

CLINICAL OUTCOMES OF PULMONARY LANGERHANS'-CELL HISTIOCYTOSIS IN ADULTS

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ABSTRACT

Background Pulmonary Langerhans'-cell histiocytosis is an uncommon interstitial lung disease in adults. It has an unpredictable course and may be associated with an increased susceptibility to the development of malignant neoplasms.

Methods We reviewed the records of 102 adults with histopathologically confirmed pulmonary Langerhans'-cell histiocytosis to ascertain their vital status and whether cancer had been diagnosed. The health status of surviving patients was quantified with the use of the 36-Item Short-Form General Health Survey. Factors potentially associated with survival after the diagnosis of pulmonary Langerhans'-cell histiocytosis were analyzed with the Cox proportional-hazards model.

Results The median follow-up period was 4 years (range, 0 to 23). There were 33 deaths, 15 of which were attributable to respiratory failure. Six hematologic cancers were diagnosed. The overall median survival was 12.5 years, which was significantly shorter than that expected for persons of the same sex and calendar year of birth ($P < 0.001$). In a univariate analysis, variables predictive of shorter survival included an older age ($P = 0.003$), a lower forced expiratory volume in one second (FEV_1) ($P = 0.004$), a higher residual volume ($P = 0.007$), a lower ratio of FEV_1 to forced vital capacity ($P = 0.03$), and a reduced carbon monoxide diffusing capacity ($P = 0.001$).

Conclusions The survival of adults with pulmonary Langerhans'-cell histiocytosis is shorter than that in the general population, and respiratory failure accounts for a substantial proportion of deaths among such patients. (N Engl J Med 2002;346:484-90.)

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PULMONARY Langerhans'-cell histiocytosis is an uncommon interstitial lung disease that is part of the spectrum of disorders called Langerhans'-cell histiocytoses. These disorders are thought to result from the proliferation of specific histiocytic cells, known as Langerhans' cells, and their infiltration of organ systems.¹⁻⁶ The course of pulmonary Langerhans'-cell histiocytosis in adults is variable and unpredictable, ranging from an asymp-

tomatic course to progressive disease that leads to respiratory failure and death over a period of months. Although little is known about the natural course of this disease or the long-term prognosis for affected adults, retrospective studies of case series have suggested that several factors are predictive of an adverse outcome.^{5,7} These factors include extremes of age; multi-organ involvement; extensive cysts and honeycombing on chest radiographs; reduced carbon monoxide diffusing capacity; physiological obstruction, as indicated by a low ratio of the forced expiratory volume in one second (FEV_1) to the forced vital capacity; prolonged corticosteroid therapy; and evidence of air trapping, as indicated by a high ratio of residual volume to total lung capacity.^{5,7} These data have been confounded by the inclusion in the studies of patients who were children at the onset of disease and by the inclusion of patients in whom the diagnosis was not confirmed by tissue biopsy. Data from several case reports and series also suggest that patients with Langerhans'-cell histiocytosis are at increased risk for cancer,⁸⁻¹² although the association between the two disorders has not been clearly defined.

We reviewed the medical records of adults (18 years or older) with histologically confirmed pulmonary Langerhans'-cell histiocytosis who were seen at our institution over a 22-year period. We compared the survival of these persons with that expected for the general population. We also identified predictors of an adverse outcome, estimated the effect of Langerhans'-cell histiocytosis on the quality of life, and estimated the risk of malignant neoplasms in our cohort of patients.

METHODS

Patients

We reviewed the medical records of 102 adults with pulmonary Langerhans'-cell histiocytosis who were seen at the Mayo Clinic between January 1, 1976, and December 31, 1998. Patients were eligible for inclusion in the study if they had pulmonary Langerhans'-cell histiocytosis with histopathological confirmation on the basis of surgical lung biopsy (94 patients), transbronchoscopic lung biopsy (6 patients), or biopsy of an organ other than the lung to-

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gether with findings on a high-resolution computed tomographic (CT) scan of the chest that were consistent with the diagnosis (2 patients). Patients less than 18 years of age at the time of the diagnosis were excluded. The study was approved by the institutional review board for medical research. Written informed consent was obtained from the patients who participated in the follow-up survey.

