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Long-term Outcomes of Adult Pulmonary Langerhans Cell Histiocytosis: A Prospective Cohort

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Take-home message

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

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 newly diagnosed PLCH patients 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 extra-pulmonary involvement in initially isolated PLCH. Survival was estimated using the Kaplan-Meier method.

Results: Two hundred six patients (mean age: 39 ± 13 years, 60% females, 95% current smokers) were prospectively followed for a median duration of 5.1 years (interquartile range [IQR], 3.2 to 7.6). Twelve (6%) patients died. The estimated rate of survival at 10 years was 93% (95% confidence interval [CI], 89-97). The cumulative incidences of CRF and/or PH were less than 5% at both 5 and 10 years, and 58% of these patients died. Twenty-seven malignancies were observed in 23 patients. The estimated standardized 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 extra-pulmonary involvement.

Conclusions: The long-term prognosis of PLCH is significantly more favourable than was previously 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-positive 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 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 extra-pulmonary LCH localizations that impact 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.

Material and methods

Study design

All patients with PLCH newly diagnosed in adulthood (i.e., 18 years of age or older) 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 standardized dedicated database and retrospectively analysed (see details in Supplementary Methods).

The patients were classified as having isolated PLCH or multisystem (MS) disease in case of extra-pulmonary 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 categorized 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].

Chronic respiratory failure was defined as a sustained decreased arterial partial oxygen pressure (PaO_2) on room air and/or the long-term use of supplemental oxygen [18]. The ESC/ERS guidelines were used for the diagnosis of PH [19, 20]

Endpoints

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, extra-pulmonary LCH localizations and malignancies during the study period.

Statistical analysis

Descriptive statistics are presented as the means ± standard deviations (SDs), medians (interquartile ranges [IQRs]) or percentages.

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 (https://www.insee.fr). The one-sample log-rank test was used to compare observed and expected survival. The standardized mortality ratio (SMR) and its 95% confidence interval (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 one second (FEV_1) data over time.

The cumulative incidences of CRF, PH, extra-pulmonary 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 standardized 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 (https://www.R-project.org/) software. All tests were two-sided with p-values of 0.05 denoting statistical significance.

Results

Study population at diagnosis

Two hundred nine patients fulfilled the inclusion criteria. Three patients were excluded after the 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 (1.9%) patients (bone: n = 2; diabetes insipidus: n = 2) with a median interval of -3.4 years (IQR -6.5 to -2.3).

Fifteen smoking-related diseases were concurrently present in 14 patients: COPD (n=4), respiratory bronchiolitis with interstitial lung disease (n=1); ischemic cardiomyopathy (n=4), ischemic cerebrovascular disease (n=4); 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); gastroesophageal reflux disease (n=4). Eleven patients had associated autoimmune disorders: thyroiditis (n=5); multiple sclerosis (n=2); systemic lupus erythematosus (n=1); autoimmune hepatitis (n=1); autoimmune haemolytic anaemia (n=1); 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 (89.3%) patients, denoting the recent development of

PLCH (Table 1). As expected for recent PLCH, most patients had a typical nodulocystic 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. Eighteen of these patients had a pneumothorax, 18 underwent lung function measurements more than 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 (13.3%) patients.

Follow-up

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

During the study period, among the 196 current smokers at diagnosis, 76 (38.8%) patients were weaned from tobacco, whereas one ex-smoking patient resumed smoking during his follow-up. Seventeen (8.3%) patients 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 MEK inhibitor trametinib (n = 1). One patient underwent lung transplantation 2.7 years after the diagnosis of PLCH.

Survival

Twelve (6%) patients died during the study, including one patient who died one year after lung transplantation. The median time from PLCH diagnosis to transplantation or death was 3.0 years (IQR 2.1-4.3). 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 large 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 four 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.

The results of univariable analyses of patient characteristics at diagnosis that were associated with survival are detailed in Supplementary Table 1. In the multivariable model, only an 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 2. In this multivariable Cox model involving 167 patients with available FEV_1 measurements at diagnosis, only an older age and a lower FEV_1 were still associated with the risk of mortality (Table 3).

Chronic respiratory failure and pulmonary hypertension

Twelve (5.8%) patients had CRF, which was present at the time of PLCH diagnosis in 5 patients, and 7 patients developed CRF during follow-up. The long-term use of supplemental oxygen was recorded for 7 patients (at diagnosis, n = 2; during follow-up, n = 5). For patients who did not receive oxygen, the median PaO_2 was 59 mmHg (IQR 57-63). 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, 8 also had PH, which was confirmed by RHC in 7 patients (mPAP=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 8 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 3.

