Blood stem cell transplantation to treat cystic lung light chain deposition disease

To the Editor:

Light chain deposition disease (LCDD) is a rare disease resulting from non-amyloid immunoglobulin (Ig) light chain deposition in tissue. In systemic LCDD, plasma cell dyscrasia is common and renal involvement is almost always present, sometimes with damage to other organ systems (cardiac, hepatic and neurological systems). LCDD can be limited to the lungs, presenting as multiple cystic lung disease, nodules or bronchiectasis. Cystic lung related to LCDD (CL-LCDD) was recently described in patients referred for lung transplantation to treat end-stage multiple cystic lung disease [1]. In the reported cases, blood and bone marrow examinations did not reveal clonal plasma cell proliferation. Here we report the first case of CL-LCDD revealing a B-cell extrapulmonary lymphoproliferative disorder and the results of treatment for the underlying haematological disease with autologous peripheral blood stem cell transplantation during the CL-LCDD. Despite respiratory insufficiency, lung transplantation was actually not considered because of the underlying disease.

A 37-year-old Caucasian female was referred to Toulouse University Hospital (Toulouse, France) with cough, dyspnoea and fever of 5 months duration. The patient had sinusitis and bronchitis in infancy, and a close family member had been treated for lymphoma. She had recently quit smoking (smoking history: 10 pack-years). Physical examination revealed only one small indurated cervical lymphadenopathy. Pulmonary function tests showed an obstructive pattern with profound hypoxaemia and altered diffusing capacity of the lung for carbon monoxide: forced expiratory volume in 1 s (FEV1) was 1700 mL (56% predicted), vital capacity was 2500 mL (73% predicted), total lung capacity was 103% predicted, diffusing capacity of the lung for carbon monoxide corrected for haemoglobin was 47% predicted and the partial pressure of oxygen in arterial blood was 42 mmHg. A computed tomography (CT) scan revealed diffuse thin-walled cystic formations associated with segmental atelectasis, emphysematous-like changes, bilateral bronchiectasis, and calcified hilar and subcarinal lymph nodes (fig. 1a). Positron emission tomography (PET)-CT revealed minimal uptake in the subcarinal lymph node. Histology of endobronchial biopsies revealed typical LCDD characterised by an inflammatory infiltrate with extracellular amorphous eosinophilic deposits (fig. 1b), negative Congo-red staining and no birefringence under polarised light. Immunofluorescence assays of frozen tissue revealed intense labelling for anti-κ light chain antibody. The diagnosis was CL-LCDD.

An extensive search for extrapulmonary organ involvement was negative. Serum densitometry revealed a small monoclonal IgM κ peak (0.29 g·L\(^{-1}\)), with associated hypogammaglobulinaemia (6.64 g·L\(^{-1}\)). No cryoglobulinaemia was found. The level of κ serum free light chains (sFLC) and κ/λ sFLC ratio were increased to 1290 mg·L\(^{-1}\) (normal range: 3.3–19.4 mg·L\(^{-1}\)) and 156.17 (normal range: 0.26–1.65), respectively. Bone marrow cytology revealed no signs of a plasma cell disorder. A bone marrow biopsy demonstrated a lymphoplasmacytic lymphoma with positive staining for IgM κ. Mediastinoscopy revealed lymphadenopathy with infiltration by the lymphoma and by light chain deposits without amyloidosis.

The treatment course is in figure 1c. Corticosteroids at 1 mg·kg\(^{-1}\) improved the cough, dyspnoea, FEV1 and κ-sFLC level. The patient then underwent six chemotherapy cycles with bortezomib, cyclophosphamide, dexamethasone and rituximab. The first three cycles were effective, but then clinical deterioration was observed. The CT findings were not modified. Second-line chemotherapy was implemented with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone. Hypoxaemia, CT findings and κ-sFLC level worsened after two cycles. The patient underwent autologous peripheral blood stem cell transplantation after high-dose melphalan (200 mg·m\(^{-2}\)), which was well tolerated, with a rapid improvement in sFLC level. Although CT revealed a progression of emphysematous-like lesions, at 30 months, the patient was still alive. Long-term oxygen therapy was limited to deambulation, the κ-sFLC level was reduced to 4.3% of the initial level (55 mg·L\(^{-1}\)) and FEV1 was stable (50% predicted).

