monoxide; DT = deceleration time; E = early; HDM = high-dose melphalan; IVC = inferior vena cava; IVRT = isovolumetric relaxation time; IVS = interventricular septal; LDH = lactate dehydrogenase; LV = left ventricle, ventricular; LVEF = left ventricular ejection fraction; PAS = pulmonary artery systolic; PCWP = pulmonary capillary wedge pressure; PPE = primary pulmonary effusion; RV = right ventricle, ventricular; SCT = stem cell transplantation; TP = total protein; TMF = transmitral flow; TSH = thyroid-stimulating hormone

Amyloidosis is a family of diseases caused by the overexpression of proteins that deposit in tissues as insoluble β-pleated fibrils, disrupting organ function. In patients with primary systemic amyloidosis (AL), clonal plasma cells secrete monoclonal Ig light chains that deposit in the kidney, heart, nerves, and other tissues.[1] Parenchymal lung involvement occurs in approximately 28% of AL patients and does not affect survival.[2,3]

Pleural effusions have not been well-studied in AL patients. The literature includes 18 cases of systemic amyloidosis and pleural effusions; however, less than half of these cases documented underlying plasma cell dyscrasia.[4–13] Characteristically, these effusions

persist despite aggressive diuresis and direct drainage of the pleural space. Amyloid-induced cardiomyopathy often accompanies pleural effusions in the AL population, suggesting that effusions may be primarily a consequence of ventricular dysfunction. Low oncotic pressure resulting from AL-related nephrotic syndrome represents another mechanism for effusion formation. The inability of diuretic therapy to resolve AL effusions and the frequency of reported exudative pleural fluid chemistries, however, imply that altered hydrostatic forces may not be the principal mechanism driving pleural fluid accumulation.

To define the contributions of cardiac dysfunction and nephrotic-range proteinuria to AL pleural effusions, we compared clinical and laboratory parameters in AL patients with persistent pleural effusions (PPEs) to AL cardiomyopathy patients without pleural effusions.

Materials and Methods

Patients

We reviewed the records of patients referred to the Amyloid Research and Treatment Program at Boston University Medical Center between 1994 and 2001 for the treatment of AL. A diagnosis of AL required demonstration of amyloid deposits by Congo red staining and detection of monoclonal Ig protein in serum, urine, bone marrow, or tissue biopsy specimen. PPEs were defined as large pleural effusions seen on a chest radiograph (occupying one third or more of the hemithorax) that persisted despite aggressive diuresis (*ie*, prerenal azotemia and/or postural hypotension) and one or more large-volume thoracenteses (*ie*, $\geq$ 750 mL). The control group was composed of AL patients with cardiac involvement in the absence of pleural effusions. Cardiac amyloid infiltration was defined by transthoracic echocardiographic interventricular septal thickening (*ie*, $\geq$ 12 mm) that was not explained by systemic hypertension or aortic valve stenosis. All patients underwent ECGs, echocardiograms, pulmonary function testing, serum and urine chemistry testing, 24-h urinary protein determination, measurement of thyroid-stimulating hormone (TSH) levels, serum and urine immunofixation electrophoreses, bone marrow biopsies, and fat pad aspiration. Patients with senile, secondary, or familial amyloidosis were excluded from the study, as were patients with regional wall motion abnormalities consistent with coronary artery disease on two-dimensional echocardiography. Available pleural and endomyocardial biopsy specimens were stained with Congo red dye and were viewed by polarized light microscopy to detect amyloid deposits. The Institutional Review Board at Boston University Medical Center approved the review of medical records for patients with AL.

Pleural Fluid Analysis

Total protein (TP) and lactate dehydrogenase (LDH) levels from serum and pleural fluid were measured. *Transudative character* was defined as a TP pleural fluid/serum ratio < 0.5, and an LDH pleural fluid/serum ratio < 0.6, with pleural fluid LDH levels less than two thirds of the upper limit of normal for serum LDH. TP or LDH ratios exceeding one or more of these parameters were designated as *exudative pleural effusions*. Cell numbers, WBC differential counts, and pleural fluid cytology were reported when available.

Echocardiographic Examinations

Two-dimensional and Doppler echocardiograms were obtained as previously described[14] using standard equipment (Sonos 5500; Hewlett-Packard; Andover, MA). Mean interventricular septal (IVS) thickness (averaging IVS and left ventricular [LV] posterior wall thickness) and LV fractional shortening were calculated from chordae-level M-mode images. Apical four-chamber views were used to record transmitral flow (TMF)-velocity patterns. LV outflow tract velocity and pulmonary venous flow were documented on VHS tape at 100 mm/s.[14]

Transmitral, LV outflow tract, and pulmonary venous velocity patterns were established offline by computerized planimetry (Color Cineview Plus; TomTec Imaging Systems; Unterschleissheim, Germany). The mean data were derived from three or more consecutive beats. TMF velocities defined early (E) and late (A) filling waves, and E-wave deceleration time (DT). Systolic pressure, diastolic pressure, and diastolic/systolic pressure ratios were derived from pulmonary venous velocity flow measurements. *Isovolumetric relaxation time* (IVRT) was defined as the interval between the end of LV outflow tract flow and initial TMF.