Extra-pulmonary LCH involvement

One hundred fifty-seven patients had isolated PLCH at diagnosis. Eight (5.1%) of these patients developed extra-pulmonary LCH during follow-up. The cumulative incidence of extra-pulmonary LCH was 5.9% (95% CI 1.8-10.1) at both 5 and 10 years (Supplementary Figure 1).

Malignant diseases

Twenty-seven malignancies were observed in 23 (11%) patients. These malignancies occurred before (n = 11, median time -3.1 years, [IQR -6.2 to -2.1]), concurrent with (n = 6), or after the diagnosis of PLCH (n = 10, median time 4.1 years, [IQR 3.1-5.0]). No patients had previously received chemotherapy for PLCH (Supplementary Table 4).

Eleven lung carcinomas (7 after PLCH diagnosis) were observed (Table 4). Six patients were current smokers and 5 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 5 ex-smokers had ceased smoking for a median duration of 4 years (IQR 3-5) 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 2). Compared with the expected numbers of cases of lung cancers 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, since 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, extra-pulmonary 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.

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 2 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 the identification of PLCH 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 *BRAF* status of PLCH lesions was 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 could underestimate the occurrence of PH during longer follow-up. These complications are associated with a poor prognosis, as approximately 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 emphasizes 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 extra-pulmonary LCH localizations during follow-up in patients with initially isolated PLCH. In these patients, the performance of extra-thoracic 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 widely vary according to the extent of LCH, the selected population, and the treatment (chemotherapy or radiation) the patients had eventually received for LCH. Here, haematological malignancies accounted for 7 (30%) of the 27 observed neoplasms and did not occur after the diagnosis of PLCH during the study period. The reasons LCH, including PLCH, patients are prone to developing haematological malignancies remain unclear. An increased rate of myeloid

neoplasia mutations was reported in patients with Erdheim-Chester disease (ECD), 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 both 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 5 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 to 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 at a longer time. Although our cohort included a large number of patients, it involved a population from a single-centre, which raises the question of the generalizability 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 as 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 was previously 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 the occurrence 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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Conflict of interest

GL reports travel grants from Vitalaire outside the submitted work. ASG reports personal fees from Medtronic and Astrazeneca outside the submitted work. AT reports personal fees from Chiesi and BMS, travel grants from Vitalaire, Astrazeneca, Teva and Boehringer Ingelheim outside the submitted work. All other authors declare no competing interests.

Data sharing

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.

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Tables

Table 1. Characteristics of the PLCH patients at the time of diagnosis.

	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	2
History of pneumothorax	24 (11.7)
Before diagnosis	6
Median time, (IQR), month	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[¶]	
Nodulocystic	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 % predicted, n = 152	102.2 ± 15.9
RV % predicted**,** n = 150	123.3 ± 34.6
RV/TLC % predicted**,** n = 150	116.1 ± 26.0
FEV_1 % predicted, n = 167	89.6 ± 18.6
FVC % predicted, n = 158	95.1 ± 18.7
FEV_1/FVC %, n = 158	79.9 ± 10.2
D_{LCO} % predicted, 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% predicted	103 (81.1)

Data are expressed as the means ± SDs or n (%).

*One patient had multisystem PLCH histologically confirmed on a skin biopsy. The other patient had a typical nodulocystic pattern on lung HRCT and was exposed to import passive smoking.

†All smokers

‡ Surgical lung biopsy (n=44); extrathoracic LCH localisation (n=22).

§Nine patients had > one extra-pulmonary LCH localization; other: peripheral lymph node n = 1; central nervous system n = 1.

#4 patients had pneumothorax before and at diagnosis.

¶Histological confirmation in 26%, 33% and 64% of patients with nodulocystic, 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.

PLCH: pulmonary Langerhans cell histiocytosis; SD: standard deviation; 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 second; FVC: forced vital capacity; D_{LCO}: diffusing capacity for carbon monoxide.

Table 2. Characteristics of the 12 PLCH patients who died during the study period.

Patient	Age at diagnosis	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

*This patient died one year after lung transplantation.

†Treated with cladribine.

