Eur Respir J 2012; 40: 905–912
DOI: 10.1183/09031936.00210711

Serial computed tomography and lung function testing in pulmonary Langerhans' cell histiocytosis

Abdellatif Tazi, Karima Marc, Stéphane Dominique, Cédric de Bazelaire, Bruno Crestani, Thierry Chinet, Dominique Israel-Biet, Jacques Cadranel, Jacques Frija, Gwenael Lorillon, Dominique Valeyre and Sylvie Chevret

ABSTRACT: Little is known about longitudinal lung function variation in patients with pulmonary Langerhans' cell histiocytosis (LCH). The contribution of serial lung computed tomography (CT) to managing these patients has not been evaluated.

This long-term retrospective study included 49 patients who were serially evaluated by lung CT and pulmonary function tests. The lung function variation was categorised as improvement or deterioration. The extent of the CT lesions was correlated with lung function.

Lung function deteriorated in ~60% of the patients. Forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) were the parameters that most frequently deteriorated. A subgroup of patients experienced a dramatic decline in FEV_1 within 2 yrs of diagnosis. Airway obstruction was the major functional pattern observed. In a multivariate analysis, % predicted FEV_1 at diagnosis was the only factor associated with the incidence of airway obstruction. The increase in cystic lesions on the lung CTs was associated with impaired lung function but did not anticipate the decline in FEV_1 or $D_{L,CO}$.

Serial lung function tests are essential for following patients with pulmonary LCH, who frequently develop airway obstruction. A lung CT at diagnosis is informative, but routine sequential CTs seem less useful. A prospective study is needed to characterise those patients with early progressive disease.

KEYWORDS: Airway obstruction, diffuse cystic lung disease, multicentre study, smoking cessation

Pulmonary Langerhans' cell histiocytosis (LCH) is an uncommon disorder that occurs predominantly in young smokers [1–4]. The natural history of pulmonary LCH is widely variable and difficult to predict in an individual patient [5–8]. It has been suggested that older age, evidence of obstruction, air trapping (an increased residual volume (RV)/total lung capacity (TLC) ratio) and a reduced diffusing capacity for carbon monoxide ($D_{L,CO}$) at diagnosis are associated with the development of respiratory failure and increased mortality [5, 6, 9]. However, scant information is available concerning the longitudinal variations in lung function over time, particularly over a long period.

The eventual contribution of high-resolution computed tomography (HRCT) to predicting the outcome of patients with pulmonary LCH has not been evaluated. Nodules may progress over time to cysts that may remain stable or progress [10]. The extent of the cystic lesions present on HRCT has been correlated with impaired $D_{L,CO}$ and an impaired forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio at a given time point [11, 12] and (more recently) during follow-up in a small series of patients [13]. Those authors stated that the patients with declining lung function had severe cystic alterations on lung computed tomography (CT), but few patients in their series progressed [13].

We conducted a long-term retrospective multicentre study of a large cohort of patients with pulmonary LCH who were serially evaluated by HRCT and lung function testing. We had the following objectives:

AFFILIATIONS
For affiliations details, please refer to the Acknowledgements section.

CORRESPONDENCE
A. Tazi
Service de Pneumologie
Hôpital Saint Louis
1 Avenue Claude Vellefaux
75475
Paris cedex 10
France
E-mail: abdellatif.tazi@sls.aphp.fr

Received:
Dec 01 2011
Accepted after revision:
Feb 14 2012
First published online:
March 22 2012

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material available from www.erj.ersjournals.com

1) to evaluate the longitudinal variation in lung function parameters; 2) to compare the HRCT findings and lung function results during follow-up; and 3) to identify the factors that predict eventual outcome in these patients.

MATERIALS AND METHODS

Design of the study, setting and subject selection

This was a retrospective study involving seven French teaching hospital pulmonary departments. All the consecutive patients referred to these centres for pulmonary LCH from June 1989 to January 2005 were sequentially included in this study, provided that they were serially evaluated by two or more HRCTs and lung function tests performed at $\geqslant$6-month intervals.

49 patients with pulmonary LCH were selected to be reviewed retrospectively in the cohort. This study was approved by the institutional review board of Bichat Hospital, Paris, France (number IRB00006477).

Diagnosis of pulmonary LCH

The diagnosis of pulmonary LCH was based on one of the following criteria: 1) disease proven by lung biopsy; 2) a positive biopsy of an extra thoracic localisation of the disease or the presence of diabetes insipidus associated with characteristic lung HRCT findings; or 3) the combination of an appropriate clinical setting, a typical lung HRCT pattern (showing both nodules and cysts) and exclusion of the alternative diagnoses.

Data collection

Data on the patients' demographics, clinical presentation, smoking habits and treatments of interest were retrieved from the medical records.