Pulmonary Function Testing

Forced spirometry (*ie*, FVC and FEV_1) and the diffusing capacity of the lung for carbon monoxide (DLCO) using the single-breath method were measured (SensorMedics; Yorba Linda, CA) according to American Thoracic Society recommendations.[15] Static lung volumes were determined using a constant-volume, whole-body plethysmograph, as described by Dubois and coworkers.[16]

Treatments and Survival

Treatment options included the following: (1) high-dose melphalan (HDM) (100 to 200 mg/m^2 IV) with autologous stem cell transplantation (SCT) support; (2) conventional chemotherapy consisting of "continuous" oral melphalan[17] or oral cyclic prednisone and melphalan, cyclophosphamide (one myeloma patient), or fludarabine (one patient with Waldenström macroglobulinemia); and (3) no chemotherapy. Survival was calculated from the initial visit to the Amyloid Clinic.

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Statistical Analysis

Demographic, laboratory, and echocardiographic data were compared among subgroups of patients by *t* test for continuously measured variables and by χ^2 test for dichotomous variables. All analyses were calculated (SAS for Windows; SAS Institute, Inc; Cary NC) using a two-tailed significance value of 0.05. The generalized Wilcoxon test for equality of survival was used to compare survival among subsets of the PPE and cardiac groups.[18]

Results

Between 1994 and 2001, 636 patients with AL were referred to the Amyloid Treatment and Research Program at Boston University Medical Center for evaluation. Thirty-five patients (6%) had large pleural effusions on screening chest radiographs that failed to resolve with direct drainage and aggressive diuresis. Five patients with PPEs had multiple myeloma, and one patient had Waldenström macroglobulinemia. One hundred twenty patients with cardiac amyloid infiltration in the absence of pleural effusions (cardiac group) constituted the control group.

Demographics and hematologic profiles of the PPE group and cardiac group (no PPE) were statistically similar (Table 1). Plasma cell burden based on bone marrow biopsy and quantitative Ig levels differed between groups, reflecting the six patients with lymphoproliferative disorders in the PPE group. Monoclonal λ-light chain expression predominated in both groups and was not preferentially associated with PPEs. Both groups had similar spectra of extrathoracic organ involvement, although the cardiac group had more frequent renal disease (81% vs 61%, respectively; p = 0.01). The median Southwest Oncology Group performance status score of the PPE group was lower than that of the cardiac group (2.0 vs 1.0, respectively; p = 0.079).

Pleural Fluid Character

Pleural effusions were categorized as transudates or exudates according to the criteria of Light et al.[19] Complete pleural fluid and serum chemistries measurements (*ie*, TP and LDH), cell counts, Gram stain data, and culture data were available in 25 cases (Table 2). Exudative pleural effusion chemistries occurred in a significant proportion of cases (37%). The diagnosis of exudative effusions was predicated on high TP levels in 55% of cases, and 45% had elevated LDH levels. WBC counts (median, 306 cells/μL) were equally distributed among lymphocytes, monocytes, and histiocytes. Neutrophil counts of > 20% occurred infrequently (*ie*, 17% of cases). Mesothelial cell counts ranged from 0 to 28%. Clonal plasma cells were not detected. No positive bacterial, mycobacterial, or fungal cultures were found.

Echocardiographic Profiles

Every study patient underwent transthoracic echocardiography. The median IVS thickness was 14.5 mm in the PPE group and 14.0 mm in the

Table 1—*Clinical Characteristics

Characteristics	Pleural Effusions (n = 35)	No Pleural Effusions (n = 120)	p Value
Age, yr	59 (47–75)	60 (39–82)	0.729
Gender			
Men	57%	67%	0.300
Woman	43%	33%	
Bone marrow plasma cell population, %	10 (5–40)	10 (5–20)	0.010
Monoclonal light-chain isotype			
κ	17%	19%	
λ	83%	81%	0.787
Sedimentation rate, mm/min	41 (2–133)	42 (3–145)	0.419
Quantitative Ig levels, mg/dL			
IgG	857 (47–3290)	960 (166–3290)	0.017
IgA	107 (5–2300)	133 (7–353)	0.091
IgM	67 (9–1356)	69 (1356)	0.408
Organ involvement			
Renal	60%	82%	0.008
Gastric	71%	81%	0.188
Neurologic	31%	38%	0.933
Soft tissue	6%	3%	0.344
SWOG performance status	2.0 (0–3)	1.0 (0–3)	0.079
Thoracenteses	3 (1–8)	0	

*Values given as median (range), unless otherwise indicated. SWOG = Southwest Oncology Group.