PLCH: pulmonary Langerhans cell histiocytosis; M: male; F: female; LCH: Langerhans cell histiocytosis; CRF: chronic respiratory failure; PH: pulmonary hypertension; CMML: chronic myelomonocytic leukaemia.

Table 3. Multivariate analyses of the characteristics of 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

*A lower FEV_1 was associated with an increased risk of mortality.

†17 patients received systemic treatment for LCH.

PLCH: pulmonary Langerhans cell histiocytosis; LCH: Langerhans cell histiocytosis; HR: hazard ratio; CI: confidence interval; FEV_1: forced expiratory volume in 1 second.

Table 4. Characteristics of the 11 patients with lung carcinoma observed in the cohort of PLCH patients.

Patient	Age at PLCH diagnosis	Sex	Type of lung carcinoma	Time to PLCH diagnosis (years)	Age at diagnosis of lung carcinoma	Smoking status (pack-years)	Treatment of lung carcinoma	Status Alive/dead
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

PLCH: pulmonary Langerhans cell histiocytosis; M: male; F: female; EGFR: epidermal growth factor receptor.

Figure legends

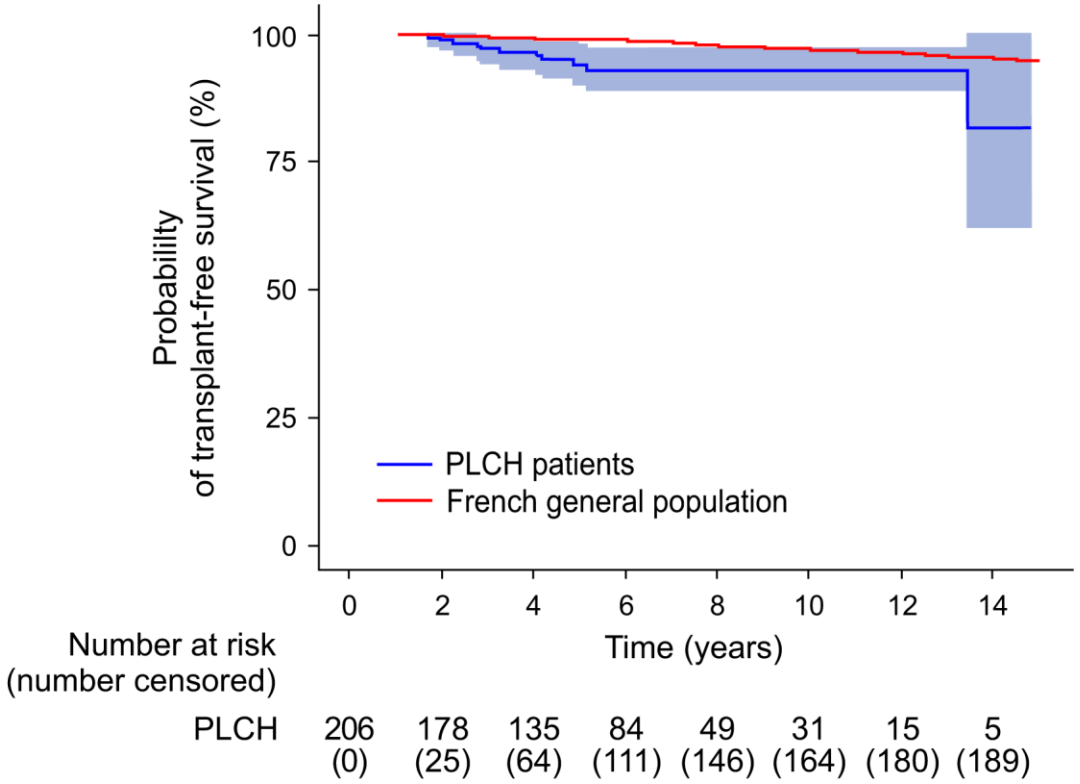
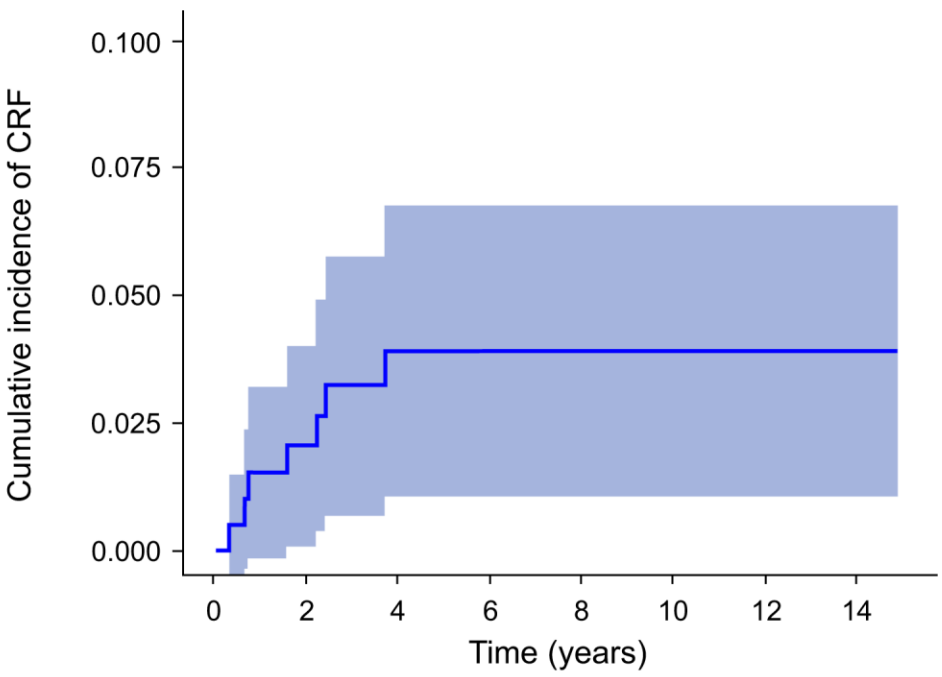


