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LETTERS

Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan

To the Editors:

Pulmonary Langerhans' cell histiocytosis (LCH)/histiocytosis X is a rare smoking-related interstitial lung disease that predominantly affects adults aged 20–40 yrs. It is commonly associated with irreversible airflow obstruction and highly variable clinical outcomes. The disease may regress spontaneously or following smoking cessation; however, in 20–30% of cases it progresses to chronic respiratory insufficiency. Despite encouraging results in case series and reports [1], no established efficacy on disease outcomes has been demonstrated with corticosteroids, vinblastine or cladribine.

Although rare in patients with early disease, severe precapillary pulmonary hypertension (PH; group 5 in the clinical classification of PH) [2] is frequent in patients with advanced pulmonary LCH. Precapillary PH was present in all 21 consecutive pulmonary LCH patients [3], and in 92% of 39 patients referred for lung transplantation [4] in two series. Lung transplantation is considered the therapy of choice for end-stage pulmonary LCH and chronic respiratory insufficiency, especially among patients who exhibit severe PH [4]. Whether therapy for PH may affect long-term outcomes of disease and impact timing of transplantation is currently unknown. Here, we report the long-term improvement of LCH-associated PH in a patient treated using the dual endothelin receptor antagonist bosentan, obviating the need for lung transplantation.

A male aged 25 yrs was referred to our centre in 1987 with pulmonary LCH. He had smoked for <3 yrs and discontinued smoking when aged 24 yrs. Diagnosis of LCH was made at 22 yrs, with central nervous system (diabetes insipidus, hypogonadism), pulmonary (recurrent bilateral pneumothoraces) and biopsy-proven cutaneous involvement. Pleurodesis with lung biopsy was performed by open surgical parietal pleurectomy. Lung biopsy confirmed LCH, with end-stage destruction of distal bronchiolar walls. Neither Langerhans' cell infiltration nor granulomas of pulmonary artery walls were observed. Computed tomography of the chest showed typical nodules and numerous small thick- and thin-walled cysts predominating in the upper lobes of the lungs. Forced vital capacity and forced expiratory volume in 1 s were 65% of predicted values (table 1). The carbon monoxide diffusion coefficient was normal (92% pred), with moderate hypoxaemia on room air (arterial oxygen pressure (P_{a,O_2}) 8.7 kPa).

In 1994, the patient's residual volume had increased and hypoxaemia worsened; the patient was given glucocorticoid therapy during 1 yr, without improvement of pulmonary LCH. The patient successively received vinblastine, chlormethine, carmustine, thalidomide, vepeside and cladribine for LCH skin lesions; long-term improvement was observed on cladribine. The course of disease was characterised by progressive worsening of lung function parameters and chronic respiratory failure (table 1). Long-term nasal oxygen was started in 1999.

In 2003, the patient presented with increased dyspnoea (New York Heart Association (NYHA) functional class III), with no evidence of right heart failure. Pulmonary function testing showed a marked obstructive defect with increased residual volume (table 1), severe hypoxaemia (6.1 kPa on room air), and severe impairment of pulmonary gas and carbon monoxide transfer. His 6-min walk distance was 335 m, with a decrease in oxygen saturation during assessment on room air to 73%.

At this time, the patient was referred for lung transplantation. Transthoracic echocardiography showed increased estimated systolic right ventricular pressure (62 mmHg) with dilated right heart cavities. Right heart catheterisation demonstrated precapillary PH, with a mean pulmonary arterial pressure of 41 mmHg, a cardiac index of 1.9 $L \cdot min^{-1} \cdot m^{-2}$, and a pulmonary vascular resistance of 649 $dyn \cdot s \cdot cm^{-5}$. Isotopic measurement of right systolic ejection fraction was 15%. Pulmonary embolism was excluded by lung perfusion scan and spiral high-resolution computed tomography. Results of haematological and biochemical tests were within normal ranges. Serology for human immunodeficiency virus was negative. Given the severity of disease, heart and lung transplantation were considered; however, therapy for PH was proposed and inscription on the transplantation list delayed until the next planned assessment. The patient was treated using diuretics and warfarin, and bosentan was started in June 2003.