Table 2—*Pleural Fluid Characteristics

Characteristics	Values
Chemistries	
Pleural/serum TP ratio	0.30 (0.12–0.81)
Pleural/serum LDH ratio	0.38 (0.16–0.98)
Pleural LDH, U/L	106 (31–212)
Transudative effusions	16/25 (64)
Exudative effusions	10/27 (37)
Cell counts	
RBCs/μL	1,084 (7–190,625)
Total WBC/μL	306 (20–6,188)
Neutrophil, %	10 (0–90)
Lymphocytes, %	37 (0–98)
Monocytes, %	31 (0–92)
Histiocytes, %	30 (0–93)
Mesothelial cells, %	14 (0–28)

*Values given as median (range) or No. (%).

cardiac group (p = 0.472) [Table 3]. In no case was myocardial thickening accompanied by systemic hypertension or significant aortic value stenosis. All patients undergoing endomyocardial biopsies (9 PPE patients and 29 cardiac patients) had amyloid cardiac deposits confirmed.

Echocardiographic estimates of median LV systolic function (ie, LV ejection fraction [LVEF]) in the PPE and cardiac groups (50% vs 55%, respectively) were statistically similar (p = 0.283) [Table 3]. Right ventricular (RV) abnormalities were reported in 81% of patients in the PPE group and 79% of patients in the cardiac group. Median pulmonary artery systolic (PAS) pressures trended higher (*ie*, 40 vs 35 mm Hg, respectively; p = 0.081) and RV hypokinesis occurred more frequently among PPE patients (51% vs 31%, respectively; p = 0.033). Closer analysis failed to support pulmonary hypertension as a significant contributor to pleural fluid formation. Specifically, the frequency of elevated PAS pressures (*ie*, > 30 mm Hg) in the PPE and cardiac groups was statistically indistinguishable (54% vs 45%, respectively; p = 0.333), with normal pressures occurring in nearly half of each group. Other markers of elevated right heart pressures such as right atrial dilatation and inferior vena cava (IVC) distension were also equally distributed between groups (p = 0.312).

To examine the association of amyloid infiltrative cardiomyopathy with transudative pleural fluid formation, we compared echocardiographic data in PPE patients with transudative and exudative fluid profiles. The transudative subgroup had greater median (± SD) IVS thickening and lower LVEF values than did the exudative subgroup (IVS, 15.0 ± 4.0 vs 14.0 ± 3.5 mm, respectively; LVEF, 48.5 ± 13.1% vs 50.0 ± 6.0%, respectively). The differences in IVS and LVEF among these subgroups of PPE patients did not achieve statistical significance, however (IVS, p = 0.645; LVEF, p = 0.346).

Diastolic dysfunction, a characteristic of AL cardiac disease, can raise filling pressures and induce pulmonary edema or pleural effusions. To examine LV compliance, Doppler echocardiographic studies were performed on a subset of patients in the PPE and cardiac groups. All examined parameters including E and A TMFs, transmitral DT, IVRT, and pulmonary venous flow documented diastolic dysfunction in both groups (Table 4). We compared published Doppler profiles from healthy subjects (peak diastolic velocity E/A ratio, 1.3; DT, 195 ms; IVRT, 84 ms[20]) to profiles from the two study groups. In PPE and cardiac patients, TMF E/A ratios increased 56% and 29%, respectively, DTs decreased 29% and 21%, respectively, and IVRTs declined 23% and 12%, respectively. The accentuated E diastolic ventricular filling and diminished ventricular relaxation exhibited by these studies typ-

Table 3—*Cardiac Characteristics

Characteristics	Pleural Effusions	No Pleural Effusions	p Value
IVS, mm	14.5 (9–22)	14.0 (12–28)	0.472
LVEF, %	50 (25–65)	55 (10–70)	0.269
RV, %			
Normal	18	21	0.737
Thickened	64	68	0.610
Dilated	18	15	0.656
Hypokinesis	55	31	0.011
IVC or RA dilatation	55	45	0.331
PAS, mm Hg	40 (26–58)	35 (22–56)	0.093
PAS, > 30 mm Hg	54%	45%	0.333
RA	12 (9–16)		
PAP†	31 (22–42)		
PCWP	20 (7–29)		
CO	4.00 (1.88–6.30)		
CI	2.10 (1.35–3.80)		

*Values given as median (range), unless otherwise indicated. CO = cardiac output; CI = cardiac index; RA = right atrium; PAP = pulmonary artery pressure.
†Value given as mean (range).

Table 4—*Echocardiographic Analysis

Variables	Pleural Effusions (n = 14)	No Pleural Effusions (n = 23)	p Value
FS	0.31 ± 0.10	0.33 ± 0.10	0.412
TMF E/A	2.06 ± 1.45	1.68 ± 1.02	0.368
TMF E-wave DT	0.139 ± 0.032	0.155 ± 0.050	0.305
IVRT	0.065 ± 0.027	0.074 ± 0.026	0.292
PVF D/S	1.92 ± 1.73	1.78 ± 1.24	0.775

*Values given as mean ± SD, unless otherwise indicated. FS = fractional shortening; E/A = E/A filling; IVRT = isovolumetric relaxation time; PVF D/S = pulmonary venous flow diastolic/systolic ratio.

ify the compliance changes induced by amyloid infiltration.[20–22] There were no statistical differences in ventricular filling parameters between the PPE and cardiac groups.