All of the HRCT scans were centrally analysed by two radiologists (C. de Bazelaire and J. Frija) and a chest physician (A. Tazi), without knowledge of the clinical or functional findings. The lung HRCT lesions were classified as has been previously described [10]. Each lung was divided into three areas, from the lung apices to the domes of the diaphragm, and semi-quantitative CT scores were established for each area to estimate the nodule profusion and the extent of the cysts. The results were obtained by consensus. The global nodular and cystic CT scores were calculated by adding the nodule extent and cyst values obtained from the three areas of the lung (giving maximum values of 18 and 24, respectively). Based on the CT scores, the patients were classified as having low, intermediate and high nodular CT scores, and low, intermediate, high and very high cystic CT scores. Additional details on the methods used to determine the lung CT scores are provided in the online supplement.

Lung volumes were evaluated by plethysmography (except for two patients), and FEV1 and FVC by the flow–volume curve. $D_{L,CO}$ was measured using the single-breath method. The predictive values were determined as has been previously described [14]. Obstruction was defined as FEV1/FVC ratio $<$70% [15].

End-points of the study

Two outcomes were considered: deterioration or improvement of lung function from the baseline measurements. For each parameter, variations of $\geqslant$10% in the FEV1 or FVC, or of $\geqslant$15% in the $D_{L,CO}$ defined improvement or deterioration [16]. The overall lung function outcome was defined by whether there was an increase or decrease of $\geqslant$10% in the FEV1 and/or FVC, and/or of $\geqslant$15% in the $D_{L,CO}$. In cases of discrepancies, the impaired parameter was used as the overall lung function outcome. If the changes were $<$10% for FEV1 and FVC, and $<$15% for $D_{L,CO}$, lung function was considered to be stable.

Times to developing airway obstruction and restriction were also computed.

Statistical analysis

The descriptive statistics of the study groups are presented. Mean$\pm$SD or median (interquartile range (IQR)) values are reported. Receiver operating characteristic (ROC) curves for the HRCT scores were plotted to delineate the patients with obstructive or restrictive patterns at diagnosis, with the area under the ROC curve (AUC) used as a measure of discrimination.

Patient follow-up was the interval between the date of the first examination and the date of an event; the patients who neither deteriorated nor improved and who did not develop obstructive or restrictive functional defects were censored at the reference date (September 2005). Thus, the actual follow-up varied according to the patients' date of inclusion in the study and was up to 16 yrs. As the patients were enrolled sequentially from 1989 to 2005 and the study ended in September 2005, statistical methods for time-to-event data were used to account for the censoring of the data. The cumulative incidences of lung function deterioration, lung function improvement and obstructive or restrictive patterns over time were estimated separately. Cox proportional hazards models were used to calculate the relative hazards of lung function deterioration or improvement associated with different population characteristics while fully adjusting for potential confounders. To assess the influence of smoking cessation, a Cox model with a time-dependent covariate was used.

All of the statistical tests were two-sided, with p-values $\leqslant$0.05 denoting statistical significance.

RESULTS

Study population

The demographic characteristics, clinical features, lung function tests and HRCT score subgroups at diagnosis are shown in table 1. Among the 47 patients evaluated by plethysmography, 23 (49%) patients had normal lung volumes, 21 (45%) had air trapping and three (6%) patients had a mild restriction (TLC 78.7$\pm$0.6% predicted), either isolated (n=2) or associated with obstruction (mixed pattern, n=1). Among the whole study population (n=49), 15 (31%) had an obstructive pattern (FEV1 74.4$\pm$13.7% pred; FEV1/FVC 65.1$\pm$3.4%). The $D_{L,CO}$ was decreased in 35 (81%) of the 42 patients in whom it was initially measured.

46 patients had both nodules and cysts in their lung HRCTs and three patients had an isolated cystic pattern. At the time of diagnosis, the mean HRCT nodular score was 6.6$\pm$3.4 and the mean cystic score was 11.9$\pm$6.1.

Nine patients received steroids for 22.9$\pm$11.7 months and one received vinblastine alone for 19 months, while two were treated with both prednisone and vinblastine for 19 and 40 months, respectively.

TABLE 1 The characteristics of the patients at the time of their pulmonary Langerhans' cell histiocytosis diagnosis

Characteristic	Subjects
Subjects n	49
Age yrs	30.5±7.2
Male sex	24 (49)
Smoking status	
Current smokers	46 (94)
Ex-smokers	3 (6)
Exposure pack-yrs	22±19
Symptoms	38 (77.5)
Cough	25 (51.0)
Dyspnoea (NYHA II/III)	10/1 (22.5)
Pneumothorax	9 (18.5)
Respiratory + constitutional	11 (22.5)
No symptoms	11 (22.5)
Histological confirmation	35 (71)
Surgical lung biopsy	30 (61)
Extra-pulmonary biopsy	5 (10)
TLC# % pred	100.4±16.5
FVC % pred	89.1±18.6
RV# % pred	129.4±47.8
RV/TLC# % pred	126.5±38.0
FEV_1 % pred	77.6±21.9
FEV_1/FVC %	72.8±12.6
$D_{L,CO}$ % of pred (n=42)	62.8±22.6
HRCT nodular score subgroup	
Low	31 (63)
Intermediate	16 (33)
High	2 (4)
HRCT cystic score subgroup	
Low	14 (29)
Intermediate	15 (31)
High	10 (20)
Very high	10 (20)

Data are presented as mean±SD or n (%), unless otherwise stated. NYHA: New York Heart Association; TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; RV: residual volume; FEV_1: forced expiratory volume in 1 s; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography. #: n=47.

