A 45-year-old female with a history of dyspnoea

Case report
A 45-year-old female originally presented in January 2001 with a 25 pack-year history of tobacco use, a 2 year history of dyspnoea on exertion, fatigue and polycythaemia. Right heart catheterisation showed a pulmonary artery pressure of 54/26 mmHg (mean 37) with a cardiac index of 2.3 L/min m². An open lung biopsy was performed and the samples from histopathological examination are shown in figure 1.

Figure 1
Open lung biopsy specimens stained with haematoxylin and eosin. Scale bars=200 µm (a, b) and 20 µm (c).

Task 1
Interpret the histopathological findings from the open lung biopsy and suggest a diagnosis.
The patient abstained from tobacco, but noted persistent dyspnoea and was referred for lung transplant evaluation 10 months after the initial diagnosis. At the initial evaluation in November 2001, she was placed in functional class II, on supplemental oxygen, diuretics and anticoagulants. Physical examination disclosed an accentuated second heart sound and a 2/6 holosystolic murmur, which was consistent with tricuspid regurgitation. Pulmonary function studies were remarkable only for an isolated reduction in the diffusing capacity and she managed 288 m during a 6-minute walk test (6MWT). Chest radiography and high-resolution computed tomography (HRCT) were performed (figures 2 and 3).

Evaluations for chronic thromboembolic disease, sleep-disordered breathing, collagen-vascular disease and congenital cardiac anomalies were unrevealing. Right heart catheterisation showed significant worsening of pulmonary hypertension. A diagnosis of pulmonary Langerhans’ cell histiocytosis was made.

Task 2
Interpret the chest radiograph and the HRCT scan.

The patient abstained from tobacco, but noted persistent dyspnoea and was referred for lung transplant evaluation 10 months after the initial diagnosis. At the initial evaluation in November 2001, she was placed in functional class II, on supplemental oxygen, diuretics and anticoagulants. Physical examination disclosed an accentuated second heart sound and a 2/6 holosystolic murmur, which was consistent with tricuspid regurgitation. Pulmonary function studies were remarkable only for an isolated reduction in the diffusing capacity and she managed 288 m during a 6-minute walk test (6MWT). Chest radiography and high-resolution computed tomography (HRCT) were performed (figures 2 and 3).

Task 3
At this stage, how would you progress with the management of this patient?
After 6 months of treatment, the patient noted subjective improvement, walked 79 m further during a 6MWT and remained in functional class II (Table 1). Right heart catheterisation performed 1 year after demonstrated a 14% decline of the mean pulmonary arterial pressure (PAP) and a 50% improvement in the cardiac index (CI). Eighteen months after starting treatment, she continued to work full time, maintained a busy lifestyle, remained in functional class II and was removed from the transplant list. After 2 years on bosentan, 6MWT distance declined by ~70 m, although she was still in functional class II. Six months later, right heart catheterisation confirmed the worsening of pulmonary haemodynamics to the pretreatment level. During this 2.5-year period, both the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) had declined by 400 mL.

Discussion
Pulmonary Langerhans’ cell histiocytosis (PLCH) is a smoking-related interstitial lung disease characterised by proliferation and infiltration of Langerhans’ cells into the lung parenchyma [1].

The clinical course of PLCH in adults is unpredictable, ranging from spontaneous regression to progressive respiratory failure even after smoking cessation [2, 3]. Pulmonary hypertension (PH) is a well-known complication of PLCH, which is almost invariably present and often severe [4].

In the latest classification scheme, PH associated with PLCH is distinguished from the categories of pulmonary arterial hypertension (PAH) and PH associated with lung diseases and/or hypoxaemia [5].

There is no proven therapy for PLCH patients with PH, and treatment during the waiting period for lung transplantation is challenging. The case presented here involved a patient with PLCH with severe PH, who experienced improvement and prolonged stabilisation for >2 years with bosentan, an oral endothelin (ET)1 receptor antagonist.

ET-1 is a potent endogenous vasoconstrictor and smooth muscle mitogen that has been implicated in the pathogenesis of PH [6, 7]. Patients with idiopathic pulmonary arterial hypertension (IPAH) have increased plasma levels and

| Date of diagnosis | Initial listed | Listed for lung transplant and bosentan started | 6 months after bosentan | 12 months after bosentan | 24 months after bosentan | 30 months after bosentan |
|-------------------|---------------|---------------------------------------------|---------------------|---------------------|---------------------|---------------------|
| PAP (mmHg) | 54/26 (37) | 100/44 (64) | 86/35 (55) | 80/30 (50) | 70/25 (45) | 60/20 (40) |
| CO/CI (Fick) | 3.8/2.3 | 3.4/2.0 | 3.4/1.9 | 3.4/1.9 | 3.4/1.9 | 3.4/1.9 |
| A-V O2 difference | NA | 5.8 | 4.1 | 6.8 | 8.2 |
| RAP (mmHg) | NA | 12 | 10 | 10 | 10 |
| PAWP (mmHg) | 18 | NA | 12 | 15 | 15 |
| PVR (wood) | 209 | NA | 107 | 123 | 123 |
| 6MWT (m) | 288 | 367 | 367 | 295 | 220 |
| Resting SaO2 (%) | 94 | 94 | 92 |
| FVC (L) | 1.5 | 1.2 | 1.2 |
| FEV1 (L) | 0.22 | 0.24 | 0.23 |
| TLC % predicted | 105 | NA | 115 |
| DL,CO % predicted | 29 | NA | 26 |
| Weight (kg) | 68 | 78 | 80 |

