Chapter 13

Pulmonary hypertension in pulmonary Langerhans' cell histiocytosis

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SUMMARY: Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon disorder of unknown aetiology that predominantly affects young adult smokers. In patients with advanced disease, who develop airway obstruction and extensive cystic lesions on high-resolution computed tomography (HRCT), pre-capillary pulmonary hypertension (PH) is frequently observed, though no clear relationship exists between PH and extent of parenchymal lung disease and/or hypoxia. This observation suggests that alternate or additional pathomechanisms contribute to an intrinsic pulmonary vasculopathy that involves both the pre-capillary arterioles and post-capillary venous compartment, in addition to possible pulmonary veno-occlusive disease (PVOD)-like lesions.

Patients with PLCH who develop PH have a particularly poor prognosis and early referral for lung transplantation assessment is recommended. Encouraging recent data suggest that agents licensed for use in pulmonary arterial hypertension (PAH) (group 1 of the PH classification) confer improvements in pulmonary haemodynamics and are generally well tolerated. Further investigation into the use of medical therapy in this population is warranted.

KEYWORDS: Cystic lung disease, lung transplantation outcome, pulmonary hypertension, pulmonary Langerhans' cell histiocytosis

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Eur Respir Monogr 2012; 57: 161–165.

DOI: 10.1183/1025448x.10019611
Print ISBN: 978-1-84984-025-5
Online ISBN: 978-1-84984-026-2
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon disease of unknown aetiology that most commonly affects young adult cigarette smokers [1, 2]. PLCH belongs to the spectrum of Langerhans' cell histiocytosis, a group of disorders characterised by the infiltration of various organs by numerous Langerhans' cells, which are often organised into granulomas [1, 2].

In adults, PLCH occurs most often as a single-system disease, and is characterised by the infiltration and destruction of the walls of distal bronchioles by Langerhans' cell granulomas [1, 2]. The natural history of the disease is widely variable. PLCH may resolve spontaneously, remain stable or progress to respiratory failure in a minority of patients [1, 2]. In patients with progressive disease, who frequently develop airway obstruction, extensive cystic lesions are the main finding on high-resolution computed tomography (HRCT) [3]. In these patients, pulmonary hypertension (PH) is a common complication that occurs several years after PLCH diagnosis in the majority of cases [4–6]. Notably, an isolated decline in diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) during the follow-up of PLCH patients should lead to investigation for the presence of PH [6].

The most recent revision of the classification system of PH identifies five different subcategories that are distinguished by virtue of their underlying pathomechanisms and clinical management [7, 8]. The fifth subcategory comprises a group of heterogeneous disorders, for which the aetiology is unclear or multifactorial [7]. PH that arises as a complication of PLCH belongs to this group [7, 8]. As is the case in several other chronic lung diseases, PH developing in the context of PLCH may be the result of chronic hypoxaemia and/or disruption of normal pulmonary biomechanics [7]. Yet a subset of patients with advanced PLCH have demonstrated markedly increased pulmonary vascular resistance (PVR) that is considered disproportionate to the extent of parenchymal lung disease [4–6]. In contrast to other parenchymal lung diseases (*e.g.* chronic pulmonary obstructive disease (COPD) and idiopathic pulmonary fibrosis (IPF)), the impairment in exercise capacity that classically affects PLCH patients is predominantly related to pulmonary vascular involvement as opposed to ventilatory limitation [9]. Indeed, a previous case series of PH complicating the course of PLCH reported a lack of correlation between lung function parameters and pulmonary haemodynamic indices, suggesting that pulmonary vascular involvement affecting PLCH patients may develop independent of the burden of parenchymal destructive lesions [4].

Haemodynamics

In a recent report by DAURIAT *et al.* [10], 92% of 36 patients with PLCH referred for lung transplantation had PH as confirmed by right heart catheterisation (RHC), with a mean pulmonary arterial pressure (P_{pa}) above 35 mmHg detected in 72.5% of cases. This observation is consistent with results from previous investigators, who found that 44–100% of PLCH patients referred for lung transplantation had a mean P_{pa} of 35 mmHg or over [4, 10]. Moreover, disproportionate PH may develop in patients who do not have evidence of end-stage pulmonary disease, as suggested by findings from a study by CHAOWALIT *et al.* [11] who evaluated 17 symptomatic PLCH patients from a retrospective cohort of 123 patients using transthoracic echocardiography (TTE). These authors found an estimated systolic pulmonary arterial pressure (sP_{pa}) above 35 mmHg in 13 (76.5%) cases and sP_{pa} above 65 mmHg in seven patients. Although the exact prevalence of severe PH in PLCH patients remains unknown, these data indicate that it is likely to occur more frequently than in other chronic lung diseases that comprise group 3 of the updated PH classification (PH related to chronic lung diseases and/or hypoxia) [4, 7, 8].