Bosentan therapy was followed by improved dyspnoea (to NYHA functional class II), 6-min walking distance (by +109 m) and haemodynamics (table 1). Adjunction of sildenafil in 2007 did not provide further improvement and was discontinued after 3 months for claimed intolerance.

To the present day, clinical improvements with bosentan therapy have been maintained for a total of 7 yrs. Due to the observed improvements in clinical status, inscription on the transplantation list was postponed.

Although the prevalence of PH in patients with pulmonary LCH is not precisely known, PH is reported to be present in the vast majority of patients with end-stage disease undergoing evaluation for lung transplantation [3, 4], with an interval from the first respiratory symptoms to referral for transplantation of 11 ± 2.6 yrs (range 1.3–25 yrs). PH in the context of pulmonary

TABLE 1 Overview of clinical, functional and haemodynamic features

	Year of assessment				
	1988	1998	2003	2007	2009–2010
NYHA	I	II	III	II	II
FVC % pred	65	61	65	70	71
FEV_1 % pred	65	44	40	45	40
FEV_1/VC %	81	52	49	50	44
RV % pred	51	150	139	133	171
$D_{L,CO}$ % pred	69	16	<5	7	7
K_{CO} % pred	92	19	5	15	10
P_{a,O_2} at rest# kPa	8.7¶	7.8¶	9.4+	9.1+	9.5+
6-min walk distance m	ND	ND	335	378	444
RVSP mmHg	ND	40	55	45	41
P_{pa} mmHg	ND	ND	41	ND	30
P_{pcw} mmHg	ND	ND	13	ND	10
PVR dyn·s·cm^{-5}	ND	ND	649	ND	300
CI L·min^{-1}·m^{-2}	ND	ND	1.9	ND	2.6
RAP mmHg	ND	ND	9	ND	5
S_{V,O_2} %	ND	ND	63	ND	69
REF %	ND	ND	15	33	32
Therapy	None	Nasal oxygen commenced	Nasal oxygen, bosentan commenced	Nasal oxygen plus bosentan	Nasal oxygen plus bosentan

NYHA: New York Heart Association functional class; FVC: forced vital capacity; VC: vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; RV: residual volume; $D_{L,CO}$: transfer factor for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; RVSP: right ventricular systolic pressure at echocardiography; P_{pa}: pulmonary arterial pressure; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; RAP: right atrial pressure; S_{V,O_2}: mixed venous oxygen saturation; REF: isotopic measurement of right systolic ejection fraction; ND: not determined. #: nasal oxygen; ¶: air; +: 4 L·min^{-1}.

LCH may be severe, with pulmonary arterial pressures $\geqslant$35 mmHg observed in 72% of patients, and $\geqslant$45 mmHg observed in 45% of patients [4]. The severity of PH may be markedly greater in patients with pulmonary LCH than with idiopathic pulmonary fibrosis (despite similar P_{a,O_2}) and chronic obstructive pulmonary disease [3]. When present, PH may contribute to exercise limitation and dyspnoea and possibly reduced survival [5].

The pathophysiology of PH in pulmonary LCH is likely to be multifactorial, with contributions from chronic hypoxaemia, abnormal pulmonary mechanics and vascular remodelling. The pulmonary granuloma in LCH produces a number of cytokines and growth factors implicated in PH, including platelet-derived growth factor [6]. Pulmonary haemodynamics in LCH-related PH are similar to those in idiopathic pulmonary arterial hypertension, are unrelated to lung function variables [3, 7] and are associated with severe histopathological vascular changes including medial hypertrophy, intimal fibrosis, proliferation leading to lumen obstruction and frequent venous involvement [3]. These observations support the hypothesis of vascular remodelling and intrinsic pulmonary vascular disease independent of involvement of small airways and lung parenchyma. However, PH has not been reported in the absence of advanced parenchymal lung disease. Of note, severe PH developed while our patient was treated with supplemental oxygen during 4 yrs with adequate correction of hypoxaemia, ruling out further haemodynamic improvement as a result of oxygen. Taken together, these observations provide a rationale for the use of PH-specific therapy in the management of patients with pulmonary LCH and severe PH, although this has not yet been adequately evaluated.