Data Collection

The following clinical data were abstracted from the patients' medical records: symptoms and age at presentation, sex, presence or absence of a history of smoking, results of physical examination and laboratory tests, treatment at the time of the initial diagnosis, coexisting medical conditions, and the results of pulmonary-function studies, which were performed in our laboratory with the use of standard techniques.¹³ Pulmonary-function data that were collected included plethysmographically determined total lung capacity, forced vital capacity, FEV₁, the ratio of FEV₁ to forced vital capacity, and the carbon monoxide diffusing capacity. A restrictive pattern was defined as a total lung capacity that was less than 80 percent of the predicted value and a normal or high ratio of FEV₁ to forced vital capacity. An obstructive pattern was defined as an FEV₁ that was less than 80 percent of the predicted value and a ratio of FEV₁ to forced vital capacity that was less than 0.75.^{14,15}

We determined the vital status of patients by reviewing medical records and available death certificates. Follow-up data, including symptoms, were obtained from a questionnaire sent to all surviving patients included in the study, with follow-up by telephone for patients who did not return the questionnaire.

Survival

Survival was determined from the date of the diagnosis of pulmonary Langerhans'-cell histiocytosis to the date of death or the date on which the patient responded to the survey. Cumulative survival probabilities were estimated with the use of the Kaplan-Meier method and were compared with the life expectancy for white persons of the same sex and calendar year of birth in the general U.S. population.¹⁶ The one-sample log-rank test was used to compare actual and expected survival. Factors potentially associated with survival were analyzed with the use of the Cox proportional-hazards model. The expected probability of survival at 10 years was determined for each patient on the basis of sex and calendar year of birth, with the use of life tables for white persons in the U.S. population.¹⁶ In the Cox proportional-hazards model, the association of each potential predictor with survival was adjusted for the expected probability of survival at 10 years.

Malignant Neoplasms

The relative risks of hematologic cancers (*International Classification of Diseases for Oncology, 2nd Revision* codes 9590 to 9595, 9650 to 9667, 9670 to 9717, 9731, 9732, 9861, 9868, 9950, and 9962) were estimated with the use of age- and sex-specific incidence rates for cancer, based on data from the Surveillance, Epidemiology, and End Results program for the period from 1973 to 1998.¹⁷ To minimize the potential influence of referral bias on the results, the analysis was performed with person-years defined as the number of years that patients were observed from the diagnosis of pulmonary Langerhans'-cell histiocytosis to the diagnosis of cancer or the last contact. For each type of cancer, the expected number of cases was computed by multiplying the number of age- and sex-specific person-years by the incidence. The risk ratio was calculated as the ratio of the total number of observed cases of cancer to the total number of expected cases, and the 95 percent confidence interval was calculated with the assumption of a Poisson distribution for the number of observed cases.

Health Status

We measured health status with the use of the 36-Item Short-Form General Health Survey (SF-36), which was part of the ques-

tionnaire sent to the patients. Responses to the SF-36 portion of the survey were scored according to published guidelines.¹⁸ Standardized T scores, scaled so that the mean score was 50 with a standard deviation of 10 for the reference population, were calculated with the use of age- and sex-specific mean scores and standard deviations for the SF-36 scales in the general U.S. population.¹⁸ For each of the eight scales, the one-sample t-test was used to compare the mean T score with a score of 50. In all cases, two-sided tests were used, with a P value less than or equal to 0.05 considered to indicate statistical significance.

RESULTS

The clinical characteristics of 102 patients (40 men and 62 women) at the time that pulmonary Langerhans'-cell histiocytosis was diagnosed are summarized in Table 1. In 94 patients (92 percent), the diagnosis was established by surgical lung biopsy. Of the 102

TABLE 1. CHARACTERISTICS AT THE TIME OF THE DIAGNOSIS OF PULMONARY LANGERHANS'-CELL HISTIOCYTOSIS IN 102 ADULTS.*

CHARACTERISTIC	VALUE
Sex (no.)	
Male	40
Female	62
Age (yr)	
Mean	40.3±13.0
Median	38.0
Range	18-70
Smoking status (no.)	
Current	69
Previous	28
None	4
Unknown	1
Smoking history (pack-yr)†	
Mean	27.2±21.7
Median	20
Range	1-100
Symptoms (no.)	
None	15
Cough	51
Dyspnea	39
Malaise or fatigue	16
Pneumothorax	12
Pleuritic chest pain	10
Weight loss	9
Fever	8
Hemoptysis	1
Extrapulmonary involvement (no.)‡	17
Pituitary	8
Bone	7
Skin	4
Lymph nodes or liver	4

*Plus-minus values are means ±SD.

†Pack-years of smoking are given for the patients who were current or former smokers at the time of the diagnosis.

