Long-term outcomes of adult pulmonary Langerhans cell histiocytosis: a prospective cohort

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Shareable abstract (@ERSpublications)
The long-term prognosis of PLCH is significantly more favourable than has previously been reported. Patients must be closely monitored after diagnosis to detect and manage severe complications early. https://bit.ly/3asyshv

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Abstract

Background The long-term outcomes of adult pulmonary Langerhans cell histiocytosis (PLCH), particularly survival, are largely unknown. Two earlier retrospective studies reported a high rate of mortality, which contrasts with our clinical experience.

Methods To address this issue, all patients with newly diagnosed PLCH referred to the French national reference centre for histiocytoses between 2004 and 2018 were eligible for inclusion. The primary outcome was survival, which was defined as the time from inclusion to lung transplantation or death from any cause. Secondary outcomes included the cumulative incidences of chronic respiratory failure (CRF), pulmonary hypertension (PH), malignant diseases and extrapulmonary involvement in initially isolated PLCH. Survival was estimated using the Kaplan–Meier method.

Results 206 patients (mean age 39±13 years, 60% female, 95% current smokers) were prospectively followed for a median duration of 5.1 years (IQR 3.2–7.6 years). Of these, 12 patients (6%) died. The estimated rate of survival at 10 years was 93% (95% CI 89–97%). The cumulative incidences of CRF and/or PH were <5% at both 5 and 10 years, and 58% of these patients died. 27 malignancies were observed in 23 patients. The estimated standardised incidence ratio of lung carcinoma was 17.0 (95% CI 7.45–38.7) compared to an age- and sex-matched French population. Eight (5.1%) of the 157 patients with isolated PLCH developed extrapulmonary involvement.

Conclusion The long-term prognosis of PLCH is significantly more favourable than has previously been reported. Patients must be closely monitored after diagnosis to detect severe complications early.

Introduction

Langerhans cell histiocytosis (LCH) is a rare neoplastic inflammatory disorder driven by activating mutations in the mitogen-activated kinase (MAPK) pathway in $CD1a^+$ cells infiltrating the involved tissues [1–3]. Adult pulmonary LCH (PLCH) occurs almost exclusively in current or ex-smokers of both sexes, with a peak incidence between 20 and 40 years of age [4].

The prognosis of PLCH is highly variable and difficult to predict in an individual patient, ranging from spontaneous resolution, particularly after smoking cessation, to chronic respiratory failure (CRF) and pulmonary hypertension (PH), ultimately leading to lung transplantation or death [4]. In a small

multicentre retrospective study, approximately half of the patients had worse lung function within 5 years after diagnosis [5]. We previously conducted a prospective study on the 2-year natural history of PLCH and identified a subgroup of patients whose lung function deteriorated early after diagnosis [6].

In contrast, the long-term outcomes of PLCH remain largely unknown. Two earlier retrospective studies reported a high rate of mortality among PLCH patients [7, 8], which contrasts with our clinical experience. The results of these studies should be interpreted with caution given the potential selection bias related to their retrospective design. In addition, although CRF and PH may develop in patients with PLCH [4, 7–10], the incidences of these complications during the course of the disease have not been assessed. Similarly, whether and to what extent patients with isolated PLCH secondarily develop extrapulmonary LCH localisations that affect their outcome has not been studied [11, 12]. Finally, the incidence of malignancies, particularly lung cancer, in PLCH patients [8, 13–15] warrants further evaluation.

In the present study, we took advantage of our registry-based prospective large cohort to address these issues with the main objective of determining the survival of these patients, who are generally young, and determining the factors at diagnosis that are associated with mortality.

Methods

Study design

All patients with PLCH newly diagnosed in adulthood (*i.e.* ⩾18 years old) who were referred between January 2004 and April 15, 2018, were eligible for inclusion in the study. The study ended on October 31, 2018.

The diagnosis of PLCH was either histologically confirmed in a biopsy of an involved tissue or based on the combination of an appropriate clinical picture, a typical nodulo-cystic pattern on lung high-resolution computed tomography (HRCT) and the exclusion of alternative diagnoses [6] (see details on the diagnostic process in supplementary methods).