Correlation between HRCT and lung function at diagnosis

At diagnosis, the HRCT nodular score was not correlated with any lung function parameters or with a restrictive or an obstructive pattern. By contrast, the HRCT cystic score was inversely correlated with the FEV_1, FEV_1/FVC ratio (r= -0.7, p<0.0001), and $D_{L,CO}$ (r= -0.38, p=0.01) and positively correlated with air trapping (RV/TLC % pred; r=0.63, p<0.0001). The 15 patients with airway obstruction had higher HRCT cystic scores than the patients without obstruction (17.6±5.9 and 9.4±4.1, respectively; p<0.001). The HRCT cystic score at diagnosis discriminated between the patients with and without an obstructive lung function pattern, with AUC of 0.86 (95% CI 0.73–0.99). A cut-off value of 14 for the HRCT cystic score predicted an obstructive pattern with a sensitivity of 80% and a specificity of 91.2%. There was no difference in tobacco consumption at diagnosis among these patients (p=0.51).

Evolution of lung function and HRCT findings during follow-up

The median follow-up was 36 months (IQR 17–67 months), with a median of two longitudinal and lung function evaluations (IQR 1–3 months). Six (12.2%) patients were lost to follow-up before any deterioration of their lung function after a median time of 3 yrs of follow-up. Table 2 shows the lung function outcomes for the study population. These results were confirmed when estimating the cumulative incidence of patients with either deteriorated or improved lung function over time (fig. 1).

The changes in the different lung function parameters varied considerably, with the $D_{L,CO}$ being the parameter that improved the least frequently (table 2 and fig. 1). It is noteworthy that among the 19 patients who had an impaired FEV_1 during follow-up, 10 (52.6% or 20.5% of the study population) had deteriorated soon after their diagnoses. The median FEV_1 decrease within the first 2 yrs for these 10 patients was -235 mL (IQR -340– -200 mL; -18% compared to the values at diagnosis, IQR -21– -11%), whereas it was -30 mL (IQR -195–100 mL) for the nine patients whose FEV_1 deteriorated later (-6% of the value at diagnosis, IQR -13– -4%).

Six patients developed a new-onset airflow obstruction, among whom one patient displayed a mixed pattern (TLC 83% and 79% pred, respectively, at diagnosis and at 68 months of follow-up). Thus, 21 (43%) patients had an obstructive pattern at some point (mean FEV_1 1,900±655 mL (54.4±16.8% pred) at the time of last follow-up). Conversely, the three patients who had mild restriction at diagnosis had normal TLCs at their last evaluations.

The variations in the nodular and cystic CT scores over time were inversely correlated (p<0.05). Overall, the mean nodular score decreased during the follow-up. At the final follow-up, 45 (92%) of the patients had a low nodular CT score, and four (8%) of the patients had an intermediate CT nodular score. By contrast, the mean value of the cystic HRCT score increased over time (p<0.01). At the last evaluation, 26 (53%) patients had a high or very high CT cystic score.

The effects of smoking cessation on the variations in the lung function and HRCT findings

Of the 46 patients who were current smokers at diagnosis, 16 stopped smoking during the follow-up, with a median time to cessation of 11 months (IQR 0–24.5 months). The lung function results and HRCT nodular and cystic scores of these patients at diagnosis were similar to those who continued to smoke (not shown). No statistical differences in lung function outcomes, including decline *versus* improvement of FEV_1, were observed between the two groups of patients (table 3). The hazard ratio (HR) for developing airflow obstruction during follow-up was not significantly different after smoking cessation (p=0.66). No significant differences were observed between the mean nodular and cystic CT scores of the patients who ceased smoking and the scores of those who continued to smoke.

Correlation between HRCT and lung function during follow-up

The variations in the HRCT nodular score over time and lung function outcomes were not correlated (p=0.91). Conversely, the variations in the HRCT cystic score were inversely correlated

TABLE 2 Lung function outcomes in the complete study population

Lung function	Improvement	Deterioration	Cumulative incidence of deterioration at 5 yrs %
Overall	10 (20.5)	28 (57)	59.4
FVC	9 (18.3)	11 (22.5)	24.7
FEV1	8 (16)	19 (39)	42.6
***D*L,CO#**	2/40 (5)	18/40 (45)	47.9

