Confocal LASER endomicroscopy in Niemann–Pick disease type B

To the Editor:

A 41-year-old female was referred to our institution for a recent worsening of chronic cough and dyspnoea that had slowly increased over the past 6 years. She had never smoked, had no notable medical history and was not under any medication. She had two healthy children and no past family history. In 1999, some initial pulmonary function tests (PFTs) were performed in another centre to explore her chronic cough, showing a subnormal forced vital capacity (2.64 L, 95% of predicted) and diffusing capacity of the lung for carbon monoxide (D_{LCO}; 90% of predicted). Chest computed tomography (CT) showed an interstitial lung disease (ILD) with interlobular septa thickening in the upper lobes associated with ground glass opacities (figure 1a). No definitive diagnosis was made and the patient was lost to follow-up.

20 years later, she was referred to our pulmonology department for further investigation of a recent worsening of her cough and slowly progressive dyspnoea. The clinical examination was unremarkable, except for the perception of crackles in the lung bases. Oxygen saturation was 97% on room air. The CT scan identified similar findings characterised by mild smooth thickening of the interlobular septa and intralobular lines, ground glass opacities and cysts mainly in the lower lung zones (figure 1b). No honeycombing, pleural effusion or mediastinal adenomegaly were observed. A prominent hepatosplenomegaly was also noted. Haemoglobin was 13.3 $g{\cdot}dL^{-1}$, the blood leukocyte count was $8.4{\times}10^{9}{\cdot}L^{-1}$ and platelet count was 160 $G{\cdot}L^{-1}$. The serum levels of creatinine and C-reactive protein were 43 $\mu mol{\cdot}L^{-1}$ and 2.7 $mg{\cdot}dL^{-1}$, respectively. Liver enzymes, lipid profile and haemostasis parameters were inconspicuous; gamma globulins were 13.8 $g{\cdot}L^{-1}$. Angiotensin-converting enzyme was normal at 33 $U{\cdot}L^{-1}$ (12–68 $U{\cdot}L^{-1}$). Antinuclear antibodies, as well as granulocyte-macrophage colony-stimulating factor autoantibodies, were negative. No proteinuria was detected. The PFT demonstrated a restrictive pattern with a total lung capacity of 3.11 L (73% pred), and a forced expiratory volume of 2.24 L in 1 s (95% pred), 2.65 L forced vital capacity (96% pred) and a 73% of predicted D_{LCO}. The arterial blood gas analysis was normal (pH 7.4, 88 mmHg arterial oxygen tension and 41 mmHg arterial carbon dioxide tension). 6-min walk distance was 450 m (77% pred) with a minimal saturation of 90%. In the right lower lobe, a real-time probe-based confocal LASER endomicroscopy (pCLE; Cellvizio®) was performed. The patterns of distribution of elastin fibres and fibrillar organisation in segmental and subsegmental bronchi appeared normal [1]. The underlying elastin structure was not visualised in alveoli. Cystic areas were not imaged. We observed fluorescent intra-alveolar globular complexes of 20–30 µm filling the alveolus, associated with a high intra-alveolar cellularity (figure 1c). A bronchoscopy, macroscopically normal, revealed on bronchoalveolar lavage (BAL) an alveolitis (750 cells per mm^3) mainly composed of macrophages (81%) with foamy cytoplasms (figure 1d), also with 15% lymphocytes and 4% neutrophils. The BAL cultures of were all negative. Foamy macrophages in the BAL fluid were intensely positive for periodic acid–Schiff (PAS), while no extracellular PAS stained material was detected, and lightly positive with Oil Red O. A transbronchial lung biopsy in the right lower lobe revealed alveolar spaces filled by numerous foamy macrophages (figure 1e). The alveolar septa was not distorted. No granuloma was observed. A decreased acid sphingomyelinase activity in the blood leukocytes was observed (patient 0.15 *versus* controls 1.07 $nmol{\cdot}h^{-1}{\cdot}mg^{-1}$). Sanger sequencing of the *SMPD1* gene identified a homozygous deletion (c.1829_1831delGCC) in exon 6, chromosome 11, which deletes Arg610, ultimately establishing the diagnosis of Niemann–Pick type B disease (NPB) [2].

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This study presents the very first pCLE images of Niemann–Pick type B disease. This minimally invasive approach, at the crossroads between imaging and histology, may represent a valuable tool in the differential diagnosis of ILDs, including NPB. https://bit.ly/2D5Bfju

