Pulmonary Langerhans' cell histiocytosis following autologous haemopoietic progenitor cell transplantation

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Introduction
Langerhans' cell histiocytosis (LCH) is a proliferative histiocytic disorder of unknown origin. The lesions of LCH contain single or multifocal proliferation of histiocytes similar in phenotype to dendritic Langerhans' cells (1). The disorder ranges in clinical severity from a solitary eosinophilic granuloma of bone to a generalised disease with multiple organ involvement. Primary involvement of the lung is rare and only few isolated cases have been reported (2). Occasionally, pulmonary LCH has been reported to be associated with Hodgkin's disease (3); the underlying pathogenic mechanism of such association remains unknown. Here, we report the case of a 19-year-old patient who developed pulmonary LCH 2 months after receiving an autologous haemopoietic progenitor cell transplantation (AHPCT) for Hodgkin's disease.

Case Report
A 19-year-old male presented with exertional dyspnoea. The patient had smoked one pack of cigarettes daily for the last 7 years. In 1991, he was diagnosed with nodular sclerosing Hodgkin's disease with both mediastinal and right axilar lymph node involvement (stage III) and treated with six courses of chemotherapy and mantle radiotherapy. In 1994, he received three additional cycles of chemotherapy because of recurrent Hodgkin's disease. Due to the lack of response he was admitted to our hospital to be treated with an AHPCT. Before transplantation, he did not complain of respiratory symptoms, the chest X-ray was normal and pulmonary function tests were within normal limits. Intensive combination chemotherapy: BCNU 558 mg (in day 6), VP-16 624 mg (days 5–2), cytarabine 372 mg (days 5–2), and cyclophosphamide 5200 mg (days 5–2), was used as conditioning regimen. Two months after transplantation, he noticed exertional dyspnoea. Physical examination was unremarkable. Similarly, the haematological and biochemical values were within normal limits. Both chest X-ray and high resolution CT scan showed normal lung and mediastinal structures. Nevertheless, pulmonary function tests revealed a restrictive ventilatory pattern, together with reduced CO diffusing capacity (DLCO) and moderate hypoxaemia. An incremental exercise test showed a reduced exercise tolerance with marked decrease of arterial PO₂. These functional abnormalities strongly suggested an underlying interstitial lung disorder associated with autologous transplantation. Fiberoptic bronchoscopy showed no macroscopic abnormalities. The differential cell count of bronchoalveolar lavage (BAL) fluid contained 100% of alveolar macrophages and the percentage of CD4-positive cells reached 6% (normal <3%) (4). Bacterial, acid-fast bacilli, Pneumocystis carinii stain and fungal cultures were negative. Histological examination of transbronchial biopsy specimens showed normal lung parenchyma. Due to the absence of specific diagnosis, an open lung biopsy was performed.

The histopathological study of lung tissue showed a focal enlargement of the interstitial spaces containing large histiocyte-like cells with convoluted nuclei. Immunohistochemical study demonstrated positivity of these cells for protein S-100 (Fig. 1). We considered these findings diagnostic of LCH. It is commonly accepted that conventional stainings are sufficient to suspect this lesion, and the positivity of convoluted histiocytic cells for S-100 confirms the diagnosis of LCH (5). No evidence of pulmonary infection and/or a lymphoproliferative disorder was detected in any of the sections. The patient was initially treated with 60 mg/day prednisone that was slowly tapered (Fig. 2). At the present time, 2 yr after transplantation, he is without respiratory complains and pulmonary function tests have improved substantially, although both a moderate reduction of DLCO and mild arterial Ω₂ desaturation still persists during exercise.

Discussion
The most striking finding in the present case was the development of pulmonary LCH after AHPCT, which was not associated with detectable radiological signs
FIG. 1. (a) Photomicrograph of lung biopsy specimen showing thickening of interalveolar septa by accumulation of S-100 positive cells. (S-100, 100 ×). (b) Detail of large cells with convoluted nuclei showing positivity for S-100. (S-100, 630 ×).

despite extensive granulomatous histological involvement. Pulmonary LCH has not been previously reported after autologous bone marrow transplantation of AHPCT. However, development of pulmonary LCH after combined chemotherapy and radiotherapy for Hodgkin's disease has been described in anecdotal cases (3). Although the exact mechanism of this association remains undecided, most authors suggest that both radiotherapy and chemotherapy might serve as a stimulus for abnormal proliferation of histiocytes (6–9). The singular involvement of the lung in our case is consistent with a reactive process following combined chemotherapy and mediastinal radiotherapy previous to AHPCT. However, there is no way to decide if this case represents a development of pulmonary LCH after AHPCT or if it was present before but accelerated by the procedure, as previously suggested (3).

In pulmonary LCH, chest X-ray usually reveals a diffuse reticulonodular pattern with micronodules measuring 2–5 mm in diameter and pulmonary cysts that predominate in the upper lobes (2,8). However, in occasional cases chest X-ray can be normal (14) and CT scan of the lung may disclose focal or diffuse abnormalities (10). In the present case, high resolution CT scan failed to demonstrate abnormal signs, despite the fact that this technique has shown to be the most sensitive for pulmonary LCH (11). We hypothesize that the small size of pulmonary nodular lesions in our case was below the scan resolution (1 mm). It is of note that pulmonary function tests, including an incremental exercise test, were highly sensitive in detecting the functional impairment produced by the parenchymal lung disorder. Milburn et al. (12) have already highlighted the high sensitivity of lung function measurements in detecting pulmonary abnormalities after bone marrow transplantation, even before the development of radiographical infiltrates. Therefore, as shown by the present case, it is highly recommendable to perform pulmonary function tests before and after autologous transplantation, in order to have a close follow-up of the clinical outcome of patients undergoing this procedure. Because of the high incidence of spontaneous remission in untreated patients, the efficiency of different immunosuppressive therapeutic strategies for pulmonary LCH remains unknown (2). Several studies have reported the usefulness of corticosteroids with or without associated chemotherapy (13,14). Since that severe impairment of pulmonary function at the time of diagnosis has negative prognostic value in patients with Langerhans' cell histiocytosis (15) an early intervention may be beneficial in terms of survival. In our patient, whose pulmonary function was closely monitored, we have shown substantial clinical and functional improvement after corticosteroid therapy and cessation of smoking (Fig. 2).
References