Data are presented as n (%), unless otherwise specified. For each parameter, changes of ⩾10% in forced expiratory volume in 1 s (FEV1) or forced vital capacity (FVC) or of ⩾15% in diffusing capacity of the lung for carbon monoxide (*D*L,CO) constituted improvement or deterioration. The overall lung function outcome was defined based on increases or decreases of ⩾10% in FEV1 and/or FVC and/or of ⩾15% in *D*L,CO. In case of discrepancies, the impaired parameter was used. The patients whose lung function was stable (neither improved nor deteriorated) are not shown. The estimated cumulative incidences of deterioration in lung function parameters at 5 yrs were calculated considering the competing risks framework for overall lung function and according to each lung function parameter. #: serial *D*L,CO results were available for 40 patients.

with variations in *D*L,CO (p=0.0001), FVC (p=0.0001) and FEV1 (p=0.002). Among the 19 patients whose FEV1 deteriorated, 10 (52.6%) had higher HRCT cystic scores, as compared to two (25%) among the eight patients whose FEV1 improved. Once the HRCT cystic score increased, however, the HR for a deteriorating FEV1 was not significantly increased (HR 2.1, 95% CI 0.47–9.64; p=0.32). The increase in the HRCT cystic score did not precede the deterioration in the FEV1 or the *D*L,CO (fig. 2).

Prognostic analyses

None of the factors evaluated at diagnosis was significantly associated with FEV1 deterioration. Notably, the FEV1 at

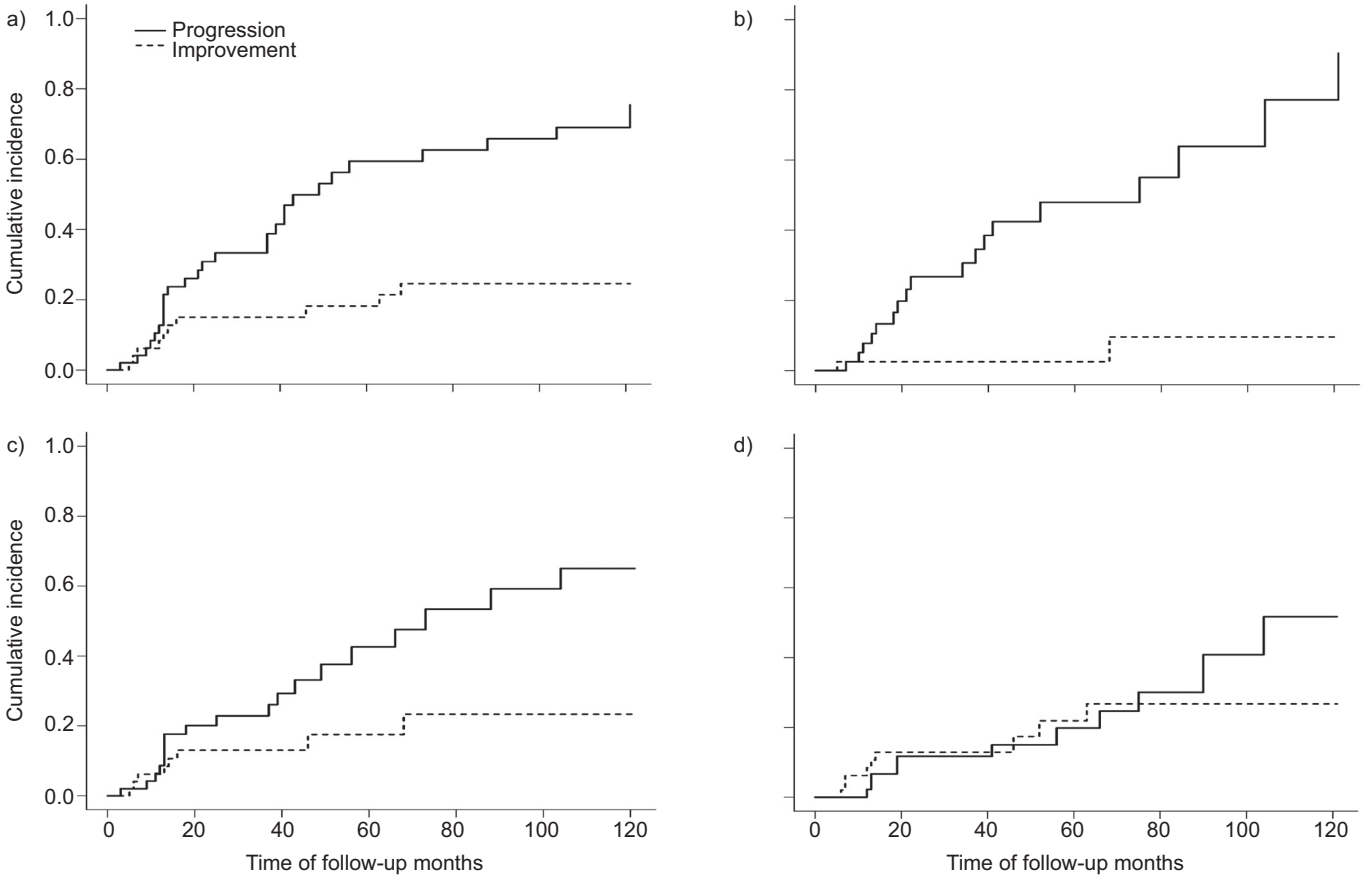

FIGURE 1. The estimated cumulative incidences of deterioration or improvement in the lung function of the study population over time. a) Overall lung function. Increase or decrease of ⩾10% in forced expiratory volume in 1 s (FEV1) and/or forced vital capacity (FVC) and/or of ⩾15% in diffusing capacity of the lung for carbon monoxide (*D*L,CO). In case of discrepancies, the impaired parameter was used; b) *D*L,CO; c) FEV1; d) FVC.

