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Original Article

Pulmonary Langerhans cell histiocytosis: A comprehensive analysis of 40 patients and literature review

Davide Elia, Olga Torre, Roberto Cassandro, Antonella Caminati, Sergio Harari *

U.O. di Pneumologia e Terapia Semi-Intensiva, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare Ospedale San Giuseppe MultiMedica, via San Vittore 12, 20123 Milano, Italy

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ABSTRACT

Background: Pulmonary Langerhans cell histiocytosis (PLCH) is a rare interstitial disease affecting primarily young adult smokers. In order to highlight the clinical features of the disease, we conducted a retrospective analysis on clinical data of PLCH patients followed at our center; moreover, we reviewed the current literature on PLCH.

Method and results: Between January 2004 and July 2014, 40 patients with PLCH were evaluated at our Division. The average patients' age was 40 (±14) years, and 22 of them were females. Diagnosis was based on search of CD1a+ cells in the bronchoalveolar lavage (10 patients), lung biopsy (8 patients), or cystic bone lesion's biopsy (2 patients); in 12 patients, diagnosis was achieved on the basis of the clinical-radiological data.

The principal manifestation of PLCH was the presence of cysts involving upper lung zones with costophrenic sparing on chest CT scan (in 25 patients); micronodular pattern in the middle-upper zone and combination of the two radiological patterns were less frequently observed (in 9 and 6 patients, respectively). Pulmonary hypertension was found in 4 patients. Extra pulmonary manifestations were diabetes insipidus, bone lesions, and skin involvement (in 5, 7, and 1 patient, respectively).

For 25 patients, smoking cessation was the only required therapy. Treatments with low dose of prednisolone, vinblastine and prednisolone, or 6-mercaptopurin were reserved for patients with major pulmonary or extrapulmonary involvement (for 11, 4, and 5 patients, respectively).

In conclusion, PLCH is a rare, multi-systemic disease; early diagnosis, accurate staging and smoking cessation are considered critical in PLCH management.

1. Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder. The true incidence of this disease is not known, because large published studies mostly originate from referral centers and, thus, the disorder is likely to be underdiagnosed in the general population. LCH can be diagnosed in any age group, but it most commonly affects children between one and 3 years of age with an estimated incidence of 3–5 cases per million children; the estimated incidence of LCH in adults is approximately 1–2 cases per million [1].

LCH can be clinically divided into three groups: single-system, low-risk multisystem, and multisystem with *risk-organ* involvement. In patients with single system LCH, systemic symptoms such as weight loss or fever are usually absent. Single-system LCH may involve a single site (unifocal) or multiple sites (multifocal) of the following organs/systems: bone, skin, lymph nodes (excluding draining lymph node of another LCH lesion), lungs, or central nervous system. More rarely, the disease may involve the thyroid and thymus.

Multisystem LCH is characterized by involvement of two or more organs/systems, with or without involvement of *risk-organs. Risk organs* include the bone marrow, liver, and/or spleen, and denote a worse prognosis. In contrast to the term *risk organs*, the term *central nervous system (CNS)-risk areas* include the mastoid, sphenoid, orbital, ethmoid, or temporal bones and indicate an increased risk of CNS involvement.

Multisystem lesions predominantly occur in children. Historically, multisystem variants of the disease used to be known by a variety of names, such as: Letterer–Siwe disease (an aggressive multiorgan histiocytosis of infants and children that affects the liver, spleen, lymph nodes, lungs and bones), Hand–Schuller–Christian syndrome (a disseminated, chronic histiocytosis characterized by the triad of skeletal lesions, exophthalmus and central diabetes insipidus), histiocytosis X (solitary or multiple histiocytosis of bone or lung), and Hashimoto–Pritzker syndrome [2].

Pulmonary Langerhans cell histiocytosis (PLCH) is an interstitial lung disease whose clinical manifestations may involve a single organ or be multisystemic. It is a rare and probably misdiagnosed disease and, therefore, its incidence and prevalence are not well established. This disease mainly affects young adult smokers with an equal gender distribution; however, males tend to develop symptoms at earlier age than females.

* Corresponding author. Tel. +39 02 85994580; fax: +39 02 85994400.
E-mail address: sharari@ilpolmone.it (S. Harari).

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The aim of this paper was to highlight the clinical features of the disease. For this purpose we analyzed the clinical data of PLCH patients who were evaluated at our center and we reviewed the current literature.

2. Methods and results

A retrospective analysis was conducted on clinical data of 40 patients with PLCH who visited our center between January 2004 and July 2014 (Table 1). The majority of these patients (62.5%) were diagnosed in our center; the remaining patients were referred to our hospital for a second opinion.

The mean age of the patients (45% males and 55% females) was 40 ± 14.4 years (range, 16 to 75 years). All patients had a smoking history (25 ± 15 pack/years) and, at the time of first evaluation, 21 of them (52.5%) were ex smokers.

The most common manifestations that led to the diagnosis of PLCH were dyspnea on exertion (in 15 patients), dry cough (in 13 patients), and pneumothorax (in 7 patients); less common symptoms were diabetes insipidus (in 2 patients), bone lesions (in 2 patients), and hemoptysis (in 1 patient; see Table 2).