‡A total of 17 patients had extrapulmonary involvement: 2 had both pituitary and bone involvement, 1 had pituitary and skin involvement, 1 had involvement of the bone and liver, 1 had pituitary and lymph-node involvement, and 1 had involvement of both lymph nodes and the liver.

patients in the study, 29 underwent transbronchoscopic lung biopsy, but the findings were diagnostic in only 6 of the 29, confirming prior reports that transbronchoscopic biopsy has a limited role in the diagnostic workup for pulmonary Langerhans²-cell histiocytosis.¹⁹ Staining for the S-100 and CD1a antigens was used in three of the six positive biopsy specimens to facilitate identification of Langerhans' cells.^{20,21} The diagnosis in the remaining 23 patients (who had a nondiagnostic transbronchoscopic lung biopsy) was established by surgical lung biopsy. Pulmonary-function data, which were available for 82 patients, are summarized in Table 2.

High-resolution CT studies of the chest were performed in 29 patients at the time of the diagnosis. The most common abnormality was the presence of nodules, which were seen in 20 patients; in 5 of these patients, the nodules were described as cavitating. Lung cysts were identified in 11 patients. Four patients had a combination of lung cysts and nodules. The abnormalities were present predominantly in the upper

and middle lung fields in 18 patients. Other reported abnormalities were ground-glass attenuation in three patients (reported in association with lung nodules in two patients and as the sole abnormality in one), patchy consolidating infiltrates in one patient, and mediastinal adenopathy in two patients (associated with lung nodules in both).

In 16 cases, the radiologist reported that the CT findings were highly suggestive of pulmonary Langerhans²-cell histiocytosis. In the other 13 cases, the radiologist's report indicated that the findings were not typical of pulmonary Langerhans²-cell histiocytosis, and in 9 of these cases, the report suggested an alternative diagnosis. Only three deaths occurred in the subgroup of patients who underwent high-resolution CT studies of the chest at the time of the diagnosis; the number was too small to allow a meaningful statistical analysis of the findings in this subgroup.

At the time of the diagnosis, all current smokers were advised to stop smoking. For patients with minimal symptoms or none, there were no interventions except for those involving smoking cessation. Prednisone, alone or in combination with other immunosuppressive agents, was prescribed for 54 patients (53 percent) within six months after the diagnosis; 39 of these patients (72 percent) were treated with prednisone alone or, in the case of patients with multisystem disease, prednisone in combination with another drug (vinblastine in 7 patients, methotrexate in 2, cyclophosphamide in 2, etoposide in 2, and cladribine [2-chlorodeoxyadenosine] in 2). Two patients underwent surgical pleurodesis shortly after the diagnosis, and one patient underwent lung transplantation at the time of follow-up.

Survival

The median follow-up period after the diagnosis of pulmonary Langerhans²-cell histiocytosis was 4 years (range, 0 to 23). There were 33 deaths, 15 of which were attributable to respiratory failure. Survival was significantly shorter than that expected for healthy persons of the same sex and calendar year of birth ($P < 0.001$) (Fig. 1). The estimated rate of survival 5 years after the diagnosis of pulmonary Langerhans²-cell histiocytosis was 74 percent (95 percent confidence interval, 56 to 85 percent), and the rate of survival at 10 years was 64 percent (95 percent confidence interval, 52 to 77 percent). The estimated median survival (from the time of diagnosis) was 12.5 years. Characteristics at the time of diagnosis that were associated with survival are summarized in Table 3. The univariate analysis showed that shorter survival was associated with an older age ($P = 0.003$), a lower carbon monoxide diffusing capacity ($P = 0.001$), a lower FEV₁ ($P = 0.004$), a higher residual volume ($P = 0.007$), and a lower ratio of FEV₁ to forced vital capacity ($P =$

TABLE 2. PULMONARY FUNCTION AT DIAGNOSIS.*

CHARACTERISTIC	No. OF PATIENTS	VALUE
Total lung capacity — % of predicted	74	
Median		92
Mean		91.3 ± 18.7
Range		47–136
Residual volume — % of predicted	72	
Median		103
Mean		114.9 ± 54.4
Range		45–317
FEV ₁ — % of predicted	80	
Median		71
Mean		70.8 ± 23.8
Range		23–124
FEV ₁ /FVC	80	
Median		0.78
Mean		0.72 ± 0.16
Range		0.27–0.99
Carbon monoxide diffusing capacity — % of predicted	78	
Median		66
Mean		64.0 ± 19.5
Range		26–111
Classification of findings — no. (%)	81	
Normal		11 (13.6)
Restrictive		37 (45.7)
Obstructive		22 (27.2)
Mixed		4 (4.9)
Isolated reduction in carbon monoxide diffusing capacity		7 (8.6)

*A total of 82 patients underwent pulmonary-function testing within 12 months of the diagnosis of pulmonary Langerhans²-cell histiocytosis (median, 0 months; range, 8 months before to 7 months after the diagnosis). FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity. Plus-minus values are means ± SD.

