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Lung transplantation as a rescue option in childhood critical pulmonary Langerhans cell histiocytosis

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To the Editor,

Langerhans cell histiocytosis (LCH) is a rare disease affecting mostly children and can affect nearly all organ systems. This clonal disorder is characterized by an accumulation of pathological CD1a+ CD207+ histiocytes, in which somatic mutations are typically found in a proto-oncogene in the MAPKinase pathway. Pulmonary LCH concerned mainly cigarette smoker's adults with a peak frequency at ages 20–40 years.¹ It is reported in ~10% of children with LCH with eventual severe lung damage.²

A 26-month-old boy with chronic cutaneous scalp lesions was referred because of an acute dyspnea. Computed tomography (CT) scan revealed diffuse cystic lesions of the lungs (nodular and cystic CT scores,³ 6/24 and 14/24, respectively, Figure 1A) associated with

a compressive thyroid goiter. There was no bone lesion. Skin biopsy confirmed the diagnosis of LCH with the *BRAF* c.1457_1471del gain-of-function deletion. An induction with vinblastine-steroid led to the regression of the goiter allowing oxygen withdrawal. However, after 4 weeks of treatment, the patient remained tachypneic with persistent retractions. The CT scan showed worsening of the cystic score from 14 to 19/24, whereas the nodular score decreased from 6 to 3/24. After a national multidisciplinary team (MDT) meeting and parental consent, off-label treatment with the MEK inhibitor cobimetinib was started at an initial dose of 10 mg once daily (1.1 mg/kg/day) on a 21/7 schedule (7-day rest period in each 28-day cycle). The dose of cobimetinib was then adjusted according to the plasma levels at steady states, so that these approached the

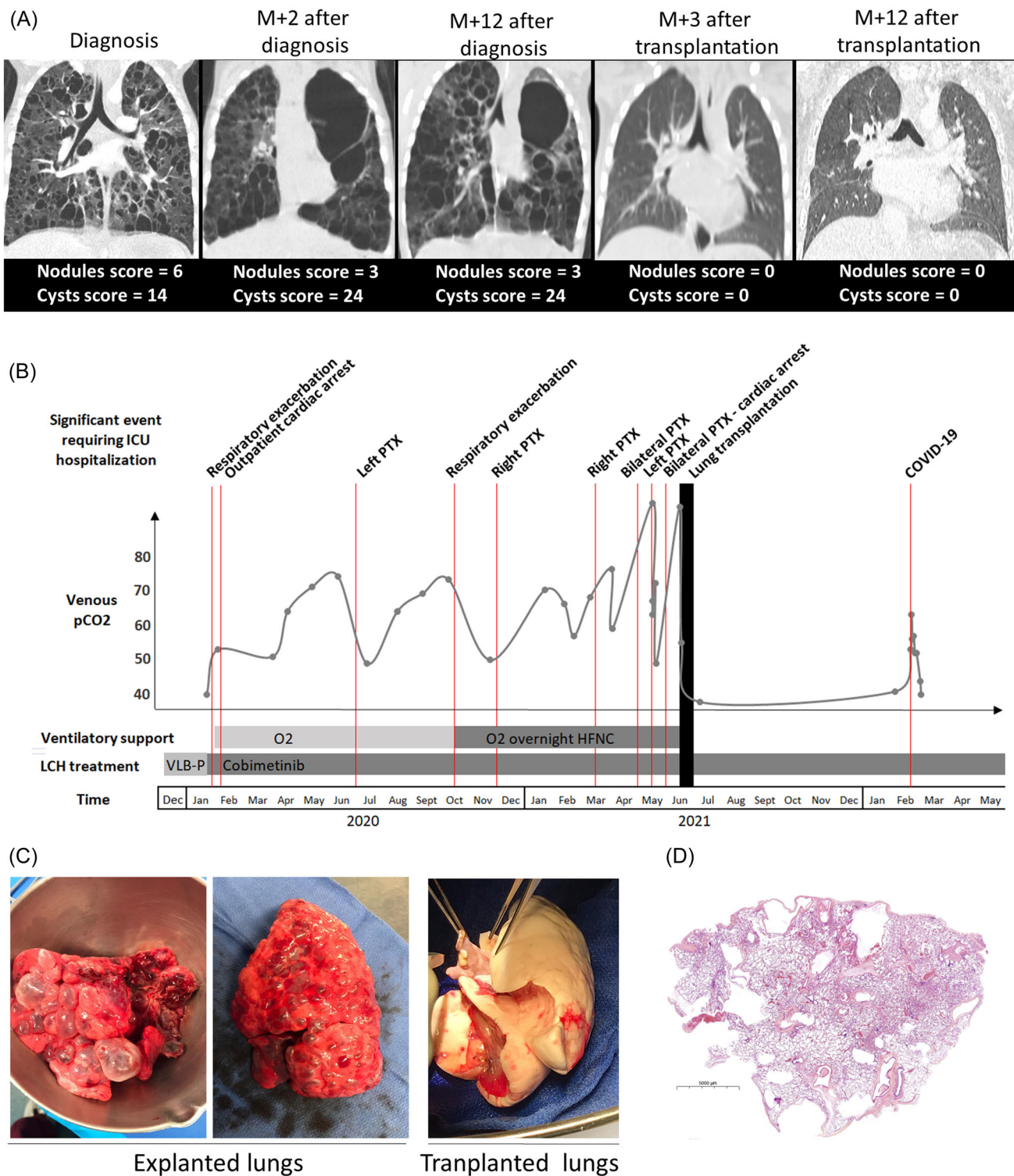


FIGURE 1 Medical course, management, and outcome of young children with destructive pulmonary LCH. (A) Thoracic computed tomographic (CT) scans during follow-up and evolution of nodular and cystic CT scores.³ (B) Evolution since diagnosis. The 11 ICU hospitalizations are represented with red lines (10 episodes) and lung transplantation by the thick black line. (C) Explanted left and right lungs compared with the transplanted lung from a 2-year-old donor. (D) Histopathology of explanted lungs showing several large cysts, mainly localized close to pleura. No granulomas were present. COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannulas; ICU, intensive care unit; LCH, Langerhans cell histiocytosis; PTX, pneumothorax.

published Cmin of 127 ng/mL. Because of undernutrition, enteral tube feeding was started, as well as substitutive immunoglobulins.