The study was approved by the Institutional Review Board of the French Institute of Medical Research and Health (IRB number 909207) and was registered with www.ClinicalTrials.gov (NCT04665674). All patients provided written informed consent for the use of their medical records for research.

Data collection

Patient medical records were retrieved from the prospective standardised dedicated database and retrospectively analysed (supplementary methods).

The patients were classified as having isolated PLCH or multisystem (MS) disease in case of extrapulmonary involvement [16]. All lung HRCT scans performed at the time of inclusion in the study were analysed by a radiologist (C de M) and two chest physicians (AT and AB) to determine the global nodular and cystic scores and categorised into subgroups as previously described [5].

Lung function tests comprised spirometry, plethysmography and diffusion of carbon monoxide (D_{LCO}) and were performed according to the European standards [17]. The predictive values were determined as previously described [6].

CRF was defined as a sustained decreased arterial oxygen tension (P_{aO_2}) on room air and/or the long-term use of supplemental oxygen [18]. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines were used for the diagnosis of PH [19, 20].

End-points

The primary outcome was survival, which was defined as the time from inclusion to lung transplantation or death from any cause.

Secondary outcomes included the cumulative incidences of CRF, PH, extrapulmonary LCH localisations and malignancies during the study period.

Statistical analysis

Descriptive statistics are presented as the mean±SD, median (interquartile range (IQR)) or n (%).

Survival from the date of diagnosis of PLCH to the date of lung transplantation, death or last follow-up was analysed using the Kaplan–Meier method and compared with the values in the general French

population matched by sex and age according to published actuarial tables (www.insee.fr). The one-sample log-rank test was used to compare observed and expected survival. The standardised mortality ratio (SMR) and its 95% CI were also calculated [21]. Univariable and multivariable Cox proportional hazards models were used for analysis of factors predictive of survival. To address time-varying measurements over time, a Cox model with a time-dependent covariate was used, in which all the predictors selected in the previous multivariable model were considered time-varying rather than time-fixed. A last observation carried forward method was used to impute missing forced expiratory volume in 1 s (FEV_1) data over time.

The cumulative incidences of CRF, PH, extrapulmonary involvement and malignancies were estimated separately in a competing framework, taking into account death and lung transplantation that occurred before the event of interest as competing risk events.

The standardised incidence ratio (SIR), corresponding to the ratio of the number of observed to the number of expected cases of lung cancer, was used as a measure of the relative risk of lung cancer in the study population. The expected number of cases of cancer was calculated by multiplying the age-, sex- and calendar year-specific cancer incidence in the French general population with the corresponding person-time at risk in our cohort [22]. The 95% CIs of the SMR and SIR were estimated assuming a Poisson distribution of the observed cases.

Statistical analyses were performed using R software (www.R-project.org/). All tests were two-sided with $p<0.05$ denoting statistical significance.

Results

Study population at diagnosis

209 patients fulfilled the inclusion criteria. Three patients were excluded after a review of their medical records, in which respiratory bronchiolitis with interstitial lung disease was retained as the final diagnosis.

The characteristics at diagnosis of the 206 patients retained in the study are shown in table 1. PLCH was preceded by the involvement of another organ in four patients (1.9%) (bone, n=2; diabetes insipidus, n=2) with a median interval of −3.4 years (IQR −6.5 to −2.3 years).

There were 15 smoking-related diseases concurrently present in 14 patients: COPD (n=4), respiratory bronchiolitis with interstitial lung disease (n=1), ischaemic cardiomyopathy (n=4), ischaemic cerebrovascular disease (n=4) and arteritis of the lower limbs (n=2). Other relevant comorbidities present in the cohort were arterial hypertension (n=10), asthma (n=4), diabetes mellitus (n=6), obesity (n=14), obstructive sleep apnoea (n=2) and gastro-oesophageal reflux disease (n=4). There were 11 patients with associated autoimmune disorders: thyroiditis (n=5), multiple sclerosis (n=2), systemic lupus erythematosus (n=1), autoimmune hepatitis (n=1), autoimmune haemolytic anaemia (n=1) and ankylosing spondylitis (n=1).