TABLE 3 Lung function outcomes according to continued smoking or smoking cessation in pulmonary Langerhans' cell histiocytosis patients who were current smokers at the time of diagnosis

Lung function	Improvement		Deterioration	
	Continued smoking	Smoking cessation	Continued smoking	Smoking cessation
Subjects	30	16	30	16
Overall	5 (17)	5 (31)	17 (56)	8 (50)
FVC	5 (17)	4 (25)	7 (23)	2 (12.5)
FEV_1	5 (17)	3 (19)	13 (43)	4 (25)
$D_{L,CO}$	1/25 (4)	1/13 (8)	13/25 (52)	4/13 (31)

Data are presented as n or n (%). n=46. The lung function parameters represent all patients, unless otherwise specified. For each parameter, changes of ⩾10% in forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC), or of ⩾15% in diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) constituted improvement or deterioration. The overall lung function outcome was defined based on increases or decreases of ⩾10% in FEV_1 and/or FVC and/or of ⩾15% in $D_{L,CO}$. In case of discrepancies, the impaired parameter was used. p-values were not significant for any of the comparisons.

diagnosis did not differ between the patients who deteriorated (2,456±987 mL; 71±24% pred) and the patients who did not (2,840±796 mL; 82±20% pred). No factor at diagnosis could distinguish the subgroup of 10 patients whose FEV_1 deteriorated within the first 2 yrs of follow-up except that, surprisingly, their mean cumulative tobacco consumption was lower compared with the remaining patients (table 4). However, the hazard of early decline of FEV_1 was not statistically modified by tobacco consumption, either unadjusted (HR 0.94, 95% CI 0.88–1.02; p=0.1) or adjusted for age and sex (HR 0.94, 95% CI 0.86–1.02; p=0.11). Furthermore, no factor at diagnosis could differentiate between the patients whose FEV_1 decreased within the first 2 yrs and those in whom it declined later. Finally, smoking cessation had no influence on whether the FEV_1 decreased within the first 2 yrs (p=0.90).

A significant difference in the cumulative incidence of airflow obstruction according to the HRCT cystic score at diagnosis was observed (p<0.0001; table 5). In the multivariate model, however, only the FEV_1 % pred at diagnosis remained significantly associated with the incidence of airflow obstruction (p=0.0006). Thus, a smaller FEV_1 % pred at diagnosis was associated with a greater risk of developing airflow obstruction.

DISCUSSION

This is the largest cohort study evaluating the long-term variations in lung function and HRCT findings in patients with pulmonary LCH. We determined the rate and lung function deterioration profile of these patients and identified a sizeable group of patients who experienced dramatic declines in their FEV_1 values early in the course of the disease. We also provided additional information concerning the prognostic value of lung HRCTs, both at diagnosis and during follow-up.

Overall, lung function deteriorated in ~60% of the patients and improved in 20%. The evolution of the different lung function parameters was heterogeneous. $D_{L,CO}$ deteriorated in approximately half of the patients, and FEV_1 deteriorated in 40% of them, while FVC significantly decreased during follow-up in a minority of the patients. Strikingly, we identified two populations of