Right heart catheterization was performed on 17 patients in the PPE group. Mean values for central venous pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure (PCWP) were all elevated above normal values (Table 3), and cardiac index was decreased. The pulmonary diastolic-PCWP differential measured < 10 mm Hg in 94% of cases, implicating LV dysfunction as the cause for mild pulmonary hypertension in these patients.[23] Notably, 42% of these PPE patients had PCWP values of < 17 cm H_2O, left heart filling pressures that infrequently are associated with pleural fluid formation.

Renal Function

There were no statistical differences in creatinine or BUN levels between AL patients with or without pleural effusions (Table 5). Serum levels of albumin and TP, which are components of oncotic pressure, were also similar between groups. Notably, the median urinary protein excretion was more than five times greater in the cardiac group than in the PPE group (2.0 vs 0.4 g/d, respectively; p = 0.077). In the cardiac group, a substantial number of patients had massive proteinuria (eight patients with proteinuria of > 10 g/d) and/or severe hypoalbuminemia (14 patients with serum albumin levels of < 2 g/dL) but no pleural effusions. Nephrotic range proteinuria (*ie*, > 3.0 g/d) occurred in 44% of the cardiac group vs 26% of the PPE group (p = 0.057). Nephrosis, alone or in combination with restrictive cardiomyopathy, rarely induced pleural effusions in patients with AL.

Thyroid Function

Hypothyroidism is a rare cause of pleural effusions.[24,25] To determine the role of thyroid function in PPEs, we compared TSH levels in the PPE and control groups. Median TSH levels were normal and statistically indistinguishable (p = 0.308) for the PPE group (4.65 μU/mL) and the control group (3.11 μU/mL). Twenty percent of PPE patients and 15% of control subjects were chemically hypothyroid (*ie*, TSH, > 5.50 μU/mL), with similarly high TSH levels (24.71 vs 22.81 μU/mL, respectively). Renal function, urinary protein levels, serum albumin levels, and echocardiographic features were statistically similar among PPE patients with normal vs high TSH values.

Table 5—*Renal Characteristics

Characteristics	Pleural Effusions	No Pleural Effusions	p Value
Creatinine, mg/dL	0.9 (0.1–5.4)	1.1 (0.5–13.7)	0.140
BUN, mg/dL	22.0 (10–180)	25.0 (4–101)	0.928
24-h urine protein, g	0.4 (0–20.74)	2.0 (0.054–23.6)	0.077
Albumin, g/dL	3.5 (1.9–4.7)	3.3 (1.0–5.1)	0.370
Total serum protein, g/dL	6.5 (4.1–10.2)	6.2 (4.1–9.3)	0.370

*Values given as median (range), unless otherwise indicated.

Pulmonary Function Testing and Pathology

Diffuse interstitial lung or pulmonary vascular amyloid infiltration frequently occurs in systemic AL disease, impairing gas diffusion capacity.[3,26] To define the association of abnormal gas transfer with pleural effusions in AL disease, lung diffusion capacity was measured employing carbon monoxide (*ie*, DLCO) and was normalized for alveolar volume. DLCO normalized for alveolar volume in the PPE group (median, 94%; range, 56 to 152%) and the cardiac group (median, 87%; range, 38 to 128%) were normal and statistically similar (p = 0.333).

Six PPE patients underwent biopsies of parietal pleura when malignancy or infection was suspected clinically. All biopsy specimens had amyloid deposits identified (Fig 1). Two cardiac patients without pleural effusions had parietal biopsies performed at autopsy that did not reveal amyloid deposits.

Management of AL Pleural Effusions

PPE patients underwent a median of three large volume thoracenteses each (range, one to eight thoracenteses) [Table 6]. Ten pneumothoraces were found in 121 thoracenteses (8%), a lower complication rate than those reported for general medical patients in academic medical centers (*ie*, 11 to 12%).[27,28] PPE patients required chest tube placement in 8 of 10 cases following iatrogenic pneumothorax, far exceeding the rates of chest tube drainage in nonamyloid populations (*ie*, 20%).[27,28]

Chest tubes were used to manage PPEs in 18 patients. In each case, daily fluid loss exceeded 500 mL for 5 to 12 days despite aggressive diuresis and fluid restriction. Pleurodesis was performed in 11 cases; seven chest tubes were removed without introducing irritant chemicals due to persistent high-volume drainage. Talc insufflation (one case) and pleural abrasion (one case) successfully obliterated the pleural space, although the risks of general anesthesia in AL cardiac disease limited the use of thoracoscopy in this series. The success of talc slurry pleurodesis via chest tube depended on the rapidity of pleural fluid accumulation at the time of drug administration. In patients with > 200 mL daily drainage, talc slurry failed to prevent fluid reaccumulation after chest tube removal. In con-