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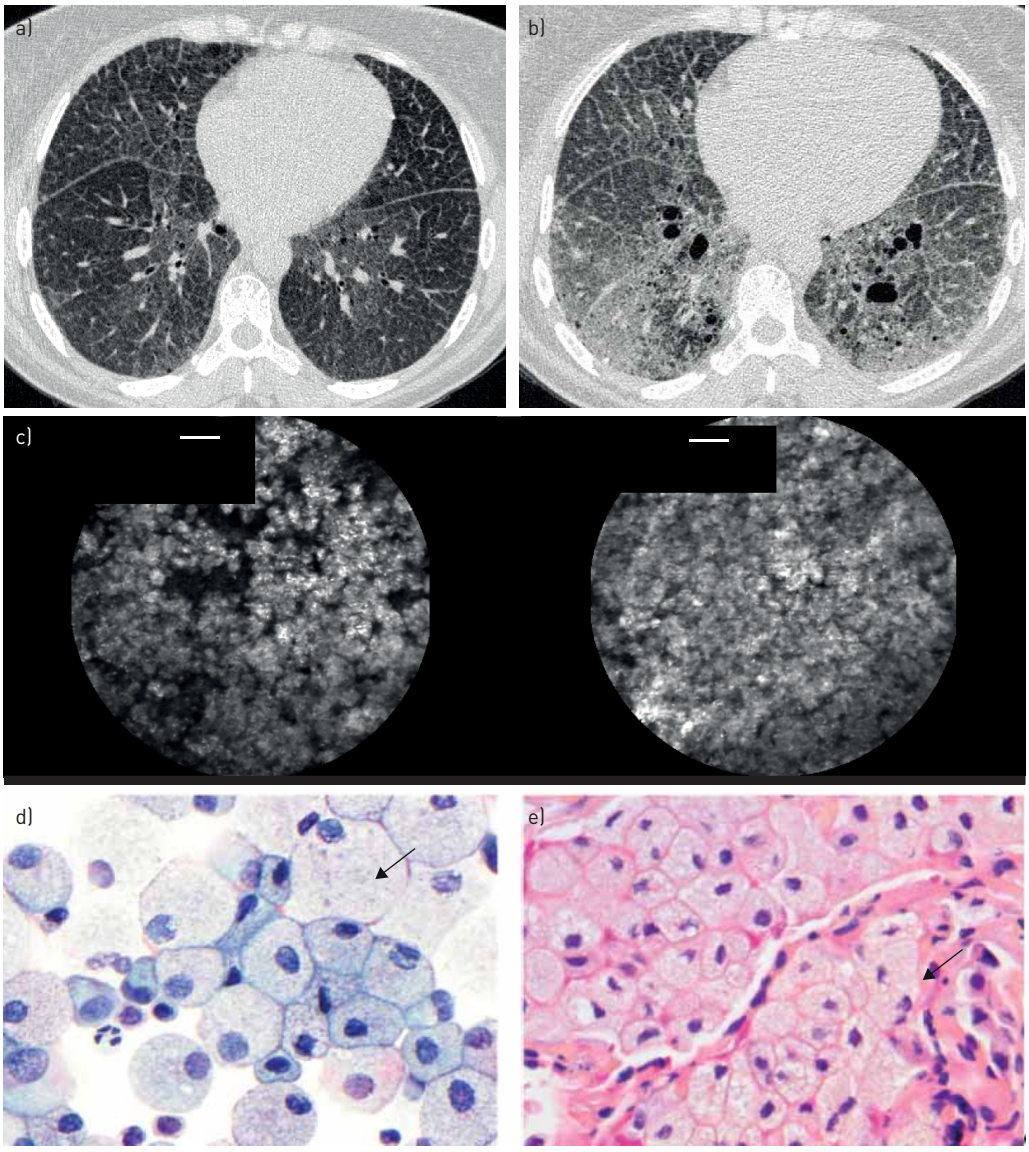

FIGURE 1 a and b) Pulmonary transversal window images of chest computed tomography scan evolution between 1999 (a) *versus* 2020 (b) showing interstitial lung disease with interlobular septal thickening, ground glass density in the upper lobes and cyst appearance with basilar predominance. c) Real-time probe-based confocal LASER endomicroscopy showing intra-alveolar content with fluorescent globular complexes of 20–30 µm filling the alveolus. Scale bar: 50 µm. d) Bronchoalveolar lavage fluid (Papanicolaou stain, original magnification ×400) revealed an alveolitis (750 cells per mm^3) composed of macrophages (81%) with foamy cytoplasms (black arrow). e) Transbronchial lung biopsy (original magnification ×64) in the right lower lobe showing foamy cell with a distended cytoplasm (black arrow) and a small nucleus.

We report here a progressive pulmonary involvement due to NPB over 20 years. NPB is a lysosomal storage disorder resulting from deficient acid sphingomyelinase activity [3] caused by a mutation in the *SMPD1* (sphingomyelin phosphodiesterase 1) gene [3]. A progressive cell infiltration by foam in reticular tissues results in dysfunctions of major organ systems such as the liver, spleen, bone marrow or lungs [4]. The main differential diagnoses for the pulmonary involvement include other storage diseases, alveolar proteinosis, sarcoidosis, amyloidosis, alveolar microlithiasis, nonspecific and desquamative interstitial pneumonia and Erdheim–Chester disease [5]. The clinical presentation is usually nonspecific, including moderate cough, chronic dyspnoea and recurrent upper respiratory tract infections [6]. Biological abnormalities are mainly characterised by thrombocytopenia and dyslipidaemia [4]. Diagnosis is strongly suggested by a decreased acid sphingomyelinase activity in blood leukocytes, and ultimately confirmed by the detection of a *SMPD1* mutation [7]. A decrease in D_{LCO} is often reported, but the extent and the pattern of interstitial abnormalities are not necessarily well correlated with other lung function parameters [5].