Figure 1. Kaplan-Meier estimates of expected and observed survival of the 206 PLCH patients during the study period. The shaded area represents 95% confidence intervals. The red line indicates expected survival for the age- and sex-matched French general population ($p < 0.001$, one-sample log-rank test).

PLCH: pulmonary Langerhans cell histiocytosis.

a



Number at risk	201	170	128	79	46	28	13	4
(number censored)	(0)	(25)	(62)	(109)	(142)	(160)	(175)	(184)

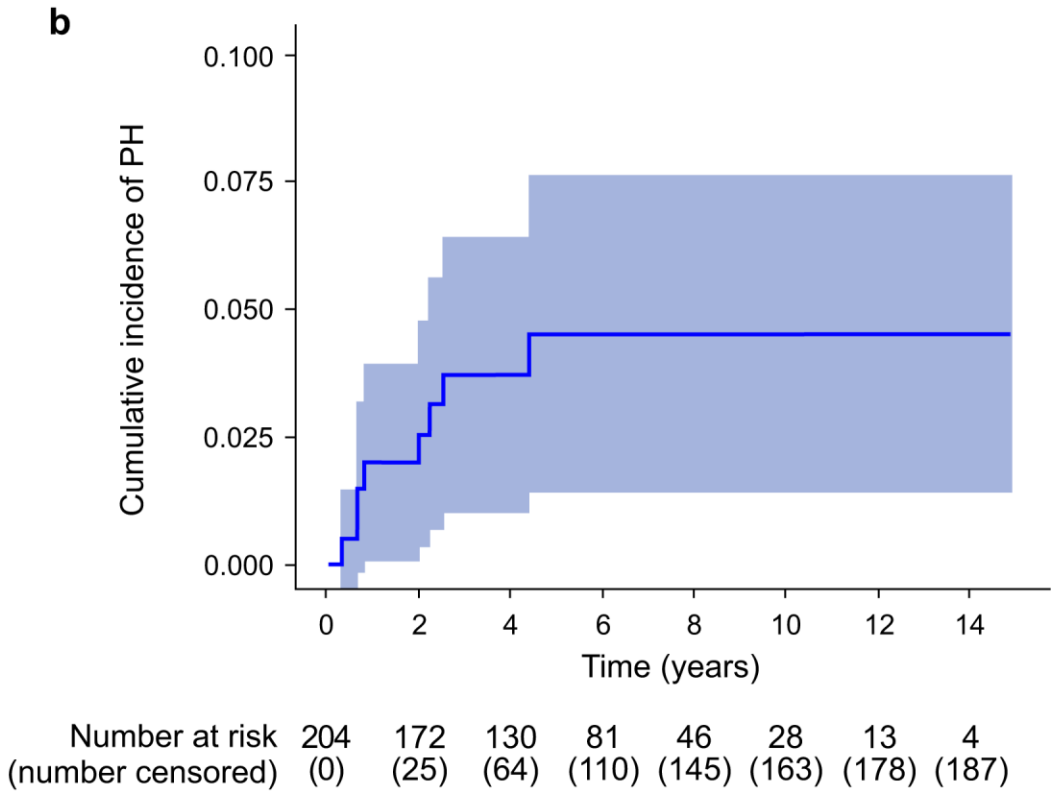


Figure 2. Cumulative incidence of CRF (a) and PH (b) among the PLCH patients during the study period. Shaded areas represent 95% confidence intervals in panels a and b.

