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 $L \cdot min^{1} \cdot m^{-2}$. An open lung biopsy was performed and the samples from histopathological examination are shown in figure 1.

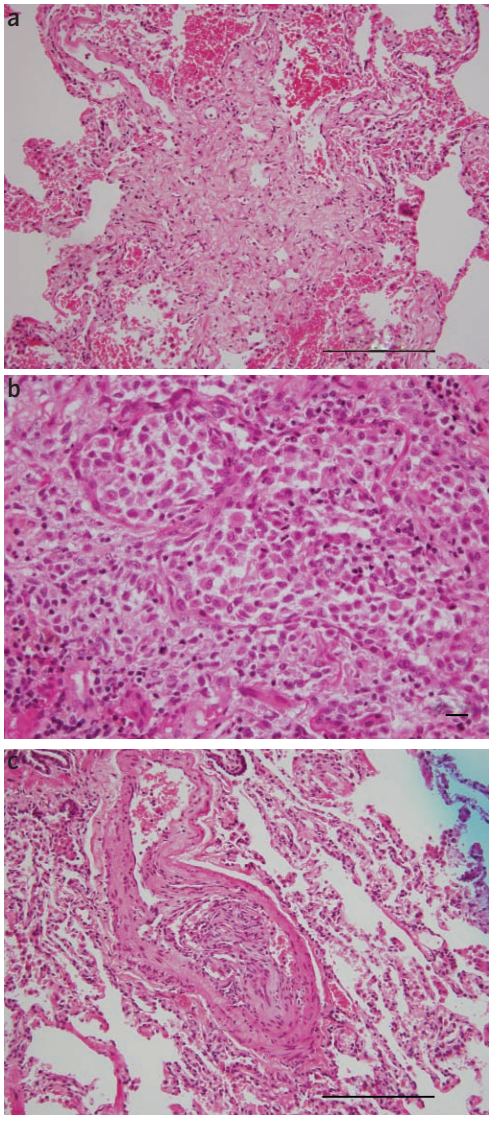

Figure 1
Open lung biopsy specimens stained with haematoxylin and eosin. Scale bars=200 μm (a, b) and 20 μm (c).

Task 1
Interpret the histopathological findings from the open lung biopsy and suggest a diagnosis.

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Answer 1

Figure 1a shows characteristic bronchocentric nodular lesions (stellate scars). Figure 1b is a high magnification of cellular infiltrate with typical delicate and folded nuclei (histocytes). These cells were S-100 positive (data not shown). Figure 1c reveals an intra-arterial angiomatoid/plexiform lesion, resembling the changes of primary pulmonary hypertension. No significant venous abnormalities were seen. A diagnosis of **pulmonary Langerhans' cell histiocytosis** was made.

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).

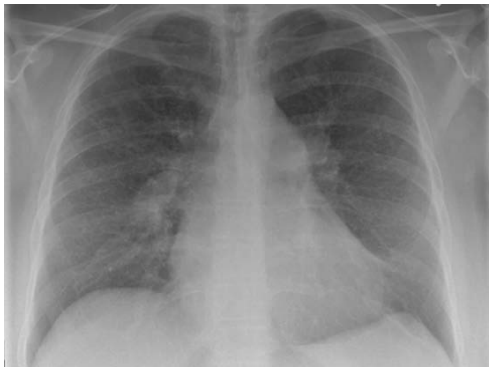

Figure 2
Chest radiograph.

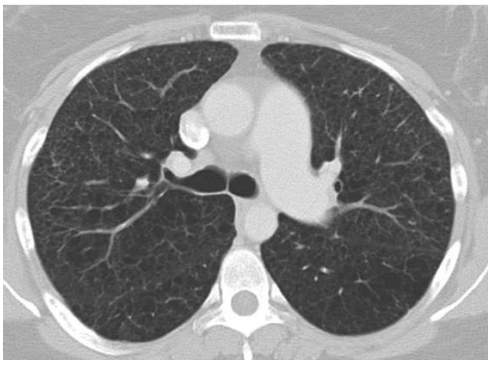

Figure 3
HRCT scan.

Task 2
Interpret the chest radiograph and the HRCT scan.

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.

Task 3
At this stage, how would you progress with the management of this patient?

Answer 2

The chest radiograph showed large pulmonary arteries and interstitial infiltrates. The HRCT scan revealed innumerable small thin-walled cysts predominantly in the upper lobes, and enlarged pulmonary arteries.

Answer 3

The patient was placed on the United Network for Organ Sharing (UNOS) waiting list for lung transplantation and bosentan 125 mg *b.i.d.* was initiated.

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 pre-treatment level. During this 2.5-year period, both the forced expiratory volume in one second (FEV_1) 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

Table 1 Pulmonary haemodynamics and pulmonary function tests

Date	01.2001	11.2001	06.2002	12.2002	12.2003	06.2004
Status	Initial diagnosis	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 (mean PAP)	54/26 (37)	100/44 (64)		86/35 (55)		80/30 (50)
CO/CI (Fick)	3.8/2.3	3.4/2.0		5.4/3.1		3.4/1.9
A–V O_2 difference	NA	5.8		4.1		6.8
RAP	NA	12		10		10
PAWP	18	NA		12		15
PVR	389	NA		637		823
6MWT m		288	367	367	295	NA
Resting S_{P,O_2} %		94		94		92
FVC L		3.5		3.31		3.05
FEV_1 L		2.52	2.44	2.43	2.03	2.1
TLC % predicted		105		NA		115
$D_{L,CO}$ % predicted		29		NA		26
Weight kg		68	72	78	80	80

CO: cardiac output; A–V O_2: arteriovenous oxygen difference; RAP: right atrial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{P,O_2}: arterial oxygen saturation measured by pulse oximetry; TLC: total lung capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; NA: not available.

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 end-point 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 plexiform 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.

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