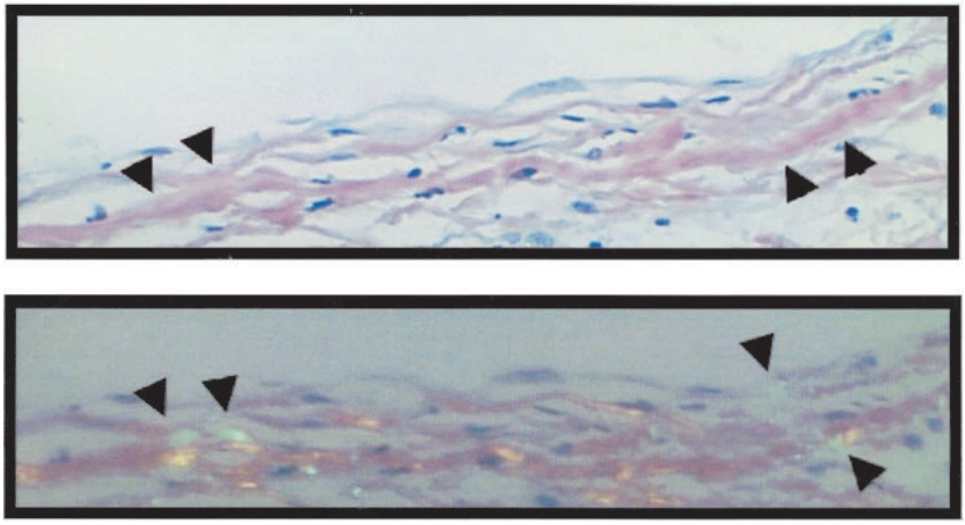

FIGURE 1. Pleural amyloid deposits in a patient with PPEs. *Top*: pleural biopsy stained with hematoxylin-eosin (original ×480). *Bottom*: amyloid birefringence under polarized light after Congo red staining (original ×480).

trast, talc slurry induced adequate symphysis of pleural surfaces to prevent fluid recurrence if introduced when chest tube drainage was < 100 mL/d. One patient had bilateral Sialastic chest tubes placed (Pleurex tubes; The Denver Company; Denver CO), allowing twice-weekly home drainage.

Survival Characteristics

Patients received supportive care if they were deemed ineligible for high-dose or oral chemotherapy due to advanced disease and poor performance status. Six untreated PPE patients had a median survival time of < 2 months, while 29 untreated cardiac patients survived for a median time of 6 months (p = 0.031) [Table 7 and Fig 2, *top*]. Patients receiving conventional oral chemotherapeutic regimens had a median survival time of nearly 9 months in both groups, while those receiving HDM and autologous SCT had similarly prolonged median survival times of 21.8 months in the PPE group and 15.6 months in the cardiac group (p = 0.405) [Fig 2, *bottom*].

Table 6—*Management of Pleural Effusions**

Variables	Values
Thoracenteses	3.0 (1–8)
Pneumothoraces	10
Chest tubes	18
Pleurodesis	11
Talc slurry/insufflation	8
Doxycycline	2
Pleural abrasion	1
Long-term chest tube drainage	1

*Values given as median (range) or No.

DISCUSSION

Our retrospective analysis identified two statistically significant differences between AL patients with PPE and those with AL cardiac disease and no pleural effusions (*ie*, the cardiac group), as follows: (1) more frequent RV hypokinesis in the PPE group; and (2) greater proteinuria in patients without effusions. Multiple echocardiographic measures of LV function failed to distinguish PPE patients from those with AL cardiomyopathy alone. Taken together, the frequency of exudative pleural fluid chemistries (37%), the refractoriness to aggressive diuresis, and the inconsistent role of LV dysfunction supported a noncardiogenic mechanism of disease.

The importance of LV vs RV dysfunction in the formation and maintenance of pleural effusions is being debated. In animals with thin visceral pleura perfused by pulmonary veins, such as dogs, elevated

Table 7—*Median Survival**

Variables	PPE Group, mo	Cardiac Group, mo	p Value
HDM/SCT	21.8 (0.9–59.3)	15.6 (0.5–95.1)	0.405
Chemotherapy	8.8 (1.6–25.2)	8.7 (0.2–53.5)	0.730
No chemotherapy	1.6 (0.1–18.6)	6.0 (0.3–31.4)	0.031

*Values given as median (range), unless otherwise indicated.