PLCH: pulmonary Langerhans cell histiocytosis; CRF: chronic respiratory failure; PH: pulmonary hypertension.

Supplementary material

Long-term Outcomes of Adult Pulmonary Langerhans Cell Histiocytosis: A Prospective Cohort

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Supplementary methods

Study design and patient evaluation during the study

The following items were recorded for the study: demographics, smoking status, cannabis consumption, clinical symptoms and signs, Langerhans cell histiocytosis (LCH) localizations, high-resolution computed tomography (HRCT) findings, lung function tests, oxygen saturation and/or blood gas analyses, long-term oxygen supplementation, Doppler echocardiography and right heart catheterization (RHC) results, systemic treatments received for LCH, the presence of malignancies, the performance of lung transplantation and survival status (deceased or alive).

For patients whose last visit was prior to the end of the study, the vital status (alive vs. deceased) was assessed through a telephone call to the patient or the relevant general practitioner. Additionally, if needed, a query was sent to the city hall (registry of births and deaths) of the town in which the patient was born.

At the diagnosis of pulmonary Langerhans cell histiocytosis (PLCH), a thorough history was collected and a comprehensive physical examination including ENT and stomatology was systematically performed to detect extra-pulmonary LCH involvement. Apart from routine blood analyses (complete blood count, blood chemistry analysis with total protein, electrolyte, creatinine, bilirubin, alanine aminotransferase, aspartic aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, C-reactive protein and fibrinogen levels and protein electrophoresis), specific investigations to evaluate extrathoracic LCH involvement were performed in individual cases based on clinical or biological suspicion [1, 2].

The differential diagnoses considered vary according to the patient's age, smoking habits, gender, clinical presentation, and lung HRCT pattern (nodulocystic, nodular or cystic) [3-5].

Briefly, in case of constitutional symptoms, infection is rigorously looked for (particularly mycobacteria, and pneumocystis *jirovec*i in case of lymphopenia). Bronchoscopy with BAL is performed to search for alternative diagnoses in case of predominant nodular, or cavitary nodules pattern at lung HRCT (infection, cavitary metastatic carcinoma, sarcoidosis or granulomatous polyangiitis…). In purely cystic presentation, LAM (either sporadic or associated with tuberous sclerosis) is the main alternative diagnosis in females. In both genders, the principal other diagnoses to consider are Birt-Hogg-Dubé syndrome, lymphoid interstitial pneumonia. Amyloidosis and light chain cystic lung disease are considered in an appropriate context. At the end of this process, in the absence of straightforward diagnosis, a surgical lung biopsy is performed, if the patients' respiratory function allows it.

LCH lung involvement was assessed by chest imaging, lung function measurement, oxygen saturation and/or blood gas analyses. The 6-minute walk test and Doppler echocardiography were indicated in patients with unexplained dyspnoea or isolated/disproportionate decrease in diffusing capacity for carbon monoxide (D_{LCO}) to detect pulmonary hypertension (PH), and if needed, PH was confirmed by cardiac catheterization [1, 6].

Follow-up visits systematically comprised assessment of smoking status, a comprehensive physical examination, chest radiography and lung function, including D_{LCO} measurement. Serial lung HRCT was indicated in case of changes in clinical, chest radiography or functional status during follow-up [1, 6]. For patients with unexplained dyspnoea or an isolated/disproportionate decrease in D_{LCO}, a Doppler echocardiography was also performed to detect PH [1, 6]. During the study, the median number of lung HRCT examinations performed was 3, (IQR 2; 5), corresponding to 0.8 HRCT examinations/patient/year of follow-up. One hundred forty-six (71%) patients had at least one Doppler echocardiography examination. For

these patients, the median number of Doppler echocardiography examinations performed was 2 (IQR 1; 4), corresponding to one Doppler echocardiography examination/patient every two years during the study period.