Pulmonary LCDD is classically described in two clinic-radiological patterns: nodular and diffuse, including CL-LCDD, apart from pulmonary disorders present in systemic LCDD. A third presentation involves the airways [2, 3]. In nodular disease, patients are usually asymptomatic or have moderate respiratory symptoms (e.g. cough and dyspnoea) with multiple nodules. Association with a lymphoproliferative disorder is common, e.g. gammopathy of undetermined significance, lymphoplasmacytic lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma or chronic lymphocytic leukaemia (CLL) [4]. The disease does not
progress to chronic respiratory insufficiency, and the prognosis is linked to malignant B-cell dyscrasia. CL-LCDD should be considered among the causes of multiple cystic lung diseases, especially with nodes or bronchiectasis. According to this case and COLOMBAT et al. [2], the level of sFLC and endobronchial biopsies using tissue frozen during a flexible bronchoscopy are useful for diagnosis. CL-LCDD has been reported in five cases [1, 2, 5]. The patients were predominantly female, were 20–64 years-old and were light or nonsmokers. Four patients showed progression to respiratory failure; one, in the absence of medical care, to death. No monoclonal peaks were detected. Two patients showed increased $\kappa$/$\lambda$ sFLC ratio [1, 5]. Bone marrow did not show plasmacytic proliferation. COLOMBAT et al. [6] found a monoclonal population of B-cells in every pulmonary tissue sample but not in blood samples. The authors did not exclude that CL-LCDD could be a form of pulmonary MALT lymphoma without the histological diagnostic criteria of the World Health Organization Lymphoma Classification. An antigen-driven primary pulmonary lymphoproliferative disorder is suggested. However, despite bone marrow and lung explant analysis, no patient had histological evidence of lymphoma.

In light chain amyloidosis, the tropism of organ involvement depends on the variability of the gene encoding for the monoclonal Ig light chain variable region [7]. However, we have no relevant data concerning LCDD.

In several case reports, the treatment for CL-LCDD associated with chronic respiratory insufficiency is lung transplantation, with a maximum follow-up of 4 years without recurrence. One patient received chemotherapy and autologous peripheral blood stem cell transplantation before lung transplantation but with an increased number of lung cysts [1]. Because the patients presented only lung disease and did not have lymphoma, lung transplantation was appropriate.

In systemic LCDD, monoclonal plasmacytic dyscrasia is frequent, and multiple myeloma, Waldenstrom’s macroglobulinaemia, lymphoma and CLL may be involved. Unlike treatment for local disease, treatment for systemic LCDD aims to reduce the sFLC level to limit the toxicity of non-amyloid deposits. With management for light chain amyloidosis, chemotherapy can be associated with peripheral blood stem cell transplantation [8].

In our case, clinical and paraclinical investigations revealed cervical and mediastinal lymphadenopathy, a monoclonal IgM peak and a marked increase in $\kappa$-sFLC level, all suggestive of lymphoma, which was
found in the lymph nodes and in bone marrow. Autologous peripheral blood stem cell transplantation was performed because of the respiratory and haematological relapse after the two lines of chemotherapy, with increased κ-sFLC level. This treatment has been shown to be efficient in light chain amyloidosis [9] and, more recently, in lymphoplasmacytic lymphoma [10]. Our case of CL-LCDD achieved respiratory stability and a haematological response, with a marked decrease in κ-sFLC level maintained over time. The consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis [11] contains no clear definition of a pulmonary response to treatment. An improvement in interstitial disease is rare. A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis [11] contains no clear definition of a pulmonary response to treatment. An improvement in interstitial disease is rare. A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis [11] contains no clear definition of a pulmonary response to treatment. An improvement in interstitial disease is rare.

Our case of CL-LCDD differs from other cases by the evidence of lymphoma and treatment choice. We are cautious because of the worsening CT evidence of cystic lesions. However, peripheral blood stem cell transplantation was efficient in ameliorating the haematological disorder and stabilising the clinical respiratory condition. As in systemic LCDD with end-stage renal disease, organ transplantation may be considered after long-term reduction of the sFLC level, but relapse is a risk [13].

We report the first case of CL-LCDD revealing a lymphoplasmacytic lymphoma with positive staining for IgM κ that was treated with autologous peripheral blood stem cell transplantation, after inefficient chemotherapy.

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We report a case of CL-LCDD that was treated with autologous peripheral blood stem cell transplantation http://ow.ly/NUQOt

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References


