CLINICAL OUTCOMES OF PULMONARY LANGERHANS’-CELL Histiocytosis IN ADULTS

ROBERT VASSALLO, M.D., JAY H. RYU, M.D., DARRELL R. SCHROEDER, M.S., PAUL A. DECKER, M.S., AND ANDREW H. LIMPER, M.D.

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 medical 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 (FEV₁) (P=0.004), a higher residual volume (P=0.007), a lower ratio of FEV₁ 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. The course of pulmonary Langerhans’-cell histiocytosis in adults is variable and unpredictable, ranging from an asym-
together 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.14 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 in the 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 questionnaire 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.19 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 Langerhans’-cell histiocytosis. Staining for the S-100 and CD1a antigens was used in three of the six positive biopsy specimens to facilitate identification of Langerhans’ cells. 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 Langerhans’-cell histiocytosis. In the other 13 cases, the radiologist’s report indicated that the findings were not typical of pulmonary Langerhans’-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 Langerhans’-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 Langerhans’-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=

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**Table 2. Pulmonary Function at Diagnosis.*"**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity — % of predicted</td>
<td>74</td>
<td>92</td>
</tr>
<tr>
<td>Median</td>
<td>91.3±18.7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>47–136</td>
<td></td>
</tr>
<tr>
<td>Residual volume — % of predicted</td>
<td>72</td>
<td>103</td>
</tr>
<tr>
<td>Median</td>
<td>114.9±54.4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>45–317</td>
<td></td>
</tr>
<tr>
<td>FEV₁ — % of predicted</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>Median</td>
<td>70.8±23.8</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23–124</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>80</td>
<td>0.78</td>
</tr>
<tr>
<td>Median</td>
<td>0.72±0.16</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.27–0.99</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide diffusing capacity</td>
<td>78</td>
<td>66</td>
</tr>
<tr>
<td>— % of predicted</td>
<td></td>
<td>64.0±19.5</td>
</tr>
<tr>
<td>Classification of findings — no. (%)</td>
<td>81</td>
<td>11 (13.6)</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>37 (45.7)</td>
</tr>
<tr>
<td>Restrictive</td>
<td></td>
<td>22 (27.2)</td>
</tr>
<tr>
<td>Obstructive</td>
<td></td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>7 (8.6)</td>
</tr>
</tbody>
</table>

* A total of 82 patients underwent pulmonary-function testing within 12 months of the diagnosis of pulmonary Langerhans’-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.
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.2

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
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 Langerhans’-cell histiocytosis has also been reported in several other studies, and this finding suggests that the disease may be causally related to smoking. Although almost all adults with pulmonary Langerhans’-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 Langerhans’-cell histiocytosis 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 Langerhans’-cell histiocytosis, which have been shown to be the result of a monoclonal proliferation of Langerhans’ cells, much like a neoplasm. 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 Langerhans’-cell histiocytosis, 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-
nosis of lymphoma,\textsuperscript{11,30} multiple myeloma,\textsuperscript{12,31} adenocarcinoma of the lung,\textsuperscript{32} and other solid tumors before, after, or at the same time as the diagnosis of Langerhans'-cell histiocytosis.\textsuperscript{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 evaluating health status in patients with other interstitial lung diseases, such as sarcoidosis.\textsuperscript{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.\textsuperscript{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).

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
\textbf{Type of Cancer} & \textbf{No. of Patients} & \textbf{Sex} & \textbf{At Diagnosis of Cancer} & \textbf{At Diagnosis of PLCH*} & \textbf{At Follow-up} \\
& & & \textbf{TOBACCO USE} & \textbf{TOBACCO USE} & \textbf{VITAL STATUS} & \textbf{SMOKING HISTORY} \\
& & & \textbf{AGE} & \textbf{TOBACCO USE} & \textbf{AGE} & \textbf{TOBACCO USE} & \textbf{AGE} & \textbf{SMOKING HISTOR} \\
& & & \textbf{yr} & \textbf{yr} & \textbf{yr} & \textbf{yr} & \textbf{yr} & \textbf{yr} \\
\hline
Hematologic & 6 & & & & & & & \\
Multiple myeloma & & F & 60 & Current & 62 & Current & 64 & Dead & 60 \\
Polycthyemia 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\textsuperscript{‡} & & F & 51 & Current & 51 & Current & 51 & Dead & 25 \\
\hline
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\textsuperscript{§} & & 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 \\
\hline
Other & 5 & & & & & & & \\
Prostate cancer\textsuperscript{§} & & M & 60 & Former & 64 & Current & 66 & Alive & 40 \\
Oligodendroglioma & & M & 45 & Current & 46 & Current & 47 & Alive & 14 \\
Metastatic squamous-cell cancer & & M & 47 & Current & 47 & Current & 53 & Alive & 85 \\
(unknown primary source) & & & & & & & & \\
Breast cancer\textsuperscript{‡} & & F & 46 & Current & 51 & Current & 51 & Dead & 25 \\
Pancreatic cancer & & F & 71 & Former & 58 & Former & 71 & Dead & 100 \\
\hline
\end{tabular}
\caption{Diagnosed Cancers in the Study Group.}
\end{table}
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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REFERENCES


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