Supplementary tables

Supplementary Table 1. Univariable analyses of the associations of baseline characteristics of PLCH patients with survival

	Number of deaths*	Value	HR	95% CI	p-Value
Age	12		1.09	1.05; 1.14	<0.0001
Sex	12	M	1.00		
		F	0.50	0.16; 1.58	0.24
Smoking exposure, pack-years	11		1.05	1.02; 1.07	0.001
Isolated PLCH	12		0.95	0.26; 3.52	0.94
Chronic respiratory failure	12	No	1.00		
		Yes	10	2.16; 46.37	0.003
TLC, % predicted, n = 152	11		0.96	0.92; 1.01	0.088
RV, % predicted, n = 150	11		1.00	0.98; 1.02	0.96
RV/TLC, % predicted, n = 150	11		1.01	0.99; 1.03	0.30
FVC, % predicted, n = 158	10		0.97	0.94; 1.00	0.056
FEV_1, % predicted, n = 167	11		0.97	0.94; 0.99	0.020
FEV_1/FVC %, n = 158	10		0.94	0.89; 0.98	0.008
D_{LCO}, % predicted, n = 127	6		0.90	0.84; 0.96	0.002
Restriction	11	No	1.00		
		Yes	2.67	0.66; 10.83	0.17
Obstruction	10	No			
		Yes	1.39	0.29; 6.56	0.68
Air trapping	11	No			
		Yes	1.80	0.55; 5.90	0.33
HRCT nodular score†, n = 196	11	Low (0-6)	1.00		
		Intermediate (7-12)	0.94	0.24; 3.65	0.93
		High (13-18)	0.86	0.11; 7.02	0.89
HRCT cystic score‡, n = 196	11	Low (0-6)	1.00		
		Intermediate (7-12)	0.61	0.07; 5.10	0.65
		High/very high (13-24)	4.05	1.14; 14.35	0.03

*Number of deaths that occurred according to the characteristic considered. †Maximal value of the nodular score = 18. ‡Maximal value of the cystic score = 24.

PLCH: pulmonary Langerhans cell histiocytosis; HR: hazard ratio; CI: confidence interval; M = male; F: female; TLC: total lung capacity; RV: residual volume; FVC: forced vital capacity;

FEV_1: forced expiratory volume in 1 second; D_{LCO}: diffusing capacity for carbon monoxide; HRCT: high resolution computed tomography.

Supplementary Table 2. Univariable analyses of the associations of time-dependent characteristics of PLCH patients with survival

Characteristics (all evaluated at time t)	**Number of deaths**	**Values**	**HR**	**95% CI**	**p-Value**
Smoking status at time t	12	Non-smoker Smoker	1.00 2.5	0.79; 7.89	0.12
Previous use of systemic treatment	12	No Yes	1.00 5.64	1.79; 17.79	0.003
Previous use of cladribine	12	No Yes	1.00 5.69	1.25; 26.04	0.025
FEV_1 (n = 167)	11		0.95	0.91; 0.98	0.003
Age	12		1.09	1.05; 1.13	<0.0001

PLCH: pulmonary Langerhans cell histiocytosis; HR: hazard ratio; CI: confidence interval; FEV_1: forced expiratory volume in 1 second.

Supplementary Table 3. Characteristics of the 14 PLCH patients with CRF and/or PH

Patient	Age at diagnosis of PLCH, years	Sex	Smoking status at diagnosis	Smoking status at CRF	Long-term oxygen	Systemic treatment	PH characteristics	Status Alive/Dead
1	58	M	Former	Former	Yes	Steroids	Confirmed (mPAP=41 mmHg)	Dead
5	33	M	Current	Current	Yes	None	Confirmed (mPAP=28 mmHg)	Dead
6	47	M	Current	Current	No	Cladribine	Confirmed (mPAP=27 mmHg)	Dead
7	48	M	Current	Current	No	None	Probable (TRV=3.31 m/s; sPAP=53 mmHg)	Dead
8*	38	F	Former	Former	Yes	Steroids	Confirmed (mPAP=25 mmHg)	Dead
9	72	F	Current	Current	Yes	Cladribine†	Confirmed (mPAP=27 mmHg)	Dead
10	49	F	Current	No CRF	No	None	Probable (TRV=2.95 m/s; sPAP=40 mmHg)	Dead
20	19	M	Current	Current	Yes	Steroids	Confirmed (mPAP=34 mmHg)	Alive
21	48	F	Current	Current	Yes	Steroids	Confirmed (mPAP=26 mmHg)	Alive
22	51	F	Current	No CRF	No	None	Probable (TRV=3.04 m/s; sPAP=47 mmHg)	Alive
23	43	M	Current	Current	No	None	None	Alive
24	59	F	Current	Current	No	None	None	Alive
25	33	M	Current	Former	Yes	Cladribine	None	Alive
26	53	F	Current	Current	No	Cladribine	None	Alive

*This patient died one year after lung transplantation.