Lung HRCT scans were available for 196 patients (the diagnosis was histologically confirmed in all remaining 10 patients for whom HRCT scans were missing). HRCT cystic scores were low to intermediate in 175 patients (89.3%), denoting the recent development of PLCH (table 1). As expected for recent PLCH, most patients had a typical nodulo-cystic pattern on lung HRCT, which explains why only 32% of patients had histologic confirmation (table 1).

Lung function assessments were not available at diagnosis for 39 patients. Of these, 18 patients had a pneumothorax, 18 underwent lung function measurements >6 months after diagnosis and three patients were lost to follow-up soon after diagnosis (their vital status could be assessed through a telephone call at the time the study ended). Airflow obstruction was present in 21 patients (13.3%).

Follow-up

Patients were followed for a median of 5.1 years (IQR 3.2–7.6 years). At study end, 188 patients (91%) were still being followed. For the remaining 18 patients, the median time of follow-up was 4.6 years (IQR 3.4–9.3 years).

During the study period, among the 196 current smokers at diagnosis, 76 patients (38.8%) were weaned from tobacco, and one ex-smoking patient resumed smoking during his follow-up. 17 patients (8.3%) received systemic treatment for their disease, which consisted of steroids alone (n=6), vinblastine (n=2), cladribine alone (n=7), cladribine followed by steroids and vinblastine (n=1), and cladribine followed by the mitogen-activated extracellular signal-regulated kinase inhibitor trametinib (n=1). One patient underwent lung transplantation 2.7 years after the diagnosis of PLCH.

TABLE 1 Characteristics of the pulmonary Langerhans cell histiocytosis (PLCH) patients at the time of diagnosis

Characteristic	
Subjects, n	206
Age, years	39.3±12.8
Sex	
Female	123 (59.7)
Male	83 (40.3)
Smoking status	
Current smokers	196 (95.1)
Ex-smokers	8 (3.9)
Pack-years	21.7±15.9
Non-smokers[#]	2 (1)
Cannabis consumption[¶]	35 (17.0)
Histological diagnosis[+]	66 (32%)
LCH extent	
Isolated PLCH	157 (76.2)
Multisystem PLCH[§]	49 (23.8)
Bone	35
Diabetes insipidus	11
Skin	6
Liver	2
Other[f]	2
History of pneumothorax	24 (11.7)
Before diagnosis	6
Median time (IQR), months	2.8 (0.8–5.9)
At the time of diagnosis[##]	18
Chronic respiratory failure	5 (2.4)
Long-term oxygen supplementation	2
Pulmonary hypertension	2
HRCT pattern, n=196[¶¶]	
Nodulo-cystic	176 (89.8)
Nodular (cavitated)	6 (3.1)
Cystic	14 (7.1)
HRCT nodular score	6.8±4.8
HRCT nodular score subgroup	
Low (0–6)	116 (59.2)
Intermediate (7–12)	54 (27.6)
High (13–18)	26 (13.3)
HRCT cystic score	6.8±4.5
HRCT cystic score subgroup	
Low (0–6)	136 (69.4)
Intermediate (7–12)	39 (19.9)
High (13–18)	15 (7.7)
Very high (19–24)	6 (3.1)
TLC % pred, n=152	102.2±15.9
RV % pred, n=150	123.3±34.6
RV/TLC % pred, n=150	116.1±26.0
FEV_1 % pred, n=167	89.6±18.6
FVC % pred, n=158	95.1±18.7
FEV_1/FVC %, n=158	79.9±10.2
D_{LCO} % pred, n=127	63.4±16.8
Lung function patterns[++]	
Normal spirometry	85 (53.8)
Obstruction	21 (13.3)
Restriction	14 (9.2)
Air trapping	59 (39.3)
Hyperinflation	21 (13.8)
D_{LCO} <80% pred	103 (81.1)

