ORIGINAL RESEARCH LETTER

Effect of cladribine therapy on lung cysts in pulmonary Langerhans cell histiocytosis

To the Editor:

Langerhans cell histiocytosis (LCH) is a group of disorders with variable presentations and outcomes. Children with LCH primarily have bone and multisystem involvement with little impact of lung involvement and usually no treatment indication for lung disease [1, 2]. Conversely, pulmonary involvement is the main determinant of morbidity and mortality in adults and is usually resistant to first-line chemotherapeutic agents used in children [3]. Pulmonary LCH belongs to the spectrum of LCH and is primarily found in smoker adults. In most cases, quitting smoking results in clinical, functional and radiological improvement at early or nodulo-cystic stages [4]. In those with progressive disease and significant lung function impairment, cladribine (a purine nucleoside analog) has been proposed as rescue therapy for progressive, refractory nodulo-cystic disease [5, 6]. However, there are currently no treatment options for patients with advanced, cystic pulmonary LCH.

Here, we report a case of multisystem LCH with advanced cystic pulmonary LCH in an adult with spectacular response to cladribine. Briefly, a 34-year-old female, current smoker, presenting with polyuria, polydipsia and low-grade fever was diagnosed with central diabetes insipidus and was started on desmopressin replacement therapy. Physical examination was unremarkable with no clinical signs of pulmonary hypertension. Echocardiography was normal. Hypophyseal micro-adenoma was found by brain magnetic resonance imaging. A full endocrinological workup was otherwise normal. Computed tomography (CT) of the chest revealed diffuse bilateral thick-walled cystic lesions and nodules sparing the lung bases (figure 1a and b). Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with CT (^{18}F-FDG PET/CT) showed increased uptake of the lung lesions (figure 1c and d). Since no lung biopsy had been undertaken, a presumptive diagnosis of pulmonary LCH was established. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were 2.85 L (74%) and 2.82 L (84%), respectively. The diffusing capacity of the lung for carbon monoxide (D_{LCO}) was 60% predicted. The patient quit smoking. However, 6 months later, lung function tests had worsened with decreases of FVC to 2.5 L (66%), FEV_1 to 2.2 L (67%) and of D_{LCO} to 57%. After written informed consent, the patient was treated with subcutaneous cladribine (0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ for 5 days per course), one course monthly for four consecutive months, along with prophylaxis against herpes zoster virus and *Pneumocystis jiroveci*, and anti-conceptive hormonal therapy which was continued until 6 months after the discontinuation of cladribine. Treatment was well tolerated. Evaluation after 4 months of treatment demonstrated dramatic improvement in pulmonary function tests, with an increase of FVC to 3.66 L (96%), FEV_1 to 2.81 L (85%) and of D_{LCO} to 64%. On chest CT, many lung cysts had disappeared and the wall thickness of others had dramatically decreased, while other cysts had paradoxically increased in size (figure 1e and f). No residual abnormal uptake was found on repeated ^{18}F-FDG PET/CT. Yet, the absence of increased uptake of ^{18}F-FDG by the lung cysts does not preclude lung function improvement following cladribine therapy [7]. At 1 year, D_{LCO} was 72% predicted, and volumes were unchanged.

Previously, two reports have been published and suggested the potential efficacy of cladribine in pulmonary LCH at bullo-cystic stage. Epaud *et al.* [8] described a child who had been treated with