†This patient was previously treated with corticosteroids.

PLCH: pulmonary Langerhans cell histiocytosis; CRF: chronic respiratory failure; PH: pulmonary hypertension; M: male; F: female; mPAP: mean pulmonary arterial pressure; TRV: tricuspid regurgitation velocity; sPAP: systolic pulmonary arterial pressure.

Supplementary Table 4. Type and time of occurrence of the 27 malignancies observed in 23 PLCH patients during the study

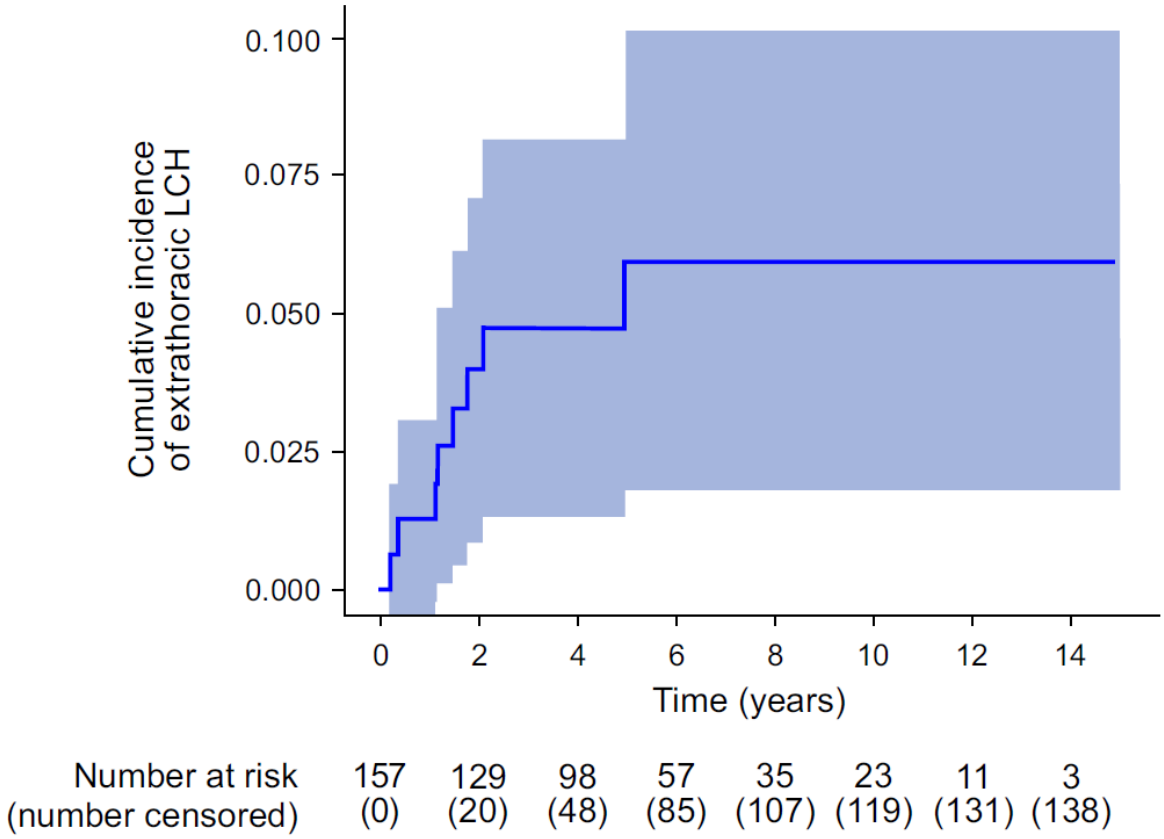
	Before PLCH (n=11)	**Concurrent with PLCH (n=6)**	**After PLCH (n=10)**
Time, median, (IQR), years	-3.13 (-6.2; -2.1)	Concurrent	4.1 (3.1; 5.0)
Solid neoplasms			
Anus	1		
Prostate	1		
Colon	1		
Stomach	1		
Lung	1	3*	7
Thyroid	1		
Spindle cell skin carcinoma	1		
Breast			3†
Haematological malignancies			
Marginal zone lymphoma	1		
Myelodysplasia	1		
Myeloma	1		
Skin lymphoma	1		
CMML		3	

