

Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension

Report of two cases

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a multisystemic disease affecting mainly the skeleton and the lungs. It is an uncommon interstitial lung disease whose radiological findings are characterized by centrilobular nodules and cysts of varying sizes of mid to upper lung distribution. Pulmonary LCH can be associated with pulmonary hypertension (PH) which is often severe. We report two cases with Pulmonary Langerhans cell histiocytosis who were referred to our pulmonary hypertension clinic because of echocardiographic signs of severe PH. Right heart catheterization confirmed the presence of precapillary PH in both patients; however in one patient the severity of PH was disproportional to lung disease, as revealed from pulmonary function tests and highresolution computed Tomography chest findings, suggesting pulmonary vascular involvement. We would like to emphasize the wide spectrum of Pulmonary LCH - associated PH and the rationale to treat some patients with specific PAH medication.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a smoke related multisystemic disease, with an estimated annual incidence of 4 cases per million population of children under the age of fifteen¹. It has a wide spectrum of clinical and pathological findings because of the invasion of a clonal growth of a differentiated cell of the monocyte-macrophage line (Langerhans cell) to various tissues². Approximately 60% of adults have lung-only disease, namely pulmonary LCH (PLCH), which is an uncommon cause of chronic interstitial lung disease (ILD). Among patients with PLCH, symptoms and signs of pulmonary hypertension (PH) of variable severity are common³. PH due to chronic lung diseases is usually moderate, mean Pulmonary Artery Pressure (mPAP) rarely exceeds 35 to 40 mm Hg, and is related to altera-

tions in blood gases, abnormal pulmonary mechanics and relatively subtle vascular remodelling⁴.

We present two cases with PLCH referred to our Pulmonary Hypertension clinic, in order to show the wide spectrum of PLCH-associated pulmonary hypertension, the multifactorial mechanisms of PH development and the need to treat some patients with specific PAH medication.

CASE REPORTS

Patient A, a 51 years-old female with a smoking history of 70 pack-years and active smoker, was diagnosed with PLCH two years before admission. The diagnosis was based on clinical and radiological findings and documented by positive immunocytochemical and cytofluorimetric study for CD1a cluster (5.4%) in bronchoalveolar lavage fluid. She was referred to our PH clinic because of clinical deterioration (WHO functional class III) and echocardiographic findings of severe PH (RVSP 60mmHg). She was

receiving oxygen 12 hours per day for the last 6 months.

Patient B, a 37 years-old female, with 40 pack-years smoking history, was diagnosed with LCH at the age of 7. The diagnosis was made by cervical lymph node biopsy and she has had symptoms of diabetes insipidus. She was referred to our PH clinic due to clinical deterioration (WHO functional class III) and echocardiographic findings of severe PH (RVSP 110mmHg). She was not under oxygen therapy.

They were both evaluated with 6-minute walk test (6-MWT), blood tests including specific markers of cardiac dysfunction (N-terminal pro brain natriuretic peptide NT-proBNP and troponin), Pulmonary Function Tests (PFTs) including Diffusion Capacity for carbon monoxide (DL_{CO}), high-resolution computed tomography (HRCT) of the lungs and CT angiography, perfusion lung scanning and Right Heart Catheterization (RHC). The results of the diagnostic workup are tabulated in Table 1.

The radiological findings of Patient's A chest HRCT,

TABLE 1. Functional status and main findings of diagnostic workup

	Patient A	Patient B
Demographic characteristics, Sex/Age (years old)	Female / 51	Female / 37
Clinical evaluation		
1. WHO functional class	III	III
2. 6-MWT (m)	390	415
3. Hypoxaemia at rest	Yes	No
Dopler echocardiography		
RVSP (mmHg)	60	110
Tricuspid Regurgitation maximal velocity V'_{max} (m/s)	3,5	4,7
PFTs		
FEV ₁ Liters (% predicted)	1,47 (54)	1,98 (79)
FVC Liters (% predicted)	1,97 (59)	2,64 (91)
FEV ₁ / FVC	0,75	0,75
TLC Liters (% predicted)	3,37 (64)	3,66 (89)
DL_{CO} (% predicted) (mmol/min/kPa)	34	58
RHC		
RAP (mmHg)	6	18
PAP (mmHg) _{Systolic/Diastolic (Mean)}	52/26 (36)	108/44 (66)
CO (L/min)	4,7	4,4
PVR dynes.s/cm ⁵ (Wood Units)	480 (6)	947 (11,8)

Abbreviations: WHO= World Health Organization; 6-MWT= 6 Minutes Walk Test; RVSP= Right Ventricular Systolic Pressure; V'_{max} = maximal velocity; PFTs= Pulmonary Function Tests; FEV₁= Forced Expiratory Volume in the first second; FVC= Forced Vital Capacity; TLC= Total Lung Capacity; DL_{CO} = Diffusing capacity of the lung for carbon monoxide; RHC= Right Heart Catheterization; RAP= Right Ventricular Pressure; PAP= Pulmonary Artery Pressure; CO= Cardiac Output; PVR= Pulmonary Vascular Resistance.