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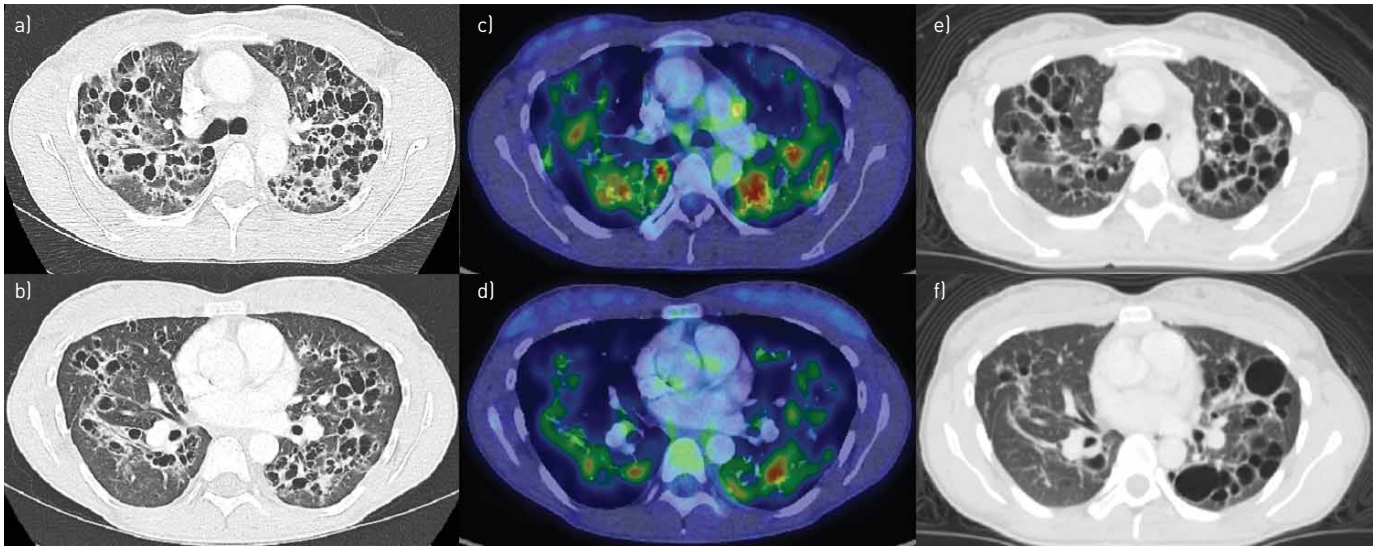

FIGURE 1 a, b, e, f) Computed tomography (CT) of the chest and c, d) positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) integrated with CT at the same anatomic level before (a–d) and after (e, f) cladribine therapy. a, b) Multiple thick-walled cysts of variable size associated with parenchymal infiltrates suggesting infiltration by inflammatory cells are visible. c, d) Increased ^{18}F-FDG uptake by lung parenchyma is visible. e, f) Heterogeneous radiological response following cladribine therapy, with disappearance of some cysts, enlargement of others, along with decreased cyst wall thickness and resolution of parenchymal infiltrates is visible.

multiple chemotherapeutic regimens for LCH. Due to lack of efficacy and disease progression, it was decided to introduce cladribine as salvage therapy. In total, the child received six cycles of subcutaneous injection of 5 mg·m^{-2} of cladribine for 5 days every 4 weeks and had undoubtedly clinical, functional and radiological improvement following cladribine therapy [8]. The most unexpected finding was the decreased number and size of the thick-walled cysts. In another study, Lorillon *et al.* [9] reported on the dramatic changes of cysts using cladribine in three current adult smokers with pulmonary LCH, previously treated with corticosteroids with or without vinblastine; yet, one patient had been diagnosed in childhood. Our case is unique because cladribine was the first-line therapy; as a result, chemotherapy preconditioning cannot be counted as a confounding factor as in previous cases. This case highlights the heterogeneous response of lung cysts to cladribine, with some cysts vanishing with treatment while others became enlarged. In addition, the decrease of wall thickness of some cysts, as well as the disappearance of other cysts, correlates well with the finding of Kim *et al.* [10] who demonstrated that lung cysts in pulmonary LCH harboured active inflammatory Langerhans cells sheets and florid granulomas regardless of the wall thickness or cyst shape (bizarre or rounded).

Our observation strengthens the evidence of the efficacy of cladribine in advanced stage pulmonary LCH in adults and, therefore, cystic changes should no longer be considered as end stage or irreversible in pulmonary LCH patients. Nevertheless, treatment trials are eagerly awaited to clarify the benefit:risk ratio, and to avoid unnecessary treatment with potentially toxic drugs.

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