In the majority of patients (25 out of 40), chest CT scanning revealed weird-shaped cysts within the lung parenchyma, with upper lobe predominance and costophrenic sparing (see Fig. 1). A micronodular pattern of the middle-upper zone was found in 9 patients. The remaining 6 patients presented with a combination of the two radiological patterns of disease.

Bronchoscopy with bronchoalveolar lavage was performed in 20 patients, and a significantly higher amount of CD1a+ positive cells (more than 5%) was detected in the lavage fluid of 50% of those patients. Definitive diagnosis was achieved through histological examination of lung specimen in 8 (20%) patients, and through histological examination of cystic bone lesion's biopsy in 2 patients. In the remaining 12 patients, the diagnosis was achieved on the basis of the clinical–radiological feature.

From the functional point of view, pulmonary function tests (PFTs) indicated a normal pattern in the majority of patients (22 out of 40); a restrictive pattern was found only in 2 patients, and an obstructive pattern was detected in 16 patients (40%). Eight patients had mild airflow obstruction, 4 patients had moderate obstruction, and 2 showed severe obstruction; the remaining 2 patients had an extremely severe obstruction (see Table 3). On average, a moderate reduction of TLCO was found. Overall, only seven patients presented with a normal TLCO value. The average 6-minute walking distance (6MWD) was 420.37 m; however, four patients walked less than 200 m, and 6 patients required oxygen supplementation to perform the test.

Twenty-four patients underwent echocardiography with evaluation of pulmonary arterial systolic pressure (PAPs) measurement. No significant morphological alterations were found. In four patients, PAPs was higher than 35 mm Hg (mean value: 66 ± 24.65 mm Hg); all these patients had an obstructive pattern on PFTs, with a mild/severe obstruction degree of airflow obstruction.

Table 1
Characteristics of patients at time of diagnosis.

	Patients
Gender (m/f)	18/22
Age (years)	40 ± 14
Years from symptoms	2 ± 3.7
Number of cigarettes smoked (pack/year)[a]	25 ± 15
FEV1 (L)	2.6 ± 0.99
FEV1 (%)	79.65 ± 24.18
FVC (L)	3.59 ± 1.08
FVC (%)	92.84 ± 20.45
FEV1/FVC	71.61 ± 14.78
DLCO (%)	60.56 ± 24.30

[a] Pack/years = (no cigarettes smoked × years of smoking) / 20.

Table 2
Symptoms at time of diagnosis.

Symptoms	Number of patients
Exertional dyspnea	15
Cough	13
Pneumothorax	7
Diabetes insipidus	2
Bone lesions	2
Hemoptysis	1

Sixteen patients had endocrine evaluation, and in 6 of them alterations of hormonal regulation were found. Five patients were diagnosed with diabetes *insipidus*: one patient had diabetes associated with panhypopituitarism, and one had diabetes associated with hypogonadism and GH deficiency. Only one patient presented with hypogonatropic hypogonadism not associated with diabetes insipidus. These findings suggest that, although diabetes insipidus is the most common endocrine alteration in PLCH, further endocrine investigations might demonstrate that alteration in the function of the anterior pituitary gland may also occur as a manifestation of PLCH.

The X-ray detected bone lesions in seven patients. In particular, 3 patients had lesions located in the femur, one patient had lesions in the petrous bone, another patient had lesions in the jaw, and the remaining two patients had lesions located in the arm bones.

One patient presented with skin involvement (an ulcerative lesion of genitalia and perianal region and of the scalp (see Fig. 2); (see Table 4)).

For a total of 25 patients, smoking cessation was the only required therapy and, the therefore, these patients were recommended to stop smoking. Therapeutic approaches were only considered for patients with major pulmonary or extra-pulmonary involvement. In detail, 11 patients were offered low dose of prednisolone as treatment of choice, 4 patients (who were visited at our center between 1997 and 2002) were treated with vinblastine and prednisolone, and 5 patients (who were visited between 2003 and 2007) were treated with 6-mercaptopurine.

3. Discussion

The present study provides a review of the clinical features of PLCH, with information on pulmonary and extra-pulmonary involvement and with emphasis on the most common symptoms and diagnostic data obtained by bronchoalveolar lavage (BAL) and pulmonary function tests.

At the moment, still little is known about the pathogenesis of PLCH. Its name comes from the fact that lesions possibly originate from cells

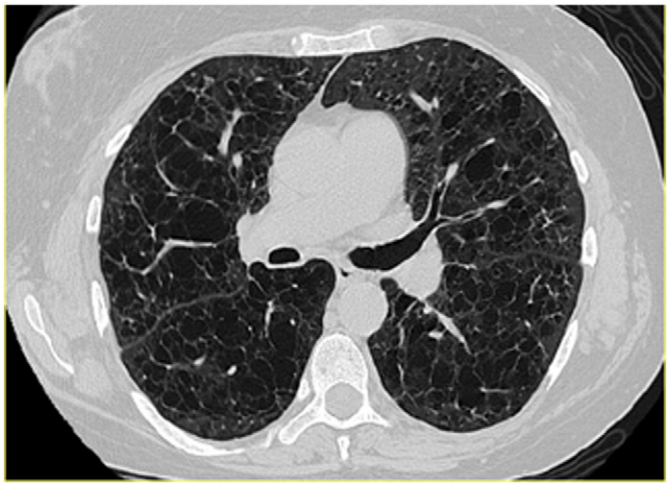

Fig. 1. Weird-shaped cyst formation on chest CT scan.