Histopathology

The typical histopathological findings of PH arising in the setting of PLCH are a severe diffuse pulmonary vasculopathy that predominantly involves the intralobular pulmonary venous compartment and, to a lesser extent, muscular pulmonary arteries (fig. 1) [4]. Although extensive pulmonary vascular involvement is typical in this form of PH, small-vessel infiltration by Langerhans' cell granulomas is rarely observed. Indeed, we observed this latter finding in only one out of 12 patients with severe PH in our initial case series [4]. The usual findings are a proliferative arteriopathy and intimal fibrosis involving small- to medium-sized pulmonary arteries in addition to intimal fibrosis and medial hypertrophy of septal veins. Notably, up to one-third of patients show a typical veno-occlusive pattern [4]. Interestingly, pulmonary vascular involvement is also

frequently observed in regions without parenchymal lesions [4, 13]. FARTOUKH *et al.* [4] found evidence from histopathological assessment of lung tissue samples examined prior to and following establishment of PH that progression of pulmonary vascular involvement occurs independently of progression of parenchymal involvement. Taken together, these observations indicate that a severe intrinsic vasculopathy that affects both the arterial and venous compartments of the pulmonary vascular tree is typical of end-stage PLCH, and these vascular changes may develop irrespective of the severity of lung parenchymal injury.

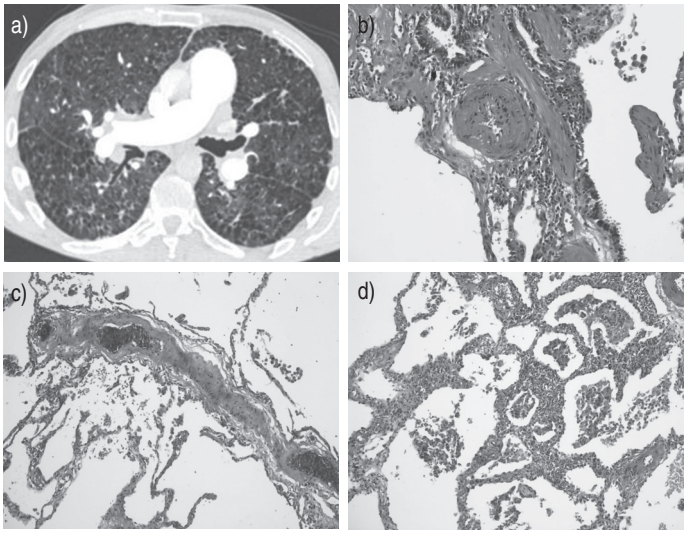

Figure 1. High-resolution computed tomography (HRCT) of the chest and pathological assessment of a patient with pulmonary hypertension associated with pulmonary Langherhans' cell histiocytosis. a) HRCT of the chest showing multiple small cysts and nodules. Pulmonary arterial remodelling and venous remodelling may be present in the lungs of patients suffering from this disease. b) Intimal concentric thickening of a small pulmonary artery. Magnification 200×; haematoxylin and eosin staining. c) Intimal fibrosis of a septal vein with partial obliteration. Magnification 100×; haematoxylin and eosin staining. d) When vein remodelling is present, small foci of alveolar capillary multiplication can be observed. Magnification 100×; haematoxylin and eosin staining. Reproduced from [12] with permission from the publisher.

Prognosis

Severe PH appears to be a major determinant of outcome in PLCH patients [11, 12, 14]. The median survival following diagnosis of PH ranges from 7.6 months to over 4 years, though different criteria have been employed to define PH in previous studies [11, 14]. We have recently reported that functional impairment, as assessed using the modified New York Heart Association (NYHA) functional classification, is a powerful prognostic factor in this population of PLCH patients [6].