FARTOUKH *et al*. [3] reported that two patients with pulmonary LCH and severe PH who received intravenous epoprostenol presented with acute pulmonary oedema, which probably resulted from increased pulmonary blood flow in the setting of veno-occlusive disease with prominent pulmonary venous involvement by LCH. Epoprostenol may therefore be hazardous in this patient population due to the frequency of veno-occlusive disease [8].

As substantial evidence links endothelin-1 to the pathogenesis of both PH and pulmonary fibrosis [9] and no alternative therapy other than transplantation was available, our patient was treated with the oral dual endothelin receptor antagonist bosentan on a compassionate use basis. Dramatic and long-term improvements in clinical manifestations and haemodynamic parameters were observed. Although this patient also received the phosphodiesterase type-5 inhibitor sildenafil, it was poorly tolerated and discontinued by the patient within 3 months, and could not therefore account for the observed clinical improvement. It is important to note that improvement of PH, despite unchanged pulmonary function, has been reported in a patient

with pulmonary LCH and PH who quit smoking and received corticosteroids [10]. Whether antiproliferative therapy such as cladribine might affect PH in patients with pulmonary arterial wall involvement by Langerhan's cells is unknown.

In conclusion, these observations demonstrate that long-term improvement of PH may be obtained using bosentan in patients with pulmonary LCH, further supporting the theory of pulmonary vasculopathy. Bosentan therapy may be considered in individual cases as a bridge to lung transplantation, which remains the therapy of choice in patients with pulmonary LCH and severe PH.

L. Kiakouama*,§, V. Cottin*,#,§, B. Etienne-Mastroïanni*, C. Khouatra*, M. Humbert¶,+ and J.F. Cordier*,#
*Hospices civils de Lyon, Hôpital Louis Pradel, Service de Pneumologie–Centre de Référence des Maladies Pulmonaires Rares, #Université de Lyon, Université Lyon I, UCBL-INRA-ENVL-EPHE, UMR754, IFR128, Lyon, ¶Université Paris-Sud, Faculté de Médecine, Kremlin-Bicêtre, and +AP-HP, Centre National de Référence de l'Hypertension Pulmonaire Sévère, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, Clamart, France. §Both authors contributed equally.

Correspondence: V. Cottin, Dept of Respiratory Medicine–Reference Centre for Rare Lung Disorders, Louis Pradel Hospital, Lyon I University, 28 Avenue du Doyen Lepine, 69677 Lyon (Bron) cedex, France. E-mail: vincent.cottin@chu-lyon.fr

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Airway stent improves outcome in intubated oesophageal cancer patients

To the Editors:

Advanced, unresectable oesophageal cancer with airway invasion has a very poor prognosis. For tumours extending into the airway lumen, the primary goals of therapy are for the palliative relief of the malignant obstruction of the oesophageal lumen and central airway and to close the fistula between the oesophagus and central airway. Palliative options include mechanical core-out, dilatation, laser ablation, electrocautery, cryotherapy, photodynamic therapy and brachytherapy [1, 2]. However, satisfactory results may not be immediate or lasting. Endoscopic stenting is effective for airway stenosis from both extrinsic compression and direct tumour invasion, and has also been shown to be useful in the treatment of tracheo-oesophageal fistulas [3]. Among patients with obstruction of the trachea and main stem bronchi with tumour invasion, respiratory failure is one of the most severe complications. Due to advances in airway stents and insertion techniques, interventional bronchoscopic procedures have been reported to facilitate weaning from mechanical ventilation [4]. Moreover, covered self-expandable metallic stents have been used to seal off tracheo-oesophageal fistulas and to avoid aspiration symptoms [5]. However, little has been reported about the effect of stent implantation in respiratory failure patients with oesophageal cancer complicated with airway invasion.

As we previously reported, Ultraflex stent (Boston Scientific, Natick, MA, USA) placement in central airway obstruction, we retrospectively included 16 intubated patients with oesoageal cancer and central airway invasion after Ultraflex stenting in our intensive care unit (ICU) from 2001 to 2009 (table 1) [6]. The outcomes including ventilator weaning rate, ICU and overall survival were described. Most patients (11 out of 16 (68.7%)) were withdrawn from the ventilator and survived after airway Ultraflex stenting. Five patients were finally discharged from hospital and received further treatment including concurrent