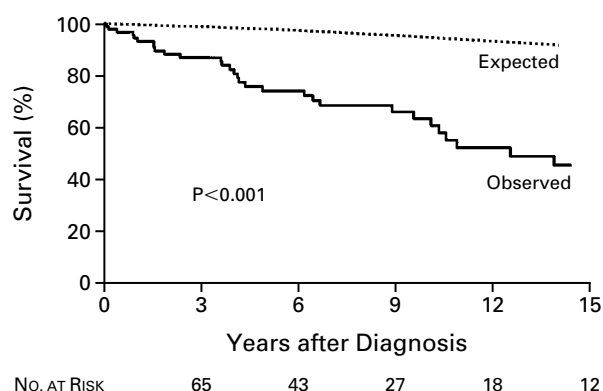


Figure 1. Kaplan-Meier Analysis of Expected and Observed Survival among 102 Adults with Pulmonary Langerhans'-Cell Histiocytosis.

The expected survival was defined as that for age- and sex-matched members of the general U.S. population.

0.03). After adjustment for expected survival at 10 years, based on life expectancy in the general population, survival was associated with a lower carbon monoxide diffusing capacity ($P < 0.001$), a lower FEV₁ ($P = 0.004$), a higher residual volume ($P = 0.005$), and former smoking (as opposed to current smoking at diagnosis) ($P = 0.03$).

Malignant Neoplasms

A total of 16 noncutaneous malignant neoplasms were identified in 14 patients in the study population (Table 4). All patients with neoplasms were current or former smokers at the time of the diagnosis of cancer, and a substantial proportion had a very long history of cumulative exposure to cigarette smoke. Seven cancers were diagnosed before the pulmonary Langerhans'-cell histiocytosis, six were diagnosed concurrently or in the same year, and three were detected after the diagnosis of pulmonary Langerhans'-cell histiocytosis. Hematologic cancers occurred in six patients, and five had primary lung cancers. There were 628 person-years of follow-up for hematologic cancers, with 2 observed cases and 0.172 expected (risk ratio, 11.6; 95 percent confidence interval, 1.4 to 41.9).

Health Status

A follow-up survey that included the SF-36 was sent to 88 patients not known to be deceased on the basis of the chart review. Of these 88 patients, 42 returned the survey, 19 had died, 5 refused to complete the survey, and there was no response from 22 patients. Of the 42 patients who returned the survey, 35 completed the SF-36; in this group, the median

period of follow-up from the diagnosis of pulmonary Langerhans'-cell histiocytosis was 6.9 years (range, 0.7 to 23.3). Analysis of the SF-36 data indicated that pulmonary Langerhans'-cell histiocytosis had a substantial effect on the health of these patients. As compared with persons of the same age and sex in the general U.S. population, the patients with pulmonary Langerhans'-cell histiocytosis had significantly lower scores for physical functioning ($P < 0.001$), ability to perform role-related activities (physical role) ($P = 0.004$), general health ($P < 0.001$), and vitality ($P < 0.001$), as well as for overall physical well-being (a composite score) ($P < 0.001$).

DISCUSSION

Our study shows that adults with pulmonary Langerhans'-cell histiocytosis have a shorter survival than members of the general population. A substantial proportion of the patients in our study died from respiratory failure. Evidence of obstruction, air trapping, and reduced carbon monoxide diffusing capacity on pulmonary-function testing appears to be helpful in identifying patients with a poor prognosis. Our study also shows that the health of persons with pulmonary Langerhans'-cell histiocytosis is impaired in several ways.