Management

There is no currently approved therapy for PH that develops in the context of PLCH. Immunosuppressive therapies and/or corticosteroids have been employed in this setting, though there is no convincing evidence to support this strategy. BENYOUNES *et al.* [15] reported an initially favourable outcome with use of corticosteroids in a single patient with PH and PLCH, but this individual subsequently underwent lung transplantation for progressive disease at our centre. Another patient with PLCH and confirmed pulmonary veno-occlusive disease (PVOD) failed to improve despite prolonged corticosteroid treatment and succumbed to right ventricular (RV) failure [13]. Thus, lung transplantation remains the treatment of choice for end-stage PLCH, especially among patients with severe PH. In a multicentre, retrospective French study that examined outcomes of 39 patients undergoing transplantation (single lung, double lung or combined heart and lung) for end-stage PLCH, the 5-year survival was 57.2%. The prevalence of PH in this population was 92%. Notably, recurrence of PLCH in the graft occurred in 20% of cases in this series, though this did not impact on post-operative survival in this study and developed predominantly in those with pre-existing extrapulmonary involvement [10].

The advent of targeted medical therapies has transformed the clinical management of pulmonary arterial hypertension (PAH) (group 1 of the PH classification). In this particular PH subgroup, these agents confer significant improvements in patient symptoms, exercise capacity and

pulmonary haemodynamics. Several authors have now suggested these treatments might confer benefits in PH complicating PLCH [4, 6, 11, 13, 16]. However, caution should be exercised before this strategy is broadly recommended, particularly because of the high frequency of PVOD-like lesions. In this setting, use of medical therapies approved for PAH (group 1 of the updated PH classification) has been associated with the development of severe acute pulmonary oedema, particularly in PLCH patients treated with intravenous epoprostenol [4]. Nevertheless, a recently reported case of a PLCH patient with severe PH who demonstrated long-term improvement following treatment with the dual endothelin receptor antagonist (ERA) bosentan, thereby obviating the need for lung transplantation, demonstrates that in certain carefully selected cases this class of agent may have a therapeutic role [16]. In a recent case series, 29 consecutive PLCH patients with PH confirmed by RHC were studied. Use of PAH therapy in 12 patients was associated with significant improvements between baseline and follow-up evaluations in both mean P_{pa} (from 56 ± 14 to 45 ± 12 mmHg, $p=0.03$) and PVR (from 701 ± 239 to 469 ± 210 dyn·s·cm^{-5}, $p=0.01$) [6]. Importantly, these haemodynamic improvements occurred without significant impact on arterial oxygen saturation (S_{a,O_2}) levels. Indeed, use of vasodilators in PH related to chronic respiratory diseases may lead to improvement in pulmonary haemodynamic indices, but this may occur at the expense of worsening gas exchange because of inhibition of hypoxic pulmonary vasoconstriction mechanisms and worsening of ventilation/perfusion (V'/Q') mismatching [17, 18]. Furthermore, in the study by LE PAVEC *et al.* [6], there were no documented episodes of pulmonary oedema among the cohort of patients treated with ERAs, phosphodiesterase type-5 inhibitors (PDE-5 I) or inhaled prostacyclin. 1-, 3- and 5-year survival estimates of the 29 patients were 96%, 92% and 73%, respectively. NYHA functional class was the only variable significantly associated with death, with a trend toward improved survival in those patients who received PAH-specific therapies. Although these data are encouraging and suggest this management approach may have a potential role in the treatment of PLCH associated with PH, well-designed studies are required to determine the benefit/risk ratio of specific PAH therapies in this unique patient population.

Conclusion

Pulmonary vascular involvement in the form of severe pre-capillary PH may be observed in patients with PLCH and often portends a particularly poor prognosis. Lung transplantation remains the treatment of choice for PLCH patients with severe PH. Recent case series indicate that PAH-specific therapies should be tested as a bridge or an alternative to lung transplantation in randomised clinical trials.

Statement of Interest

D. Montani has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Lilly, Novartis, Pfizer and United Therapeutics. In addition to being an investigator in trials involving these companies, his relationships include consultancy services and membership of scientific advisory boards. P. Dorfmüller has participated as a speaker during a bi-annual workshop organised by Actelion and has served as a project-related consultant to Pfizer. D.S. O'Callaghan has relationships with drug companies including AstraZeneca, Boeringher, Lilly, Novartis and Pfizer (speaker's fees and/or funding for attendance at international congresses). M. Humbert has relationships with drug companies including Actelion, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, Merck, Novartis, Nycomed, Pfizer, Stallergènes, TEVA and United Therapeutics. In addition to being investigator in trials involving these companies, his relationships include consultancy services and membership of scientific advisory boards. A. Tazi has received payments for lectures from MSD and GILEAD, and his travel to the ATS and ERS Congresses was funded by MSD and AstraZeneca.

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