An original aspect of this case is the slow and progressive worsening, over an extended 20-year period, with the appearance of cysts, as sometimes described [8]. The correlation between the histopathological and imaging findings can likely be explained: 1) the interlobular septal thickening is caused by an accumulation of foamy histiocytes in alveolar septa and sometimes subpleural spaces; 2) ground glass attenuations are due to partial filling of alveoli by alveolar macrophages; and 3) the development of cysts can be explained by the migration of storage cells into the bronchiolar lumen, leading to air-trapping and airspace enlargement, as proposed by Baldi *et al.* [8]. Another original point of this case is the very first pCLE description for NPB disease. A pCLE procedure uses a contrast mini-probe with a LASER directed into the alveolar space, generating real-time moving images of intra-alveolar content ("alveoloscopy") in a grayscale video sequence. Currently, the role played by pCLE in the diagnostic approach of ILDs remains limited [9]. Associating the pCLE fluorescence signal and *ex vivo* microscopy could be of interest to establish correlations for further studies. More accurate semiology analyses and correlations with CT in ILDs are strongly needed. The French protocol Microsemio-PI (NCT02961335) is ongoing in order to define the semiology of ILDs in pCLE. At the 1-year follow-up of our patient, lung exchanges had gradually decreased with a 55% D_{LCO} in 2020, compared to 201 (73%) and 1999 (90%). Interstitial infiltrates increased and more cystic lesions were observed. The patient did not meet the inclusion criteria for an ongoing trial evaluating the efficacy of enzyme replacement therapy with olipudase alfa (NCT0200469), a promising approach as suggested by limited series. A regression of ground glass opacities and reticular lesions has been observed in five patients, translating into an improvement of the D_{LCO}, increasing from 53.2% to 67.1% in 30 months [10]. The most significant changes were observed in the most severely affected patients. The outcomes of a phase 2/3 randomised controlled trial (NCT02004691) that included 36 participants are expected. A lung transplantation can be considered in cases of chronic respiratory failure [11, 12].

In conclusion, we report a progressive pulmonary involvement of NPB disease with a 20-year follow-up, as well as the very first pCLE images of this lysosomal storage disease. This minimally invasive approach, at the crossroads between imaging and histology, may represent a valuable tool in the differential diagnosis of ILDs, including NPB.

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References

1 Thiberville L, Moreno-Swirc S, Vercauteren T, *et al. In vivo* imaging of the bronchial wall microstructure using fibered confocal fluorescence microscopy. *Am J Respir Crit Care Med* 2007; 175: 22–31.
2 Levran O, Desnick RJ, Schuchman EH. Niemann–Pick type B disease. Identification of a single codon deletion in the acid sphingomyelinase gene and genotype/phenotype correlations in type A and B patients. *J Clin Invest* 1991; 88: 806–810.
3 Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann–Pick disease. *J Inherit Metab Dis* 2007; 30: 654–663.
4 Lidove O, Belmatoug N, Froissart R, *et al.* Maladie de Niemann-Pick B : à propos de 28 cas chez l'adulte. *Rev Med Interne* 2015; 36: A29.
5 Mendelson DS, Wasserstein MP, Desnick RJ, *et al.* Type B Niemann–Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. *Radiology* 2006; 238: 339–345.
6 Guillemot N, Troadec C, de Villemeur TB, *et al.* Lung disease in Niemann–Pick disease. *Pediatr Pulmonol* 2007; 42: 1207–1214.
7 Zampieri S, Filocamo M, Pianta A, *et al.* SMPD1 mutation update: database and comprehensive analysis of published and novel variants. *Hum Mutat* 2016; 37: 139–147.
8 Baldi BG, Santana ANC, Takagaki TY, *et al.* Lung cyst: an unusual manifestation of Niemann–Pick disease. *Respirology* 2009; 14: 134–136.
9 Salaün M, Guisier F, Dominique S, *et al. In vivo* probe-based confocal laser endomicroscopy in chronic interstitial lung diseases: specific descriptors and correlation with chest CT. *Respirology* 2019; 24: 783–791.

10 Wasserstein MP, Diaz GA, Lachmann RH, *et al.* Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. *J Inherit Metab Dis* 2018; 41: 829–838.
11 O'Neill RS, Belousova N, Malouf MA. Pulmonary type B Niemann–Pick disease successfully treated with lung transplantation. *Case Rep Transplant* 2019; 2019: 1–5.
12 Mannem H, Kilbourne S, Weder M. Lung transplantation in a patient with Niemann–Pick disease. *J Heart Lung Transplant* 2019; 38: 100–101.