Data are expressed as the mean±SD or n (%), unless otherwise specified. LCH: Langerhans cell histiocytosis; IQR: interquartile range; HRCT: high-resolution computed tomography; TLC: total lung capacity; RV: residual volume; FEV_1 : forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO} : diffusing capacity for carbon monoxide; % pred: % predicted. [#]: one patient had multisystem PLCH histologically confirmed on a skin biopsy, one had a typical nodulo-cystic pattern on lung HRCT and was exposed to import passive smoking; [¶]: all smokers; [+]: surgical lung biopsy (n=44) and extrathoracic LCH localisation (n=22); [§]: nine patients had >1 extra-pulmonary LCH localisation; [f]: peripheral lymph node n=1, central nervous system n=1; [##]: four patients had pneumothorax before and at diagnosis; [¶¶]: histological confirmation in 26%, 33% and 64% of patients with nodulo-cystic, nodular (cavitated) and cystic lung HRCT pattern, respectively; [++]: restriction was defined as TLC <80%, air trapping as RV/TLC ratio >120% of the predicted values, obstruction as a FEV_1/FVC ratio <70% and hyperinflation as a TLC >120% of predicted values.

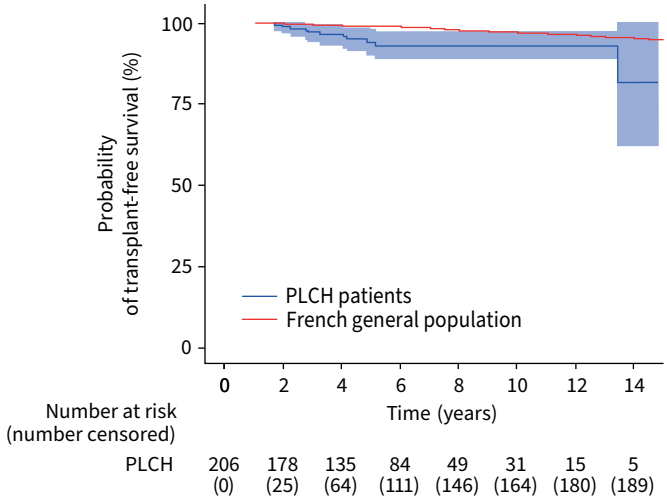

FIGURE 1 Kaplan–Meier estimates of expected and observed survival of the 206 pulmonary Langerhans cell histiocytosis (PLCH) patients during the study period. The shaded area represents 95% confidence intervals. The red line indicates expected survival for the age- and sex-matched French general population ($p<0.001$, one-sample log-rank test).

Survival

12 patients (6%) died during the study, including one patient who died 1 year after lung transplantation. The median time from PLCH diagnosis to transplantation or death was 3.0 years (IQR 2.1–4.3 years). The survival curve of the cohort of PLCH patients is shown in figure 1. The estimated survival rates at 5 and 10 years after PLCH diagnosis were 94% (95% CI 90–98%) and 93% (95% CI 89–97%), respectively. The median survival was not reached during the study period. The observed survival was significantly lower than that expected for the age- and sex-matched French general population ($p<0.001$) with an estimated SMR of 4.32 (95% CI 2.29–8.17). The period of patients' follow-up was not long enough to provide a valid estimation of the life expectancy after diagnosis of PLCH. However, the restricted mean survival time (*i.e.* life expectancy restricted to a fixed interval of time) at 10 years after diagnosis was estimated as 4 months lower than that of the age- and sex-matched French general population. Table 2 details the characteristics of the patients who died during the study. Seven (58.3%) of the deceased patients had prior CRF and/or PH.

TABLE 2 Characteristics of the 12 pulmonary Langerhans cell histiocytosis (PLCH) patients who died during the study period