*Eight patients with lung carcinomas had histological confirmation of PLCH either before or at the time of lung surgery for their tumour. The remaining two patients (one patient with metastatic lung carcinoma confirmed on liver biopsy, and one patient with lymphangitic carcinomatosis and respiratory failure) had a typical nodulocystic pattern on lung HRCT at the time of PLCH diagnosis.

†One patient with breast carcinoma had histological confirmation of PLCH and the remaining two patients presented a typical nodulocystic pattern on lung HRCT at the time of PLCH diagnosis.

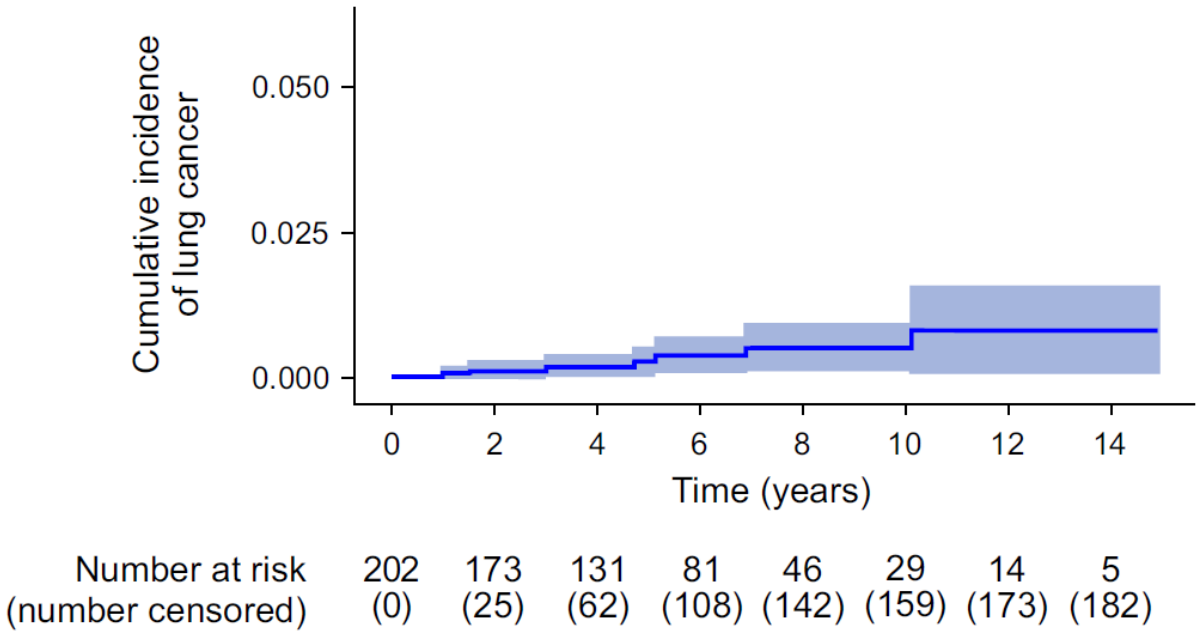
PLCH: pulmonary Langerhans cell histiocytosis; IQR: interquartile range; CMML: chronic myelomonocytic leukaemia.

Supplementary figures



Supplementary Figure 1. Cumulative incidence during follow-up of extra-pulmonary LCH localizations among the 157 patients with isolated PLCH at diagnosis. LCH involved the bone (n = 5), pituitary stalk with diabetes insipidus (n =3) or liver (n = 1). The patient with liver involvement, which occurred 2.1 years after diagnosis, also developed diabetes insipidus 4.3 years later. The shaded area represents the 95% confidence interval.

PLCH: pulmonary Langerhans cell histiocytosis.



Supplementary Figure 2. Cumulative incidence of lung carcinoma occurring after the diagnosis of PLCH. The shaded area represents the 95% confidence interval.

PLCH: pulmonary Langerhans cell histiocytosis.

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