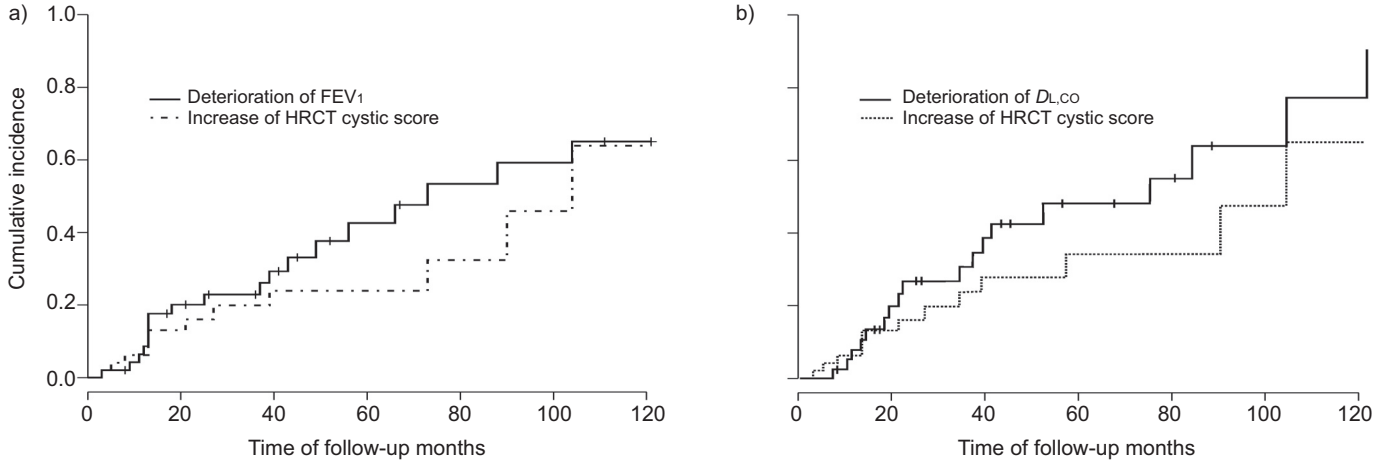

FIGURE 2. A comparison of the study population's estimated cumulative incidences of deterioration of lung function and high-resolution computed tomography (HRCT) cystic score variation over time. a) forced expiratory volume in 1 s (FEV_1); b) diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$). Although the two curves follow parallel courses, note that the increase in the extent of the cystic lesions did not precede either the FEV_1 or the $D_{L,CO}$ impairment.

TABLE 4 Characteristics of the patients whose forced expiratory volume in 1s (FEV_1) decreased within the first 2 yrs after their pulmonary Langerhans' cell histiocytosis diagnosis compared with the remaining study population

Characteristic	Decline of FEV_1 within 2 yrs	No decline of FEV_1 within 2 yrs	p-value
Subjects n	10	39	
At diagnosis			
Age yrs	28.1±8.6	31.5±7.5	0.24
Male sex	4 (40.0)	20 (51.3)	0.73
Smoking status			
Current smokers	8 (80.0)	38 (97.4)	0.10
Ex-smokers	2 (20.0)	1 (2.6)	
Exposure pack-years	11.0±9.4	24.4±20.0	0.02
TLC % pred[#]	99.4±15.9[+]	100.6±16.9	0.90
FVC % pred	86.3±18.9	89.8±18.7	0.79
FEV_1 % pred	74.7±21.6	78.3±22.2	0.65
FEV_1/FVC %	71.1±11.3	73.2±13.0	0.48
RV % pred[#]	137.1±52.4[+]	127.3±47.1[##]	0.69
RV/TLC % pred[#]	137.0±48.1[+]	123.6±35.0[##]	0.64
$D_{L,CO}$ % pred[#]	70.9±27.9[§]	60.6±20.9[¶¶]	0.39
HRCT nodular score	6.4±4.8	6.7±3.0	0.65
HRCT cystic score	13.1±7.4	11.6±5.7	0.61
During follow-up			
$D_{L,CO}$ deterioration[¶]	5/8 (62.5)[f]	13/32 (40.6)[++]	0.43
Smoking cessation	1/8 (12.5)	15/38 (39.5)	0.23

Data are presented as mean±SD or n (%), unless otherwise stated. The lung function parameters represent all patients, unless otherwise specified. TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography. [#]: at diagnosis, TLC and RV results were available for 47 patients and $D_{L,CO}$ for 42 patients; [¶]: serial $D_{L,CO}$ results were available for 40 patients; [+]: n=10; [§]: n=9; [f]: n=8; [##]: n=37; [¶¶]: n=33; [++]: n=32.

TABLE 5 Univariate prognostic analyses of the factors measured at diagnosis that were candidates for predicting the incidence of airway obstruction[#]

Characteristic	HR (95% CI)	p-value
Age per 10 yrs	0.93 (0.52–1.67)	0.81
Smoking per 10 pack-yrs	1.06 (0.87–1.28)	0.56
Dyspnoea	1.01 (0.42–2.39)	0.99
TLC % pred[¶]	1.17 (0.91–1.50)	0.22
FVC % pred[¶]	0.75 (0.57–0.99)	0.04
FEV_1 % pred[¶]	0.59 (0.45–0.77)	0.0001
FEV_1/FVC %[¶]	0.54 (0.42–0.69)	0.0001
RV % pred[¶]	1.16 (1.08–1.26)	0.0002
RV/TLC % pred[¶]	1.24 (1.11–1.39)	0.0002
$D_{L,CO}$ % pred[¶]	0.04 (0.03–0.47)	0.01
HRCT nodular score	0.91 (0.80–1.03)	0.13
HRCT cystic score	1.13 (1.05–1.21)	0.0009

HR: hazard ratio; TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography. [#]: A total of 21 (43%) out of 49 patients had an obstructive pattern (FEV_1/FVC <70%) at any time during the study; [¶]: the HR is calculated for 10% variations in the predicted values.

patients with different FEV_1 impairment profiles over time. Approximately half of these patients experienced a dramatic decline in their FEV_1 within the 2 yrs following diagnosis. The median rate of FEV_1 decline in these patients was markedly more pronounced than that reported for smokers and patients with chronic obstructive pulmonary disease (COPD) [17]. Unfortunately, we were unable to identify a predictive factor at diagnosis that identified this subgroup of patients.