In 628 person-years of follow-up, 33 deaths occurred in our cohort of patients with pulmonary Langerhans'-cell histiocytosis, 15 of which were attributed to progressive respiratory failure. Some of these deaths may have resulted from associated severe chronic obstructive pulmonary disease due to concomitant cigarette smoking, although it is impossible to determine the contribution of this disease to the deaths. Three patients died as a consequence of an associated pulmonary neoplasm. The median survival in our study, 12.5 years, is almost identical to that previously reported in a European multicenter study involving 45 patients.⁷

Our findings confirm prior reports that in patients with pulmonary Langerhans'-cell histiocytosis, physiological evidence of impaired pulmonary function, especially evidence of an obstructive ventilatory defect, is a predictor of an adverse outcome and may be helpful in identifying patients who will benefit from aggressive treatment early in the course of disease.⁷ Although no specific interventions have been shown to prolong survival, vigorous efforts to help patients stop smoking seem reasonable, particularly for patients with clinical findings that point to a poor prognosis.²² The role of immunosuppressive therapy in the care of patients with adverse prognostic indicators is not clear, since such treatment has not been objectively demonstrated to improve lung function or reduce long-term mortality.

Disseminated Langerhans'-cell histiocytosis is

TABLE 3. CHARACTERISTICS AT DIAGNOSIS ASSOCIATED WITH SURVIVAL.*

CHARACTERISTIC	No. OF PATIENTS	ESTIMATED SURVIVAL			P VALUE	
		3 YR	5 YR	10 YR	UNADJUSTED	ADJUSTED†
Overall	102	87	74	64		
Age					0.003	0.19
≤35 yr	44	94	79	62		
36–50 yr	33	93	89	75‡		
>50 yr	25	69	48	48‡		
Sex					0.69	0.38
Male	40	86	75	64		
Female	62	87	74	63		
Smoking status					0.06	0.03
Current smoker	69	83	78	69		
Former smoker	28	82	70	56‡		
Total lung capacity					0.53	0.94
<80% of predicted	21	77	60‡	50‡		
≥80% of predicted	53	93	82	70		
Residual volume					0.007	0.005
≤120% of predicted	48	98	90	75		
>120% of predicted	24	77	57	51‡		
FEV ₁					0.004	0.004
≤59% of predicted	27	75	54	47‡		
60–79% of predicted	21	100	92	73‡		
>79% of predicted	32	93	83	76		
FEV ₁ /FVC					0.03	0.21
<80	50	81	69	66		
≥80	30	100	86	57‡		
Carbon monoxide diffusing capacity					0.001	<0.001
<72% of predicted	49	83	68	54		
≥72% of predicted	29	100	100	92		

*All statistical analyses were performed with the use of the Cox proportional-hazards model, with sex and smoking status treated as categorical variables, and age, total lung capacity, residual volume, forced expiratory volume in one second (FEV₁), the ratio of FEV₁ to forced vital capacity (FVC), and carbon monoxide diffusing capacity treated as continuous variables.

†The analysis was adjusted for expected survival at 10 years, which was determined for each patient on the basis of survival data for the U.S. white population, matched according to sex and calendar year of birth.

‡Fewer than 10 patients were still alive.

thought to be associated with a worse prognosis than isolated organ involvement. Although we anticipated that extrapulmonary involvement would be predictive of an adverse outcome, it was not. However, firm conclusions cannot be drawn in view of the small number of patients included.

Most of the patients in our study were current or former cigarette smokers at the time of the diagnosis. The high prevalence of cigarette smoking among adults with pulmonary Langerhans²-cell histiocytosis has also been reported in several other studies, and this finding suggests that the disease may be causally related to smoking.^{1,2,6,22-25} Although almost all adults with pulmonary Langerhans²-cell histiocytosis are cigarette smokers, only approximately 60 percent of adults with systemic forms of the disorder have a history of exposure to cigarette smoke (unpublished data). We speculate that pulmonary Langerhans²-cell his-

tiocytosis represents a reactive polyclonal process in the lungs that is induced by antigens in cigarette smoke and is thus different from the other systemic forms of Langerhans²-cell histiocytosis, which have been shown to be the result of a monoclonal proliferation of Langerhans² cells, much like a neoplasm.²⁵

Although high-resolution CT scans showing nodular abnormalities accompanied by cystic changes, predominantly in the upper and middle lung fields, are virtually pathognomonic of pulmonary Langerhans²-cell histiocytosis,^{1,26-29} these findings were reported in only four of our patients with biopsy-confirmed disease; the majority had either cystic abnormalities or lung nodules alone. Whether the findings on high-resolution CT have any prognostic importance could not be determined by our retrospective analysis because of the small sample.

A number of investigators have reported the diag-

TABLE 4. DIAGNOSED CANCERS IN THE STUDY GROUP.