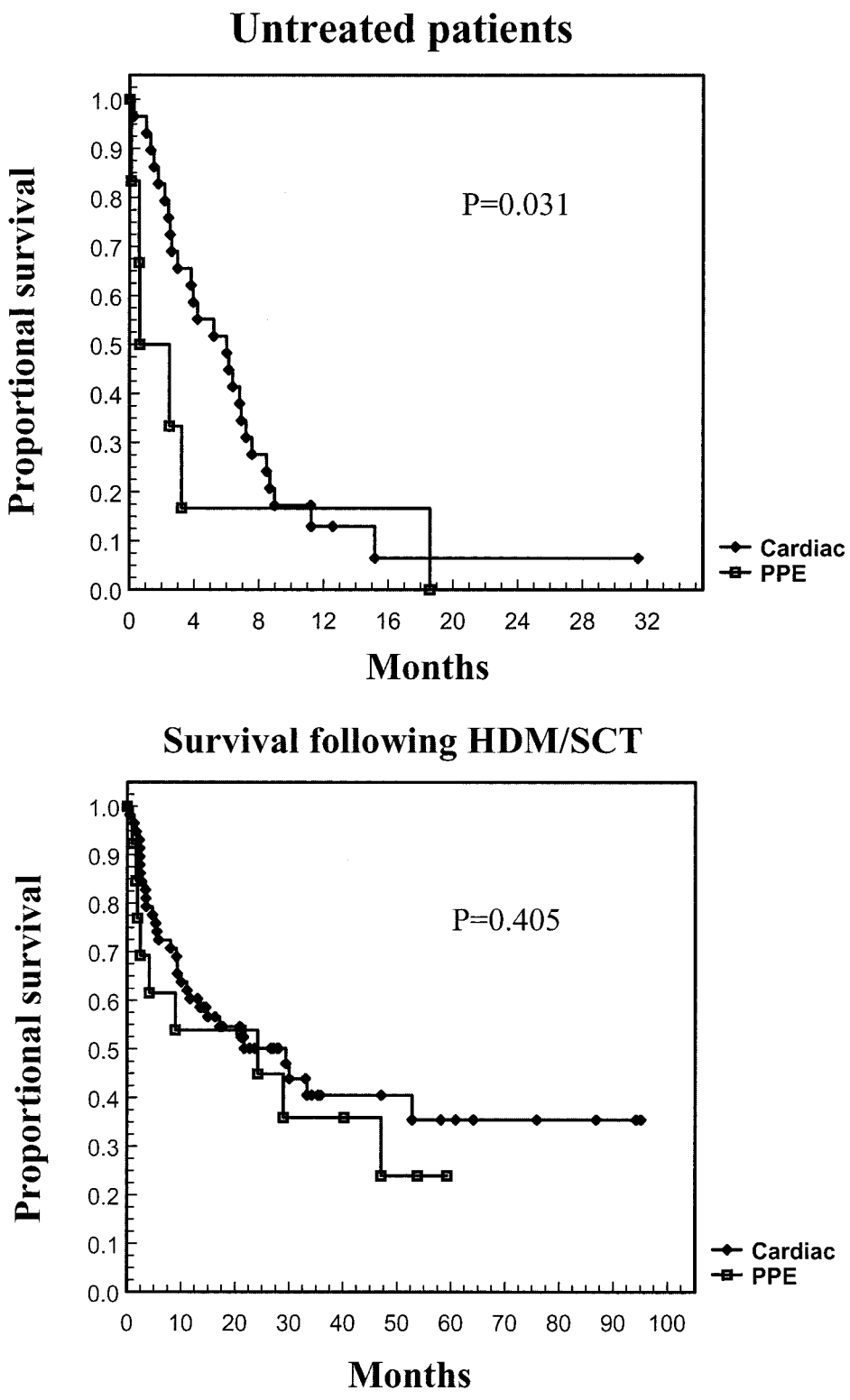

FIGURE 2. Kaplan-Meier survival curves for AL patients with PPE vs those with cardiac disease. *Top*: proportional survival among untreated patients. *Bottom*: proportional survival following therapy with HDM and SCT.

right atrial and systemic venous pressures drive pleural fluid formation.[29] In humans and sheep with thick visceral pleura perfused by bronchial arterioles, pleural effusions are associated with LV dysfunction.[30,31] Among patients with congestive heart failure, PCWP values segregate those with pleural effusions from those without pleural effusions (24.1 ± 1.3 vs 17.2 ± 1.5 mm Hg, respectively; $p < 0.001$). Pulmonary artery and right atrial pressures do not identify patients with effusions.[32] Similarly, in sheep, elevated left atrial pressures and pulmonary edema precede pleural fluid accumulation.[30]

Echocardiographic data in our AL patients failed to establish a causal relationship between LV function and PPEs. Measurements of neither LV systolic function nor diastolic filling identified patients with PPE vs those with cardiomyopathy alone. Nearly one third of the cardiac group had reduced LVEFs ranging from 10 to 45% without pleural effusions. Right heart catheterization of PPE patients documented an elevated median PCWP (20 mm Hg); however, the mean (± SD) PCWP was much lower than those reported in patients with congestive heart failure and pleural effusions (24.1 ± 1.3 mm Hg).[32] Additionally, 42% of PPE patients undergoing catheterization had a PCWP in the normal range (*ie*, ≤ 17 mm Hg), with a PCWP of < 9 mm Hg recorded in two patients. While elevated LV filling pressures contribute to the formation of pleural effusions,[31,32] our data suggested that left atrial hypertension is neither required nor sufficient to induce PPE in AL patients.