(Figure 1), were strikingly abnormal, showing reticular opacities and multiple thin-walled bilateral cysts of various sizes. The dimensions of cardiac chambers were slightly enlarged. On the contrary, the findings on Patient's B chest HRCT, (Figure 2), regarding lung parenchyma were far less prominent compared to those of Patient A, showing

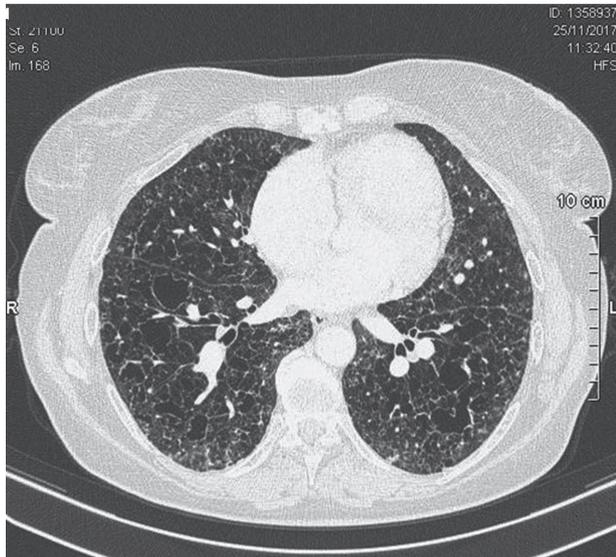


FIGURE 1. High Resolution CT (HRCT) axial image of Patient A showing multiple innumerable thin wall cysts, some bizarre shaped with nodules in the intervening lung parenchyma. Cardiac silhouette is of normal size.

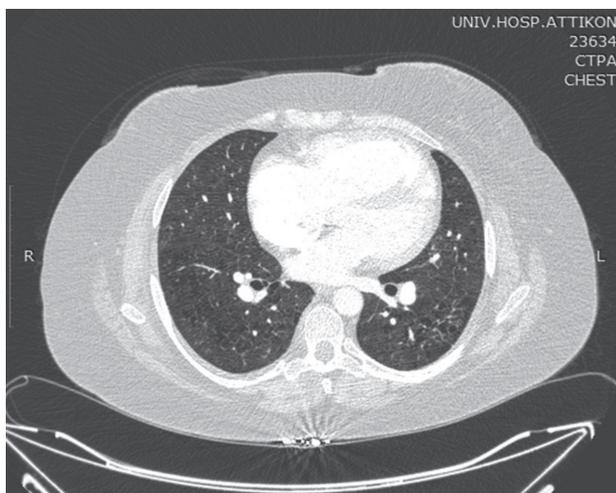


FIGURE 2. Axial CT image (lung window) of Patient B showing mosaic attenuation, small thin-walled bilateral cysts and severe enlargement of the right cardiac chambers.



FIGURE 3. In patient B, coronal reconstruction of high resolution chest CT shows multiple cystic lesions, some bizarre shaped, with an apicobasal gradient distribution and relative sparing of the lung bases and costophrenic angles.

mosaic attenuation and small thin-walled bilateral cysts. Nevertheless, there was severe enlargement of the cardiac chambers, mainly of the right ventricle.

PFTs for patient A revealed a mixed obstructive-restrictive pattern of moderate severity, whereas for patient B tests revealed an isolated moderately low diffusion capacity disturbance.

RHC confirmed precapillary pulmonary hypertension for both patients. For patient A, RHC (mPAP 36 mmHg, and Pulmonary Vascular Resistance - PVR 6 WU) revealed moderate PH which was in accordance with the severity of the underlying parenchymal lung disease and hypoxaemia, as indicated by HRCT, PFTs and blood gases. For patient B, RHC results (mPAP 66mmHg, PVR 11,8 WU) confirmed the presence of severe PH which was inconsistent with the underlying relatively mild parenchymal lung disease.

We treated patient B with specific PAH therapy including an endothelin receptor antagonist (ERA) (macitentan 10mg), a phosphodiesterase type 5 (PDE5) inhibitor (tadalafil 40 mg once daily) and subcutaneous infusion of a synthetic analog of prostacyclin (PGI₂) (treprostinil up to 50ng/kg/min). Six months later on the follow-up visit, patient's functional class was improved, recorded as late II, 6-MWT was 502 meters and this improvement was verified by RHC showing a drop in PVR at 8.1 Wood units. There were also no significant side effects except for pain at the site of infusion.

DISCUSSION

PH is a pathophysiological disorder implicated in multiple clinical conditions, often complicating the course of the majority of cardiovascular and respiratory diseases. According to 2015 ESC/ERS guidelines, PH is clinically classified into 5 groups based on the similarity of clinical presentation, pathology, haemodynamics and treatment strategy⁵. PH due to left-sided heart diseases (Group 2) and chronic lung diseases and/or chronic hypoxemia (Group 3) comprise the vast majority of patients.