Airway obstruction was the salient pattern of lung function defect observed both at diagnosis and during the course of the disease. This finding is consistent with the bronchiolar localisation of pulmonary LCH lesions [18] and with the functional pattern observed in other diffuse cystic lung diseases, such as lymphangiomyomatosis [19].

The $D_{L,CO}$ decline was isolated in some of the patients, which may suggest the development of pulmonary hypertension (PH), a known complication of pulmonary LCH [20–24]. Although echocardiography or right heart catheterisation results were not available for these patients, this assumption is consistent with a recent study we performed in patients with pulmonary LCH and PH, in whom isolated declines in $D_{L,CO}$ were associated with the development of PH [24].

In this large cohort, we confirmed that the extent of the HRCT cystic lesions is correlated with various lung function parameters [11–13]. Additionally, we found that the HRCT cystic score was both sensitive and specific for discriminating between

the patients with and without airflow obstruction, both at diagnosis and during follow-up. However, although the hazard for having airway obstruction was strikingly increased in the patients with high cystic CT scores, only the FEV_1 % pred at diagnosis remained a predictive factor for the incidence of airway obstruction in the multivariate analysis.

The extent of the nodular lesions decreased during follow-up, whereas the extent of the cystic lesions increased, as has been previously reported for smaller series [10, 13]. No patients had high nodular CT scores at the time of the last evaluation, whereas half the patients had a high or very high cystic CT score. Although this increase in the cystic CT score was correlated with deterioration in several lung function parameters, it did not precede the FEV_1 or the $D_{L,CO}$ decrease over time. Thus, the initial lung HRCT findings are useful for both the diagnosis and prognosis of pulmonary LCH, but our results suggest that routine serial CT scans add limited information to lung function measurements during patient follow-up.

Surprisingly, smoking cessation did not modify the pulmonary LCH outcomes. As this study was retrospective and no surrogate marker was available to ascertain smoking cessation, definitive conclusions should not be drawn from these results. The relatively small sample size (and thus, the limited statistical power) could also explain this negative finding. Obviously, continuing to smoke has several deleterious consequences for these patients, such as increased risk of COPD and lung cancer [25]. It should be stressed, however, that although improved pulmonary LCH has been reported in patients who have stopped smoking, the effect of smoking cessation on the outcome of the disease has not been rigorously evaluated [26].

This retrospective study has several limitations. As the patients were sequentially included during the study period, the follow-up time was variable. Although adequate statistical methods for time-to-event data were used, we cannot exclude a bias toward an over-representation of patients with unfavourable outcomes. It is also possible that the patients selected for this study may not have been fully representative of the general pulmonary LCH population, although the lung function at diagnosis of our patients was similar to the lung function reported in previous studies [5–8]. Finally, as systemic treatments were prescribed according to the physicians' discretion, we could not evaluate their effects on the pulmonary LCH outcomes. In a previous study, corticosteroid therapy was associated with poorer outcomes, probably as a result of selection bias towards more severe forms of the disease [6].

In summary, this study provides important clinical insights into the long-term lung function outcomes of patients with pulmonary LCH. In practice, serial lung function tests are important during follow-up. Lung function should be closely monitored during the first 2 yrs after diagnosis. A lung HRCT at diagnosis is informative, but routine serial CT scans seem less useful for managing these young patients, in whom the radiation burden is a concern. Prospective studies are needed to better characterise the patients who progress soon after diagnosis and to assess the effects of controlled smoking cessation on pulmonary LCH outcomes.

STATEMENT OF INTEREST

A statement of interest for D. Valeyre can be found at ww.erj.ersjournals.com/site/misc/statements.xhtml

ACKNOWLEDGEMENTS

Author affiliations are as follows. A. Tazi, K. Marc and G. Lorillon: Reference Centre for Langerhans Cell Histiocytosis, University Paris Diderot, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Saint-Louis Hospital, Paris, France; S. Dominique: University of Rouen, Pulmonary Dept, Charles Nicolle Hospital, Rouen, France; C. de Bazelaire and J. Frija: University Paris Diderot, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Radiology Dept, Saint-Louis Hospital, Paris, France; B. Crestani: University Paris Diderot, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Bichat Hospital, Paris, France; T. Chinet: University of Versailles Saint Quentin en Yvelines, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Ambroise Paré Hospital, Paris, France; D. Israel-Biet: University Paris 5, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, European Georges Pompidou Hospital, Paris, France; J. Cadranel: University Paris 6, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Tenon Hospital, Paris, France; D. Valeyre: University Paris 13, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Avicenne Hospital, Paris, France; S. Chevret: INSERM U 717, University Paris Diderot, Sorbonne Cité, Assistance Publique Hôpitaux de Paris, Biostatistics Dept, Saint-Louis Hospital, Paris, France.