AL patients with PPEs more frequently exhibited decreased RV systolic function with a trend toward higher PAS pressures. The prevalence of elevated PAS pressures and other features of RV dysfunction (*ie*, chamber enlargement, free wall hypertrophy, and right atrial or IVC dilatation) were equally represented in both groups, however. Increased PAS pressures in the PPE group could represent AL amyloid-induced pulmonary vascular disease,[26] yet normal median DLCO/alveolar volume ratios and low pulmonary artery diastolic pressure-PCWP pressure differentials argue against noncardiogenic causes of pulmonary hypertension. More importantly, noncardiogenic pulmonary hypertension has not been shown to cause pleural effusions in patients with or without AL disease.[33]

Hypoalbuminemia and the nephrotic syndrome have been implicated in pleural fluid formation.[34,35] In our study, renal function and components of plasma oncotic pressure were statistically similar in the two groups. Surprisingly, AL renal disease was more frequent, and the median urinary protein losses were fivefold higher, in the cardiac group. No pleural effusions were detected radiographically in 14 AL cardiac patients with serum albumin levels of < 2.0 g/dL. These data demonstrate that nephrotic range proteinuria and hypoalbuminemia in combination with restrictive AL cardiomyopathy do not induce pleural effusions. Similarly, a large prospective study[36] of 172 medical patients found no pleural effusions that were attributable to hypoalbuminemia alone.

The inability of aggressive diuretic therapy to resolve persistent AL effusions suggests that amyloid inhibits pleural fluid resorption. The presence of mesothelial stomata, intercellular openings, and rich networks of submesothelial lymphatics and blood vessels identify parietal pleura as the principal drainage system of the pleural space.[37] This lymphatic system is capable of increasing pleural fluid drainage 10-fold to 20-fold, exceeding 500 mL/d in a 75-kg man.[31] Limiting lymphatic drainage would impair pleural fluid and protein egress, explaining diuretic unresponsiveness and elevated fluid protein levels. Alternatively, amyloid deposition could alter pleural secretory function. We observed continued large-volume drainage (approximately 500 mL/d) from chest tubes after the normalization of cardiac filling pressures. This suggests that amyloid infiltration promotes fluid secretion by one or both pleural surfaces, potentially diminishing the requirements for left atrial hypertension in pleural fluid formation. Closed-needle biopsies confirmed extensive parietal pleural amyloid deposition in a small number of patients. While additional biopsy material would provide information on the pathogenesis of PPE, the clinical debilitation of these patients and their intolerance of pneumothorax precluded closed pleural biopsies for research purposes. Visceral surface sampling was not available to us, making it impossible to assign relative contributions of each pleural surface to PPEs.

Although limited by small sample sizes, follow-up data in untreated patients indicated significantly shorter survival times in patients with PPE (2 months) than in those with AL cardiac disease alone (6 months) [Fig 2, *top*]. The retrospective design of this study prevented a comparative analysis of survival data in patients receiving different therapies. Separate case-control analyses, however, have suggested that treatment with HDM and autologous SCT improves survival in a large group of patients with AL.[38,39] It is not yet known whether high-risk cardiac patients or PPE patients benefit similarly.

In summary, multiple echocardiographic measures of ventricular function did not distinguish AL patients with PPEs from patients with AL cardiomyopathy alone. Although RV hypokinesis occurred more frequently in the PPE group, 31% of the cardiac group had RV hypokinesis without pleural effusions. Impaired LV function appeared to con-

tribute to the formation of pleural effusions but was neither required nor sufficient to generate PPEs in patients with AL. PPEs heralded limited survival times in AL patients who had not been treated with chemotherapy, whereas the median survival time after high-dose chemotherapy was similar in both the cardiac and PPE groups. The presence of amyloid deposits in all available parietal pleural biopsy specimens from AL patients with PPE leads us to conclude that direct disruption of pleural function plays a central role in the pathophysiology of PPEs.