Patient	Age at diagnosis, years	Sex	Smoking status at diagnosis	Pack-years at diagnosis	Extent of LCH	CRF	PH	Time to death, years	Cause of death
1	58	M	Former	20	Isolated	Yes	Yes	13	Lung cancer
2	35	M	Current	10	Isolated	No	No	5	Lung cancer
3	35	F	Current	14	Multisystem	No	No	5	Lung cancer
4	49	F	Former	20	Isolated	No	No	2	Lung cancer
5	33	M	Current	30	Isolated	Yes	Yes	2	Respiratory failure
6	47	M	Current	80	Isolated	Yes	Yes	2	Respiratory failure
7	48	M	Current	30	Isolated	Yes	Yes	4	Respiratory failure
8[#]	38	F	Former	20	Multisystem	Yes	Yes	4	Pulmonary mucormycosis
9[¶]	72	F	Current	50	Isolated	Yes	Yes	4	CMML
10	49	F	Current	60	Isolated	No	Yes	3	Acute coronary syndrome
11	79	M	Former	60	Multisystem	No	No	3	Bacterial pneumonia
12	87	M	Non-smoker	0	Multisystem	No	No	2	Heart failure

LCH: Langerhans cell histiocytosis; CRF: chronic respiratory failure; PH: pulmonary hypertension; M: male; F: female; CMML: chronic myelomonocytic leukaemia. [#]: died 1 year after lung transplantation; [¶]: treated with cladribine.

TABLE 3 Multivariate analyses of the characteristics of pulmonary Langerhans cell histiocytosis (PLCH) patients at diagnosis and during follow-up associated with survival

Cox model with covariates at diagnosis			Cox model with all characteristics introduced as time-dependent covariates		
Characteristic	**HR (95% CI)**	**p-value**	**Characteristic**	**HR (95% CI)**	**p-value**
Age	1.09 (1.03–1.16)	0.004	Age	1.07 (1.01–1.13)	0.017
FEV_1[#]	0.97 (0.94–1.00)	0.042	FEV_1	0.96 (0.92–1.00)	0.046
Smoking exposure, pack-years	1.00 (0.96–1.06)	0.85	Smoking status	1.54 (0.42–5.60)	0.52
			Systemic treatment[¶]	1.53 (0.36–6.54)	0.57

HR: hazard ratio; FEV_1: forced expiratory volume in 1 s. [#]: a lower FEV_1 was associated with an increased risk of mortality; [¶]: 17 patients received systemic treatment for Langerhans cell histiocytosis.

The results of univariable analyses of patient characteristics at diagnosis that were associated with survival are detailed in supplementary table S1. In the multivariable model, only older age and a lower FEV_1 (expressed as percentage of predicted values) at diagnosis influenced the risk of mortality (table 3). The results of the univariable Cox model used to assess the impact of time-dependent variables (smoking status, systemic treatment) on survival during follow-up are detailed in supplementary table S2. In this multivariable Cox model involving 167 patients with available FEV_1 measurements at diagnosis, only older age and a lower FEV_1 were still associated with the risk of mortality (table 3).

CRF and PH

12 patients (5.8%) had CRF, which was present at the time of PLCH diagnosis in five patients and developed during follow-up in seven patients. The long-term use of supplemental oxygen was recorded for seven patients (at diagnosis, n=2; during follow-up, n=5). For patients who did not receive oxygen, the median P_{aO_2} was 59 mmHg (IQR 57–63 mmHg). The cumulative incidence of CRF at both 5 and 10 years was 3.9% (95% CI 1.0–6.8%) (figure 2a). Among all patients with CRF, eight also had PH, which was confirmed by right heart catheterisation in seven patients (mean pulmonary artery pressure 29.8±7.8 mmHg) and determined to be probable PH on Doppler echocardiography in the remaining patient based on the tricuspid regurgitation velocity (TRV) (3.31 m/s) and systolic arterial pulmonary pressure (sPAP) (53 mmHg). Two additional patients had probable PH on Doppler echocardiography and did not have CRF (TRV 2.95 m/s, sPAP 40 mmHg and TRV 3.04 m/s, sPAP 47 mmHg, respectively). Thus, PH was observed in 10 patients and was present at diagnosis in two of them, whereas the remaining eight patients developed PH during follow-up. Only one patient was off-label treated with bosentan. The resulting cumulative incidence of PH at both 5 and 10 years was 4.5% (95% CI 1.4–7.6%) (figure 2b). The characteristics of patients with CRF and/or PH are detailed in supplementary table S3.

