Should we rewrite the natural history and prognosis of pulmonary Langerhans cell histiocytosis?

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The natural history and clinical prognosis of PLCH have changed, since its first description. A long-term follow-up is recommended in order to prevent the development of malignancies.
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Pulmonary Langerhans cell histiocytosis (PLCH) is a diffuse cystic lung disease, involving several lung structures such as bronchioles, the interstitium and pulmonary vessels, to differing extents, leading to a variety of clinical phenotypes.

Since 1951, when Farinacci *et al.* [1] reported two cases of adult patients with eosinophilic granuloma (6 years later Auld [2] described the histology of Langerhans cell histiocytosis (LCH) in lung samples), many advances have been made in the knowledge of the disease, although a wide area of uncertainty remains to be explored.

LCH was, initially, described as a reactive process driven by histiocytes (phagocytic cells with mononuclear morphologic features) [3], but now it is considered the most common histiocytic neoplasm, characterised by the presence of cells with abnormal function and proliferation or differentiation, originating from the myeloid lineage [4]. Immunohistochemically, the neoplastic cells in LCH express the same surface markers found on Langerhans cells, including CD68, S100, CD1a and langerin (CD207) [3–6]. Furthermore, recently, molecular studies have shown MAPK–ERK pathway activation in over 80% of cases, including BRAFV600E (50%–60%) and MAP2K1 (15%–20%) mutations [5].

According to the number and the organs involved in LCH, the Histiocyte Society classified the different manifestations in single organ or multisystemic involvement [6]. The single organ manifestation generally affects bone, skin and the lungs, and it is characterised by a better prognosis with the potential for spontaneous remission. On the other hand, multisystemic presentation, combining vary degrees of bone, skin, hypothalamic–pituitary, lymph node, lung lesions and, more rarely, central neurological lesions, is associated to a worse prognosis, particularly when the liver, spleen and haematopoietic system, called risk organs, are involved [7–9].

Pulmonary manifestations can be observed in systemic forms of LCH, although are more common as a single organ manifestation in young adult smokers (PLCH) [9]. Chest high-resolution computed tomography (HRCT) is characterised by the combined presence of nodules, well or ill-defined, and cysts, varying in shape, size and wall thickness [10]. Pulmonary function tests may vary, according to the extent of cystic involvement and disease duration, from a normal to an obstructive and restrictive pattern, and the most common abnormality is reduction of diffusing capacity of the lungs for carbon monoxide (observed in 80–90% of cases) [11]. Data obtained from pulmonary function tests correlate with the degree of involvement at HRCT and with prognosis [8, 10–13].

Due to the wide variability of clinical phenotypes and disease behaviour, prognosis in PLCH is still unclear, ranging from spontaneous resolution, especially after smoking cessation, to the development of

chronic respiratory failure (CRF) and pulmonary hypertension (PH), leading to lung transplantation or death [8, 10, 13–18].

In this issue of the *European Respiratory Journal*, Benattia *et al.* [18] report a prospective study on a large series of incident cases of PLCH (n=206), enrolled between 2004 and 2018 in their centre, the national reference centre for this disease in France, followed for a mean duration of 5.1 years. The primary outcome was survival, defined as the time from inclusion to lung transplantation or death from any cause. Secondary outcomes included the cumulative incidences of CRF, PH, malignant diseases, and extrapulmonary involvement in initially isolated PLCH. Survival was estimated using the Kaplan–Meier method.

The results are very interesting, being in contrast with previous reports, particularly regarding survival of this disease. In fact, the estimated rate of survival at 10 years in this series was 93% and the cumulative incidences of CRF and/or PH were less than 5% at both 5 and 10 years, while in previous reports, the survival rate was 64% at 10 years [10] and a median survival duration was 13 years [13]. Furthermore, 27 malignancies were observed in 23 patients and the estimated standardised incidence ratio of lung carcinoma was 17.0 compared to an age- and sex-matched French population. Eight (5.1%) of the 157 patients with isolated PLCH developed extrapulmonary involvement.

This valuable study has provided us with important information, but, at same time, it raises some important questions. Thanks to Benattia *et al.* [18], we now know that the survival of this disease is much better than previously thought, but we have also learned that patients need to be followed over time, particularly because the risk of developing a malignancy is very high, especially for lung cancer, and also for haematological disorders. Many factors, apart from smoking, may play a role in understanding the pathogenesis and prognosis of PLCH patients, as recently suggested by the finding of the presence of loss of heterozygosis for tuberous sclerosis complex gene 2 (TSC2) in blood and urine samples in patients, not only with lymphangioleiomyomatosis, as expected, but also in those suffering from PLCH [19]. This observation could suggest that chromosomal abnormalities affecting the TSC2 gene may be observed even in diseases having cancer-like neoplastic cells [20].

Further studies should investigate the utility of screening for lung cancer by means of CT scan, as well as an early detection of respiratory failure and/or PH, which are both associated with a bad prognosis and a high risk of death or of lung transplantation (58% of this population died). Another strong argument to support the need of a long-term follow-up of these patients is the evidence that about 5% of those with an initially isolated form of PLCH develop extrapulmonary involvement over time.

Diagnostic criteria for PLCH should be better clarified, as only one-third of cases, despite being managed by a well-known referral centre for this disease, had a histological diagnosis: in fact, diagnosis was mainly reached on the basis of a typical HRCT presentation of nodules and cysts in a compatible clinical context. Bronchoalveolar lavage was not used in this study due to its low sensitivity; however, considering that it is a low-invasive technique, we think that there could still be a role for it in diagnostic work-up [21, 22].

Beyond clarifying the natural history and clinical prognosis of PLCH and supporting the long-term follow-up of these patients, Benattia *et al.* [18] highlight the importance of a tailored management for patients with PLCH, according to the intensity of respiratory symptoms, the degree of impairment of lung function, and the progression of the disease. In all cases, smoking cessation is mandatory and is the only intervention necessary in a substantial proportion of patients, while new approaches with drugs such as cladibrine and MAPK target therapy could be discussed in expert centres for selected patients with refractory disease [22, 23].

Conflict of interest: None declared.

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