The patient went through a succession of acute respiratory failures requiring nine intensive care unit (ICU) hospitalizations. The two first exacerbations required noninvasive ventilation (NIV), rapidly switched by high-flow nasal cannulas (HFNC) therapy to limit the risk of pneumothorax. He was discharged with home oxygen therapy and overnight HFNC because of hypercapnia (Figure 1B). Subsequently over 18 months, 7 exacerbations occurred, Six of them related to a pneumothorax: left side ($n = 2$), right side ($n = 2$), or bilateral ($n = 2$), the last one leading to a cardiorespiratory arrest. At this point, the child was 3.6 years old, weighted 11.3 kg, measured 92 cm. The cystic CT score had the highest value of 24. There was no pulmonary hypertension. After another national MDT meeting and with the agreement of the parents, the child was registered on the waiting list for lung transplantation with the highest degree of priority. Thirty-seven days later, a bilateral lung transplantation was performed from a deceased 2-year-old donor (D). D/recipient (R) serological status were D+/R- for cytomegalovirus (CMV) and D+/R- for Epstein-Barr virus (EBV). The explanted lung showed macroscopic bullous growths blowing all the parenchyma (Figure 1C). Histopathology of explanted lungs confirmed voluminous cysts and failed to detect pathologic CD1a CD207+ LCH cells (Figure 1D) as commonly reported in advanced pulmonary LCH. The surgical procedure was performed under extracorporeal membrane oxygenation for a duration of 3.2 h. The patient was extubated 8 h after surgery. Mycophenolate mofetil, cyclosporine, and corticosteroid were started to prevent organ transplant rejection. Acute humoral rejection occurred at Day 8 after transplantation, successfully treated by rituximab and a cyclosporine to tacrolimus switch. Valgancyclovir was administered to prevent CMV disease and cobimetinib therapy was pursued continuously, to avoid any variation in exposure to immunosuppressants due to drug interactions. The patient was discharged at home on Day 26 after the transplantation eupneic in room air. Seven months after transplantation, a polymorphic posttransplant lymphoproliferative disease was diagnosed. Rituximab combined with reduction of immunosuppression resulted in a complete clinical remission, however, with persistent plasma EBV replication. Few days after the last rituximab infusion, the patient was infected with severe acute respiratory syndrome coronavirus 2 (Omicron BA.1.18 subvariant) and had a rapid evolution toward an acute respiratory distress syndrome. He received convalescent plasma therapy and required mechanical ventilation for 12 days, with a favorable outcome without respiratory sequelae.

Since then, 22 months posttransplantation, at 5.5 years, the patient is stable under oral medications with tacrolimus, corticosteroid, cotrimoxazole, valgancyclovir, and cobimetinib. The patient is free from nutritional support and has reached his targeted weight for height (14.5 kgs). He is eupneic and his first successful lung function tests showed normal functional residual capacity and interrupter resistances but cooperation was not sufficient to perform spirometry.

Lung transplantation in children is a rare procedure, mainly reported so far in teenagers with cystic fibrosis. Recently, larger

cohorts of patients with interstitial lung diseases or other rare lung diseases were also reported.⁴ Here we report a rare case of successful pediatric lung transplantation for pulmonary LCH,⁵ which was obtained by the close interdisciplinary collaboration between the LCH reference center, the rare lung disease reference center (RespiRare), the lung transplantation, and the ICU teams. Despite a very heavy care burden, the child was able to stay at home most of the time. LCH did not seem to burden the initial phase of the lung transplantation and, after 22 months, the clinical and functional result is highly positive and the boy could recently attend school.

Regarding specific LCH therapy, the progression of the cystic CT score after 4 weeks of vinblastine steroid, a therapy reported as not very effective in adults with pulmonary LCH, contributed to the decision of an early switch with targeted therapy which efficacy has been reported in pediatric lung damage.² Alternatively, 2-chlorodeoxyadenosine was discussed but the prolonged immune deficiency induced by this treatment constituted a drawback in this context. Unfavorable outcome of lung lesions were likely linked to the natural course of the severe destructive lesions, possibly worsened by temporary use of NIV during acute respiratory exacerbations despite being used minimally to limit the risk of pneumothorax.

Cobimetinib was maintained during surgery without adverse effect on the surgical hemostasis and was pursued thereafter to prevent LCH recurrence on the transplanted organ, with a good tolerance.

In conclusion, management of severe lung involvement in children with LCH is highly challenging and require collaboration between several experts. Advisability and feasibility of lung transplantation, which should be discussed, and early use of targeted therapy may be considered.

AUTHOR CONTRIBUTIONS

Nadia Nathan and Sébastien Heritier designed the research, collected the data, and wrote the manuscript. Nadia Nathan and Sébastien Heritier have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the clinical care of the patient and/or the patient management decision. All authors critically read the manuscript.

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CONFLICT OF INTEREST STATEMENT

Jean-François Emile received honoraria from Qiagen and Pierre Fabre. The remaining authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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