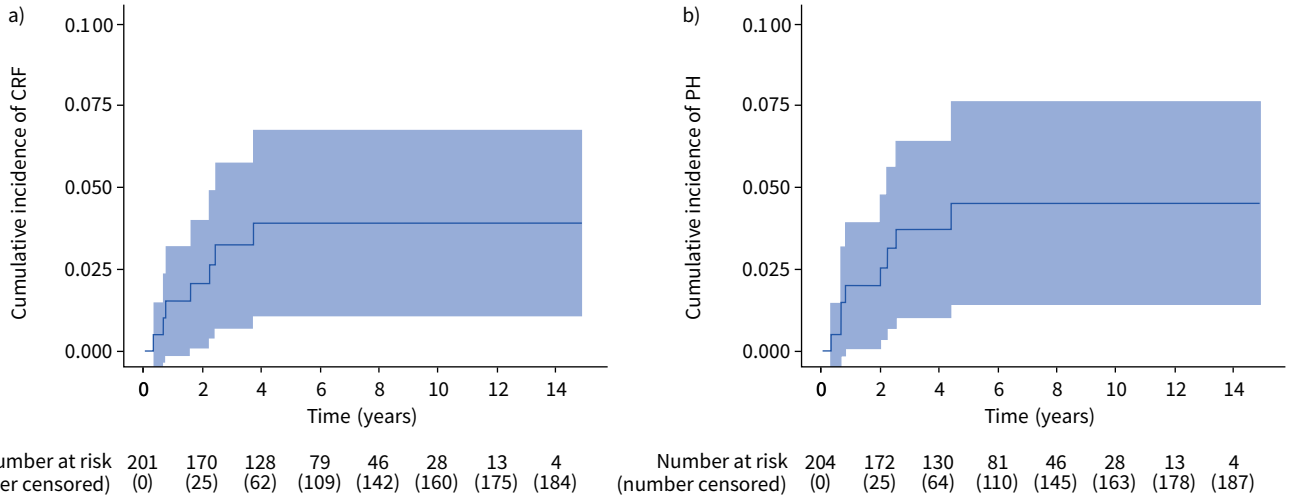

FIGURE 2 Cumulative incidence of a) chronic respiratory failure (CRF) and b) pulmonary hypertension (PH) among the pulmonary Langerhans cell histiocytosis patients during the study period. Shaded areas represent 95% confidence intervals.

Extrapulmonary LCH involvement

157 patients had isolated PLCH at diagnosis. Eight (5.1%) of these patients developed extrapulmonary LCH during follow-up. The cumulative incidence of extrapulmonary LCH was 5.9% (95% CI 1.8–10.1%) at both 5 and 10 years (supplementary figure S1).

Malignant diseases

27 malignancies were observed in 23 patients (11%). These malignancies occurred before (n=11, median time −3.1 years, IQR −6.2 to −2.1 years), concurrent with (n=6) or after (n=10, median time 4.1 years, IQR 3.1–5.0 years) the diagnosis of PLCH. No patients had previously received chemotherapy for PLCH (supplementary table S4).

A total of 11 lung carcinomas (seven after PLCH diagnosis) were observed (table 4). Six patients were current smokers and five were ex-smokers at the time of the diagnosis of lung cancer, which occurred at a mean age of 49.5±8.4 years. The smoking habits of these patients at the time of the diagnosis of lung carcinoma were as follows: age of smoking initiation 19±6.9 years; smoking duration, 26±7 years; mean number of cigarettes/day, 18.2±8; and cumulative tobacco consumption, 27±20 pack-years. The five ex-smokers had ceased smoking for a median duration of 4 years (IQR 3–5 years) before the diagnosis of lung carcinoma.

Among the 202 PLCH patients without previous or concurrent lung carcinoma at diagnosis, the cumulative incidences of lung cancer at 5 and 10 years were 2.5% (95% CI 0.0–5.0%) and 4.9% (95% CI 0.8–9.0%), respectively (supplementary figure S2). Compared with the expected number of lung cancer cases in an age- and sex-matched French population, the estimated SIR was 17.0 (95% CI 7.4–38.7). Of note, this comparison was not matched according to smoking habits, because no such data are available for the French general population.