PH associated with PLCH manifests more commonly and with greater severity than in patients with other diffuse lung disease^{6,7}. LCH is a multisystemic disease, classified in Group 5 WHO classification for PH, which encompasses diseases of unclear and multifactorial mechanisms. It is characterized by aberrant function, differentiation and proliferation of Langerhans histiocytes, which are phagocytic cells with mononuclear morphologic features¹. The aggregation of these cells in the center of the bronchiole of the lungs forms granulomatous lesions which are responsible for the small irregular or stellate nodules of centrilobular location observed in early stages chest CT⁸. As the disease progresses nodules cavitate and form cysts which finally coalesce to create asymmetrical cysts, so characteristic of LCH. Histopathologic observations have also suggested that in addition to bronchiolocentric inflammation and fibrosis, widespread vascular abnormalities are found in the majority of cases⁸. Langerhans' cell granulomas can infiltrate the walls of small and medium-sized pulmonary arteries, primarily in regions of prominent pulmonary histiocytosis X nodules, whereas medial and subintimal wall thickening may occur in areas uninvolved with pulmonary

nodules⁶. This pattern shows that among the mechanisms involved in the pathogenesis of PLCH, there is an intrinsic pulmonary vascular disease, which is independent of small airway or lung parenchyma involvement^{3,6,9,10}. It has been shown that in ILDs, even at early stages where pulmonary function tests are minimally affected, DL_{CO} and abnormal physiologic dead space ventilation (VD/VT) strongly suggest the presence of pulmonary vascular abnormalities^{9,11}. DL_{CO} was found abnormal in both our cases. For Patient A, the severely reduced DL_{CO} was in accordance with the severity of primary disease as revealed from chest imaging and PFTs. For patient B, whose radiological findings were less striking and PFTs were almost within normal limits, the moderate reduction of DL_{CO} was suggestive of PH existence. Indeed DL_{CO} has been described as the most common indicator of PH coexistence in non end-stage PLCH patients, with inexplicable symptoms and signs⁷. Because PH in PLCH is also encountered prior to end-stage disease⁷, this marker could be useful in guiding diagnosis as well as clinical monitoring of PH; the latter is important since with the advent of specific treatment options, such as endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostanoids clinical improvement has been reported^{10,12}.

Our cases present evidence that the severity of PH in patients with PLCH, does not necessarily correlate with the severity of chest imaging findings or hypoxaemia; there is a rationale of vascular involvement, supporting the use of specific PAH therapy in some cases. Therefore, patients with PLCH and echocardiographic findings of PH should be referred to a PH centre, to undergo all the necessary diagnostic work-up and finally receive the optimum for their case treatment.

ΠΕΡΙΛΗΨΗ
Πνευμονική Υπέρταση σχετιζόμενη με πνευμονική Ιστιοκυττάρωση Langerhans: Παρουσίαση δύο κλινικών περιπτώσεων

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Η ιστοκυττάρωση Langerhans (LCH) είναι μια πολυσυστηματική νόσος, που προσβάλλει κυρίως οστά και πνεύμονες. Αποτελεί σπάνιο αίτιο διάμεσης πνευμονοπάθειας και έχει ως ακτινολογικά ευρήματα κεντρολοβιδιακά οζίδια και διαφορετικού μεγέθους κύστες, που κατανέμονται στα άνω και μέσα πνευμονικά πεδία. Η πνευμονική ιστοκυττάρωση μπορεί να σχετιστεί με πνευμονική υπέρταση, που συνήθως είναι βαριάς μορφής. Παρουσιάζουμε δύο κλινικές περιπτώσεις πνευμονικής ιστοκυττάρωσης, που παραπέμφθηκαν στο τμήμα πνευμονικής υπέρτασης της κλινικής μας επειδή είχαν ηχοκαρδιογραφικά ευρήματα σοβαρής πνευμονικής υπέρτασης. Ο δεξιός καρδιακός καθετηριασμός επιβεβαίωσε την παρουσία προτριχοειδικής πνευμονικής υπέρτασης και στις δύο ασθενείς, ωστόσο στη μία εκ των δύο η βαρύτητα της νόσου ήταν δυσανάλογη της πνευμονικής παρεγχυματικής νόσου, όπως αυτή αξιολογήθηκε με δοκιμασίες λειτουργικού ελέγχου της αναπνοής και υπολογιστική τομογραφία θώρακος υψηλής ευκρίνειας, υποδηλώνοντας την παρουσία πνευμονικής αγγειακής νόσου. Θα θέλαμε να τονίσουμε το ευρύ φάσμα εκδηλώσεων της πνευμονικής υπέρτασης που σχετίζεται με την πνευμονική ιστοκυττάρωση, καθώς και το σκεπτικό της χορήγησης σε κάποιους επιλεγμένους ασθενείς ειδικής κατά της πνευμονικής αρτηριακής υπέρτασης φαρμακευτικής θεραπείας.

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Λέξεις - Κλειδιά: Ιστοκυττάρωση Langerhans, Πνευμονική Υπέρταση, Διάμεση πνευμονοπάθεια

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