TYPE OF CANCER	NO. OF PATIENTS	SEX	AT DIAGNOSIS OF CANCER		AT DIAGNOSIS OF PLCH*		AT FOLLOW-UP		
			TOBACCO		TOBACCO		AGE†	VITAL STATUS	SMOKING HISTORY
			AGE	USE	AGE	USE			
Hematologic	6								
Multiple myeloma		F	60	Current	62	Current	64	Dead	60
Polycythemia vera		M	61	Former	61	Former	62	Dead	50
Essential thrombocythemia		F	39	Current	41	Current	46	Alive	15
Chronic myelomonocytic leukemia		F	61	Current	52	Current	62	Alive	60
T-cell lymphoma		F	63	Former	53	Current	63	Dead	30
Acute myelogenous leukemia‡		F	51	Current	51	Current	51	Dead	25
Pulmonary	5								
Adenocarcinoma									
Patient 1		F	61	Current	61	Current	62	Dead	40
Patient 2		F	45	Former	66	Current	66	Dead	80
Patient 3§		M	60	Former	64	Current	66	Alive	40
Bronchoalveolar-cell carcinoma		F	54	Current	54	Current	58	Alive	35
Small-cell carcinoma		F	56	Former	56	Former	56	Dead	90
Other	5								
Prostate cancer§		M	60	Former	64	Current	66	Alive	40
Oligodendroglioma		M	45	Current	46	Current	47	Alive	14
Metastatic squamous-cell cancer (unknown primary source)		M	47	Current	47	Current	53	Alive	85
Breast cancer‡		F	46	Current	51	Current	51	Dead	25
Pancreatic cancer		F	71	Former	58	Former	71	Dead	100

*PLCH denotes pulmonary Langerhans'-cell histiocytosis.

†The age shown is the age at the time of death or the follow-up survey.

‡In this patient, acute myelogenous leukemia (subtype M2 according to the French-American-British classification) and pulmonary Langerhans'-cell histiocytosis were diagnosed at the same time, five years after the diagnosis of breast cancer. The patient received adjuvant chemotherapy after the diagnosis of breast cancer; information about the specific agents used was not available.

§This patient had both adenocarcinoma and prostate cancer.

nosis of lymphoma,^{11,30} multiple myeloma,^{12,31} adenocarcinoma of the lung,³² and other solid tumors before, after, or at the same time as the diagnosis of Langerhans'-cell histiocytosis.^{8,9,33,34} Our study showed that a variety of neoplasms were associated with pulmonary Langerhans'-cell histiocytosis. Because of the small numbers of patients and the retrospective nature of the study, a definitive conclusion about the relative risks of various cancers, especially myeloproliferative disorders, in adults with pulmonary Langerhans'-cell histiocytosis cannot be drawn, but the association should be recognized by clinicians treating such patients. Cigarette smoking, prior treatment with chemotherapeutic agents, and chromosomal or genetic abnormalities are factors that may confer a predisposition to the development of malignant neoplasms in patients with pulmonary Langerhans'-cell histiocytosis.

Although there are no published data on measures of health status in patients with Langerhans'-cell histiocytosis, the SF-36 is a sensitive instrument for eval-

uating health status in patients with other interstitial lung diseases, such as sarcoidosis.³⁵ In patients with pulmonary Langerhans'-cell histiocytosis, respiratory and constitutional symptoms, side effects of treatment, and functional limitations due to progressive respiratory impairment caused by the disease are likely to affect health.

There are several limitations of our study. We enrolled only patients with histologically confirmed disease and thus introduced a potential selection bias by excluding 15 persons with probable pulmonary Langerhans'-cell histiocytosis on the basis of the clinical history and high-resolution CT findings. These patients had minimally symptomatic disease for which a definitive diagnosis was not deemed necessary. Although their exclusion may have contributed to our data showing a poor outcome, Delobbe et al.⁷ reported a median survival that was almost identical to that in our study, even though their inclusion criteria were less stringent (with the diagnosis established by bronchoalveolar lavage in 20 of the 45 patients in their study).

Another limitation of our study was the use of death certificates to determine causes of death. The magnitude of the bias introduced into the analysis as a result of this approach is difficult to determine with certainty, but the number of deaths from respiratory failure may have been overestimated.

Our retrospective analysis shows that among adults with pulmonary Langerhans'-cell histiocytosis, long-term survival is shorter than that in the general population, health is substantially affected, and death is frequently due to respiratory complications. In addition, these patients appear to have an increased frequency of hematologic cancers. Poor physiological function at the time of the diagnosis of pulmonary Langerhans'-cell histiocytosis portends a poor prognosis. Although the condition is rare, our data provide a basis for designing prospective studies to elucidate these issues.

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