Discussion

In this prospective cohort study evaluating the long-term outcomes in adult PLCH patients, we found the following results: 1) the estimated 10-year survival was 93%; 2) CRF and PH occurred in a minority of patients early in the course of the disease; 3) in patients with initially isolated PLCH, extrapulmonary involvement rarely occurred during follow-up; and 4) PLCH patients had a high risk of malignancies, particularly lung carcinoma.

Although the survival in our cohort was significantly shorter than that in the French general population, our results are reassuring compared to those previously reported in the two earlier retrospective studies. In the present study, the estimated survival rate at 10 years was 93%. Notably, most deaths in our cohort occurred early in the course of PLCH, within a median of 3 years.

TABLE 4 Characteristics of the 11 patients with lung carcinoma observed in the cohort of pulmonary Langerhans cell histiocytosis (PLCH) patients

Patient	Age at PLCH diagnosis, years	Sex	Type of lung carcinoma	Time to PLCH diagnosis, years	Age at diagnosis of lung carcinoma, years	Smoking status, pack-years	Treatment of lung carcinoma	Status
1	58	M	Undifferentiated large cell carcinoma	1	59	19	Chemotherapy +radiation	Dead
2	35	M	Adenocarcinoma	4.7	40	10	Palliative care	Dead
3	35	F	Adenocarcinoma	5.1	40	55	Palliative care	Dead
4	49	F	Adenocarcinoma	Concurrent	49	21	EGFR inhibitor	Dead
13	45	F	Small cell carcinoma	−0.6	45	30	Chemotherapy +radiation	Alive
14	49	F	Adenocarcinoma	Concurrent	49	15	Surgery	Alive
15	44	F	Adenocarcinoma	Concurrent	44	12	Surgery	Alive
16	42	M	Adenocarcinoma	1.5	44	26	Surgery	Alive
17	65	M	Squamous cell carcinoma	3	68	75	Chemotherapy	Alive
18	43	M	Adenocarcinoma	6.9	50	23	Surgery +chemotherapy	Alive
19	41	M	Adenocarcinoma	10.1	51	18	Surgery	Alive

M: male; F: female; EGFR: epidermal growth factor receptor.

The survival of our patients was clearly better than the 74% and 64% survival rates at 5 and 10 years, respectively, reported in one study [8] and the 13-year median survival duration reported in the other study [7]. Of note, the median duration of follow-up in those two studies was similar to [7] or slightly shorter than [8] the duration of follow-up in our study. Both studies had smaller sample sizes and were retrospective, which may have introduced selection bias. Importantly, lung CT was either not performed in any patient [7] or only performed in 28% of the patients [8]. Routine lung CT allows PLCH to be identified at an early stage, as highlighted by the minority of patients in our series having a high lung cystic score at imaging [6]. Thus, the patients included in those two retrospective studies most likely had more severe disease at diagnosis than those in our cohort. Concordantly, lung function at diagnosis was significantly more impaired in the patients in these studies than in our patients [7, 8]. Finally, although we confirmed that an older age at diagnosis is associated with an increased risk of mortality in PLCH patients, only FEV_1 was predictive of survival among the lung function parameters [7, 8]. Of note, we have recently shown that the *BRAF* status of PLCH lesions is not associated with survival [3].

Only a minority (<5%) of our patients developed CRF, which was frequently associated with PH and required the long-term use of supplemental oxygen in most cases. This rate was significantly lower than the 20% reported by Delobbe *et al.* [7] and the 15% of patients who died from respiratory failure in the Vassallo *et al.* [8] study. Based on the current guidelines [19], the estimated incidence of PH is 4.5% and is mostly secondary to chronic hypoxemia but may be related to specific PLCH vasculopathy in some cases [23, 24]. Because the median time of follow-up of this study was 5.1 years, it is possible that our results underestimate the occurrence of PH during longer follow-up. These complications are associated with a poor prognosis, given that ~60% of the patients who died during this study had CRF and/or PH. Both CRF and PH occurred early in the course of the disease, either at the time of diagnosis or within 5 years of follow-up. This finding emphasises the importance of the close monitoring of PLCH patients in the first years after diagnosis to detect these complications early.