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References

1 Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995; 32:45–59
2 Berk JL, O'Regan A, Skinner M. Pulmonary and tracheobronchial amyloidosis. Semin Respir Crit Care Med 2002; 23: 155–165
3 Celli BR, Rubinow A, Cohen AS, et al. Patterns of pulmonary involvement in systemic amyloidosis. Chest 1978; 74:543–547
4 Ikeda S, Takabayashi Y, Maejima Y, et al. Nodular lung disease with five year survival and unilateral pleural effusion in AL amyloidosis. Amyloid 1999; 6:292–296
5 Knapp MJ, Roggli VL, Kim J, et al. Pleural amyloidosis. Arch Pathol Lab Med 1988; 112:57–60
6 Maeno T, Sando Y, Tsukagoshi M, et al. Pleural amyloidosis in a patient with intractable pleural effusion and multiple myeloma. Respirology 2000; 5:79–80
7 Liu YY, Lee YC, Chou TY, et al. Pulmonary alveolar-septal amyloidosis presenting as heart failure with unilateral pleural effusion: a case report. Chung Hua I Hsueh Tsa Chih (Taipei) 1999; 62:838–843
8 Bontemps F, Tillie-Leblond I, Coppin MC, et al. Pleural amyloidosis: thoracoscopic aspects. Eur Respir J 1995; 8:1025–1027
9 Smith FB, Brown RB, Maguire G, et al. Localized pleural microdeposition of type A amyloid in a patient with rheumatoid pleuritis: histologic distinction from pleural involvement in systemic amyloidosis Am J Clin Pathol 1993; 99:261–264
10 Lindemalm C, Biberfeld P, Christensson B, et al. Bilateral pleural effusions due to amyloidosis in a case of Waldenström's macroglobulinemia. Haematologica 1988; 73:407–409
11 Graham DR, Ahmad D. Amyloidosis with pleural involvement. Eur Respir J 1988; 1:571–572
12 Mathews V, Vasudevan AR, Nair S, et al. Primary systemic amyloidosis: pleural involvement with exudative pleural effusion. J Assoc Physicians India 1996; 44:345–346
13 Hughes JC, Votaw ML. Pleural effusion in multiple myeloma. Cancer 1979; 44:1150–1154
14 Koyama J, Ray-Sequin PA, Davidoff R, et al. Usefulness of pulsed tissue Doppler imaging for evaluating systolic and diastolic left ventricular function in patients with AL (primary) amyloidosis. Am J Cardiol 2002; 89:1067–1071
15 American Thoracic Society: Standardization of spirometry: 1987 update. Am Rev Respir Dis 1987; 136:1285–1298
16 Dubois A, Bothelho S, Bedell G, et al. A rapid plethysomographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956; 35:322–326
17 Sanchorawala V, Wright DG, Seldin DC, et al. Low-dose continuous oral melphalan for the treatment of primary systemic (AL) amyloidosis. Br J Haematol 2002; 117:886–889
18 Peto R, Peto J. Asymptotically efficient rank invariant test procedures (with discussion). J R Stat Soc [Ser A] 1972; 135:185–206
19 Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77:507–513
20 Tei C, Dujardin KS, Hodge DO, et al. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. J Am Coll Cardiol 1996; 28:658–664
21 Klein AL, Hatle LK, Taliercio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiography study. Circulation 1991; 83:808–816
22 Reisinger J, Dubrey SW, Falk RH. Cardiac amyloidosis. Cardiol Rev 1997; 5:317–325
23 Ornato JP, Lui CY, Donovan JP, et al. The difference between pulmonary artery diastolic pressure and pulmonary capillary wedge pressure as a hemodynamic sign of pulmonary embolism. Nebr Med J 1985; 70:164–167
24 Gottehrer A, Roa J, Stanford GG, et al. Hypothyroidism and pleural effusions. Chest 1990; 98:1130–1132
25 Leuallen EC, Carr DT. Pleural effusion: a statistical study of 436 patients. N Engl J Med 2002; 252:79–83
26 Dingli D, Utz JP, Gertz MA. Pulmonary hypertension in patients with amyloidosis. Chest 2001; 120:1735–1739
27 Collins TR, Sahn SA. Thoracocentesis: clinical value, complications, technical problems, and patient experience. Chest 1987; 91:817–822
28 Seneff MG, Corwin RW, Gold LH, et al. Complications associated with thoracocentesis. Chest 1986; 90:97–100
29 Mellins RB, Levine OR, Fishman AP. Effect of systemic and pulmonary venous hypertension on pleural and pericardial fluid accumulation. J Appl Physiol 1970; 29:564–569
30 Allen S, Gabel J, Drake R. Left atrial hypertension causes pleural effusion formation in unanesthetized sheep. Am J Physiol 1989; 257(suppl):H690–H692
31 Wiener-Kronish JP, Matthay MA. Pleural effusions associated with hydrostatic and increased permeability pulmonary edema. Chest 1988; 93:852–858
32 Wiener-Kronish JP, Matthay MA, Callen PW, et al. Relationship of pleural effusions to pulmonary hemodynamics in patients with congestive heart failure. Am Rev Respir Dis 1985; 132:1253–1256
33 Wiener-Kronish JP, Goldstein R, Matthay RA, et al. Lack of association of pleural effusion with chronic pulmonary arterial and right atrial hypertension. Chest 1987; 92:967–970
34 Chetty KG. Transudative pleural effusions. Clin Chest Med 1985; 6:49–54
35 Kinasewitz GT. Transudative effusions. Eur Respir J 1997; 10:714–718
36 Eid AA, Keddissi JI, Kinasewitz GT. Hypoalbuminemia as a cause of pleural effusions. Chest 1999; 115:1066–1069
37 Albertine KH, Wiener-Kronish JP, Staub NC. The structure of the parietal pleura and its relationship to pleural liquid dynamics in sheep. Anat Rec 1984; 208:401–409
38 Sanchorawala V, Wright DG, Seldin DC, et al. An overview of the use of high-dose melphalan with autologous stem cell transplantation for the treatment of AL amyloidosis. Bone Marrow Transplant 2001; 28:637–642
39 Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 2002; 99:4276–4282