The authors thank M. Mao (Assistance Publique Hôpitaux de Paris, Pulmonary Dept, Saint-Louis Hospital, Paris, France) and E. Savariau (Institut Universitaire d'Hématologie, Service d'Infographie, Saint-Louis Hospital, Paris, France) for their technical assistance.

REFERENCES

1 Abbott GF, Rosado-de-Christenson ML, Franks TJ, *et al.* From the archives of the AFIP: pulmonary Langerhans cell histiocytosis. *Radiographics* 2004; 24: 821–841.
2 Sundar KM, Gosselin MV, Chung HL, *et al.* Pulmonary Langerhans cell histiocytosis: emerging concepts in pathobiology, radiology, and clinical evolution of disease. *Chest* 2003; 123: 1673–1683.
3 Tazi A. Adult pulmonary Langerhans' cell histiocytosis. *Eur Respir J* 2006; 27: 1272–1285.
4 Vassallo R, Ryu JH, Colby TV, *et al.* Pulmonary Langerhans'-cell histiocytosis. *N Engl J Med* 2000; 342: 1969–1978.
5 Basset F, Corrin B, Spencer H, *et al.* Pulmonary histiocytosis X. *Am Rev Respir Dis* 1978; 118: 811–820.
6 Delobbe A, Durieu J, Duhamel A, *et al.* Determinants of survival in pulmonary Langerhans' cell granulomatosis (histiocytosis X). Groupe d'Etude en Pathologie Interstitielle de la Societe de Pathologie Thoracique du Nord. *Eur Respir J* 1996; 9: 2002–2006.
7 Schonfeld N, Frank W, Wenig S, *et al.* Clinical and radiologic features, lung function and therapeutic results in pulmonary histiocytosis X. *Respiration* 1993; 60: 38–44.
8 Travis WD, Borok Z, Roum JH, *et al.* Pulmonary Langerhans cell granulomatosis (histiocytosis X). A clinicopathologic study of 48 cases. *Am J Surg Pathol* 1993; 17: 971–986.
9 Vassallo R, Ryu JH, Schroeder DR, *et al.* Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. *N Engl J Med* 2002; 346: 484–490.
10 Brauner MW, Grenier P, Tijani K, *et al.* Pulmonary Langerhans cell histiocytosis: evolution of lesions on CT scans. *Radiology* 1997; 204: 497–502.
11 Canuet M, Kessler R, Jeung MY, *et al.* Correlation between high-resolution computed tomography findings and lung function in pulmonary Langerhans cell histiocytosis. *Respiration* 2007; 74: 640–646.
12 Moore AD, Godwin JD, Muller NL, *et al.* Pulmonary histiocytosis X: comparison of radiographic and CT findings. *Radiology* 1989; 172: 249–254.

13 Abbritti M, Mazzei MA, Bargagli E, *et al*. Utility of spiral CAT scan in the follow-up of patients with pulmonary Langerhans cell histiocytosis. *Eur J Radiol* 2011; [Epub ahead of print DOI: 10.1016/j.ejrad.2011.04.018].
14 Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 1–100.
15 Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
16 Bradley B, Branley HM, Egan JJ, *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; 63: Suppl. 5, v1–v58.
17 Kohansal R, Martinez-Camblor P, Agusti A, *et al.* The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med* 2009; 180: 3–10.
18 Kambouchner M, Basset F, Marchal J, *et al.* Three-dimensional characterization of pathologic lesions in pulmonary langerhans cell histiocytosis. *Am J Respir Crit Care Med* 2002; 166: 1483–1490.
19 McCormack FX. Lymphangioleiomyomatosis: a clinical update. *Chest* 2008; 133: 507–516.
20 Chaowalit N, Pellikka PA, Decker PA, *et al.* Echocardiographic and clinical characteristics of pulmonary hypertension complicating pulmonary Langerhans cell histiocytosis. *Mayo Clin Proc* 2004; 79: 1269–1275.
21 Dauriat G, Mal H, Thabut G, *et al.* Lung transplantation for pulmonary Langerhans' cell histiocytosis: a multicenter analysis. *Transplantation* 2006; 81: 746–750.
22 Fartoukh M, Humbert M, Capron F, *et al.* Severe pulmonary hypertension in histiocytosis X. *Am J Respir Crit Care Med* 2000; 161: 216–223.
23 Hamada K, Teramoto S, Narita N, *et al*. Pulmonary veno-occlusive disease in pulmonary Langerhans' cell granulomatosis. *Eur Respir J* 2000; 15: 421–423.
24 Le Pavec J, Lorillon G, Jais X, *et al.* Pulmonary arterial hypertension associated with pulmonary Langerhans cell histiocytosis: impact of pulmonary hypertension therapy. *Am J Respir Crit Care Med* 2011; 183: A5916.
25 Sadoun D, Vaylet F, Valeyre D, *et al.* Bronchogenic carcinoma in patients with pulmonary histiocytosis X. *Chest* 1992; 101: 1610–1613.
26 Vassallo R, Ryu JH. Tobacco smoke-related diffuse lung diseases. *Semin Respir Crit Care Med* 2008; 29: 643–650.