An important result for clinical practice was the rare development of extrapulmonary LCH localisations during follow-up in patients with initially isolated PLCH. In these patients, the performance of extrathoracic investigations should be guided by clinical suspicion.

A major concern in PLCH patients is the association with malignancies. The increased risk of both haematological and solid cancers in patients with LCH, including PLCH, has been identified previously [2, 8, 13–15, 25–29]. However, the type and rate of these malignancies vary widely according to the extent of LCH, the selected population and the treatment (chemotherapy or radiation) the patients eventually received for LCH. Here, haematological malignancies accounted for seven (30%) of the 27 observed neoplasms and did not occur after the diagnosis of PLCH during the study period. The reasons that patients with LCH, including PLCH, are prone to developing haematological malignancies remain unclear. An increased rate of myeloid neoplasia mutations was reported in patients with Erdheim–Chester disease, a MAPK-driven non-Langerhans cell histiocytic disorder [30], but we rarely identified such alterations in PLCH lesions [3]. Alternatively, LCH and myeloid malignancies may share a common progenitor clone [31–33], particularly when the diseases occur concurrently.

Lung carcinoma was by far the most common solid neoplasm observed in our cohort, and it is a major concern for young patients who smoke. Lung cancer may be diagnosed simultaneously with PLCH, but most patients developed lung cancer during follow-up.

Sadoun *et al.* [14] reported five cases of lung carcinoma in a retrospective series of 93 adult PLCH patients and attributed this increased proportion to the particularly heavy smoking habits (mean pack-years 64.7±13) in the patients who developed lung cancer. Although smoking was also clearly a determining risk factor for lung cancer in our patients, additional factors may further increase this risk. Our patients had a relatively lower cumulative tobacco consumption (mean pack-years 27±20) at the time of lung carcinoma. The mean age at the time of the diagnosis of lung cancer was 50 years, which is 10–15 years younger than the mean age at the time of the diagnosis lung cancer in France [34]. Host-related predisposing factors may possibly contribute to the increased risk of lung cancer in PLCH patients [3, 35]. However, PLCH patients undergo lung CT more frequently than the general population, which could allow an earlier detection of lung carcinoma. Further studies are needed to evaluate whether low-dose lung cancer screening CT scanning would be useful in PLCH patients.

Our study has several limitations. Because the median duration of patient follow-up was 5.1 years, our results do not necessarily reflect PLCH outcome over a longer time. Although our cohort included a large number of patients, the population was from a single centre, which raises the question of the

generalisability of our results. However, this cohort was composed of patients from across France who were referred to the national referral centre for histiocytoses, and most likely reflects the clinical picture of PLCH in France. We also did not identify the factors associated with the occurrence of CRF/PH and lung carcinoma because these analyses were not part of our study plan. The multiplicity of statistical comparisons would have limited the value of such analyses.

In summary, the results of our study are important for the information given to patients with this rare disease. Survival was significantly better than has previously been reported. At the same time, CRF and lung cancer accounted for most deaths, making smoking cessation mandatory in these patients. Close follow-up during the first 5 years after diagnosis is essential for early detection of severe respiratory complications. Further studies are needed to identify the factors associated with the development of CRF and PH as well as the increased risk of lung cancer in PLCH patients.

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The study was registered with www.ClinicalTrials.gov (NCT04665674). Requests for data supporting the results reported in the current study will be reviewed on an individual basis by the director of the hospital clinical trial unit, and data will be available following publication.

Conflict of interest: A. Benattia has nothing to disclose. E. Bugnet has nothing to disclose. A. Walter-Petrich has nothing to disclose. C. de Margerie-Mellon has nothing to disclose. V. Meignin has nothing to disclose. A. Seguin-Givelet reports personal fees for lectures from Medtronic and AstraZeneca, outside the submitted work. G. Lorillon reports travel grants from Vitalaire, outside the submitted work. S. Chevret has nothing to disclose. A. Tazi reports personal fees for lectures from Chiesi and BMS, and travel grants from Vitalaire, AstraZeneca, Boehringer Ingelheim and Teva, outside the submitted work.

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