CO: cardiac output; A-V O2: arteriovenous oxygen difference; RAP: right atrial pressure; PAWP: pulmonary arterial wedge pressure; FVC: pulmonary vascular resistance; SaO2: arterial oxygen saturation measured by pulse oximetry; TLC: total lung capacity; DL,CO: carbon monoxide diffusing capacity of the lung; NA: not available.

Table 1 Pulmonary haemodynamics and pulmonary function tests
overexpression of ET-1 in the pulmonary vasculature [8]. The dual ET-1 receptor antagonist, bosentan, has been shown to improve exercise capacity and short-term haemodynamics in patients with PAH [9]. Furthermore, bosentan delays progression of the condition, as defined by a composite endpoint of death, hospitalisation for PH, or a need for additional medical therapy [9]. In the patient presented here, the timing of improvement (i.e. lengthy period after tobacco cessation), relative stability of lung function, duration of follow-up and sequential haemodynamic data strongly suggest that her condition was positively influenced by treatment of PH with bosentan.

The degree of PH associated with interstitial lung disease (other than in autoimmune diseases [10]) is typically not severe [11]. However, recent studies have indicated that moderate-to-severe PH could be encountered in patients with certain interstitial lung diseases, such as sarcoidosis and PLCH [4, 12, 13]. In a recent report, patients with advanced PLCH had significantly higher PAP and lower CI than comparable groups with chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis [4]. Histopathological analysis showed proliferative changes of arteries and veins. However, the pleomorphic lesions that were present in this case have not been described to date. Haemodynamic derangements do not correlate with the magnitude of parenchymal disease in PLCH, and sequential histopathology in individual cases has demonstrated progression of vascular changes in spite of stability or improvement of parenchymal abnormalities. As a result, pulmonary vascular disease in PLCH appears to be independent of the parenchymal disease. The identification of veno-occlusive pathology may explain why some PLCH patients developed pulmonary oedema after starting prostacyclin, as discussed by FARTOUKH et al. [4], thus raising concern for the use of vasodilators in this group of patients. In contrast, the patient presented here showed no such deterioration and, in fact, demonstrated initial improvement and stabilisation with bosentan for an extended period of time, which may be explained by the exclusive arterial changes seen on her biopsy, or possibly due to the anti-proliferative effects of bosentan compared with the only minimal acute vasodilatory effect.

In conclusion, bosentan should be considered in patients with significant PH associated with PLCH with potential benefits similar to patients in the category of PAH.

References
1. Travis WD, Bats I, Baum JH, et al. Pulmonary Langerhans cell granulomatosis (histiocytosis X): A clinicopathologic study of 48 cases. Am J Surg Pathol 1993; 17: 371–386.
2. Magadini N, Neid A, Bishaw P, Beegard J, Pickering EA. EGD II. Pulmonary Langerhans’ cell histiocytosis: radiologic resolution following smoking cessation. Chest 2009; 135: 2452–2455.
3. Vassallo R, Ryu JH, Schrader CR, Decker PA, Limper AH. Clinical outcomes of pulmonary Langerhans’ cell histiocytosis in adults. N Engl J Med 2002; 346: 484–490.
4. FARTOUKH M, Humbert M, Capron F, et al. Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med 2000; 161: 216–223.
5. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43: Suppl. 12, S2–S12.
6. Macaam PR. Endothelin-1: a mediator of pulmonary hypertension? Pulm Pharmacol Ther 2008; 21: 125–132.
7. Chen YE, Quiri S. Endothelial dysfunction in the pulmonary vascular bed. Am J Med Sci 2000; 320: 223–227.
8. Gud A, Yonagawa M, Wakamatsu H, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993; 328: 1723–1730.
9. Rubin LJ, Budusch DB, Basti A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896–903.
10. Chang B, Wagle PM, White BA, West MA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J Rheumatol 2003; 30: 2396–2401.
11. Harari S, Comel A. Pulmonary Langerhans’ cell histiocytosis. Sarcoidosis Vasc Diffuse Lung Dis 2003; 18: 253–262.
12. Harari S, Simonneau G, de Jall F, et al. Prognostic value of pulmonary hypertension in patients with chronic interstitial lung disease referred for lung or heart-lung transplantation. J Heart Lung Transplant 1997; 16: 460–463.
13. Shou ME, Jones DB, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. Chest 2002; 122: 233–238.