CSF2RB mutation-related hereditary pulmonary alveolar proteinosis: the "long and winding road" into adulthood

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To the Editor:

Pulmonary alveolar proteinosis (PAP) refers to the inappropriate, intra-alveolar accumulation of surfactant and relates to a multitude of aetiologies [1]. The loss of respiratory reserve due to the alveolar filling may gradually lead to hypoxaemic respiratory failure and its consequences, although in a minority opportunistic lung infections and pulmonary fibrosis may ensue, modifying outcomes [1]. Irrespective of the aetiology, patients present in common a "crazy paving" pattern on high-resolution computed tomography (HRCT) scanning of the lungs and periodic acid–Schiff-positive staining on bronchoalveolar lavage-obtained cytospins or on surgical tissue samples [1]. The majority of cases are autoimmune PAP, caused by the loss of signalling of granulocyte–macrophage colony-stimulating factor (GM-CSF) due to the development of anti-GM-CSF autoantibodies. Secondary or hereditary cases of PAP are rarer. Secondary PAP relates to a multitude of clinical conditions and environmental exposures that may reduce numbers or functionality of alveolar macrophages [1, 2]. Hereditary PAP (hPAP) is usually diagnosed in children, in whom loss of signalling of GM-CSF is due to mutations in genes encoding the α- or β-chain of the GM-CSF receptor (*CSF2RA* or *CSF2RB*, respectively) [2–4]. Mutations in *SFTPB* (surfactant protein B), *SFTPC* (surfactant protein C), *ABCA3* (encoding ATP-binding cassette subfamily A member 3) and *NKX2-1* (encoding thyroid transcription factor 1 (TTF1)) may relate to the development of a wide range of surfactant accumulation abnormalities corresponding at the tissue level to PAP patterns (congenital PAP), occasionally in conjunction with pulmonary fibrosis [1, 2].

Herein we describe the ultra-rare case of a 47-year-old male smoker (90 pack-years), referred to the lung transplantation clinic for evaluation in September 2022 in the context of end-stage fibrotic interstitial lung disease (ILD) which had remained oddly unclassifiable over the past 26 years. The history of the patient started in 1996 when, aged 21 years and asymptomatic, a chest radiograph disclosed ILD. This led to an extensive work-up, documenting in 2003 PAP and pulmonary fibrosis through surgical biopsy (figure 1a). Treatment with cyclophosphamide was initiated, followed by a combination of azathioprine and corticosteroids for 24 months. Over the course of the following years, the patient dropped out from any medical care and lost all his medical records. In 2012, aged 37 years, the patient was re-admitted to another hospital due to deterioration. Levels of anti-GM-CSF antibody were not measured due to technical reasons, and the patient was managed with lobar lavage with fibreoptic bronchoscopy, with improvement [5]. HRCT was performed in 2013 (figure 1b). The patient continued to be noncompliant to any regular follow-up for years and in August 2022 (aged 47 years) he was re-admitted to a third hospital with life-threatening deterioration and hypoxaemic respiratory failure. HRCT was performed anew (figure 1c). On September 2022 the patient was referred to our centre for pre-transplant evaluation with the ambiguous diagnosis of combined PAP and pulmonary fibrosis. He was classed as late World Health Organization functional classification III, receiving long-term oxygen therapy (nasal cannula 3 $L \cdot min^{-1}$) and was listed for lung transplantation. However, a month later the patient was intubated after an episode of lung infection leading to refractory hypoxaemia and respiratory acidosis. He was transferred to the intensive care unit (ICU), to receive venovenous extracorporeal membrane oxygenation as a bridge to lung transplantation, performed 35 days later. After a rather complicated post-transplantation clinical course, due to infections, difficult weaning from mechanical ventilation and acute kidney injury, the patient was successfully discharged home from the ICU, with low oxygen needs and improved renal function and is alive 11 months after the life-saving intervention of high-emergency lung transplantation.

Shareable abstract (@ERSpublications)
Genetic analysis pre-lung transplantation diagnosed a case of hereditary pulmonary alveolar proteinosis (PAP) complicated by fibrosis in adulthood. The need for genetic testing in GM-CSF autoantibody negative and unclassifiable PAP is highlighted. https://bit.ly/3QcsYwM

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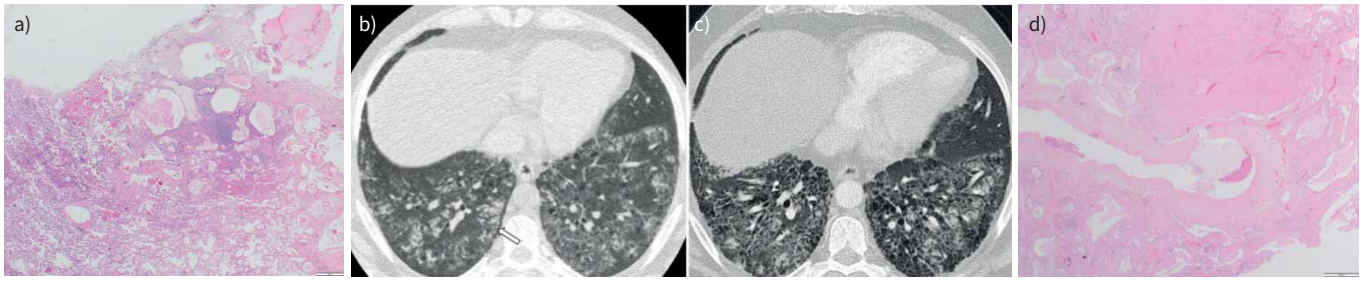

FIGURE 1 a) Histological features of lung video-assisted thoracoscopic surgery biopsy (2004, at the age of 29 years; 18 years prior to transplantation) showing pulmonary alveolar proteinosis (PAP) and chronic lymphocytic inflammation associated with interstitial cholesterol clefts granulomas and cystically dilated subpleural alveolar spaces with collagenous fibrosis; scale bar=500 µm. b) Chest computed tomography scan performed in 2013 at the age of 38 years shows extensive patchily distributed ground-glass opacities and nodular consolidations with some subpleural sparing (arrow). A few cysts are present, but there are no signs of distortion; pure crazy-paving pattern is not disclosed probably due to the hereditary nature of the development of the disease and the very long evolution in this patient. c) 9 years later, at the age of 47 years, ground-glass opacities and consolidations have dramatically decreased, replaced by numerous clustered cysts. d) Histological features of the explanted lungs showing mixed PAP and usual interstitial pneumonia (UIP) patterns with honeycombing and fibrosis on the explanted lung; note the clear demarcation between the PAP areas and UIP areas with minimal overlap (haematoxylin and eosin stain); scale bar=1000 µm.

Histological examination of the explanted lungs confirmed PAP and pulmonary fibrosis (figure 1d). Due to the early-onset pulmonary fibrosis without any other obvious explanation combined with PAP and in an effort to optimise pre-transplant evaluation, the patient underwent genetic testing for telomere-related gene mutations and proved negative. Further evaluation for surfactant- and proteinosis-related gene mutations was performed and found to be homozygous for the *CSF2RB* (NM_000395.3) nonsense variation c.631C>T, p.(Arg211*).

This variation, which is absent from the genome aggregation database (gnomAD, assessed 8 August 2023) is predicted as pathological according to the Combined Annotation Dependent Depletion (CADD) score (CADD score=36; https://cadd.gs.washington.edu/). It leads to a premature stop codon in the sixth exon out of 14, and is therefore expected to result either in the production of a severely truncated protein or the absence of protein production through activation of the nonsense-mediated mRNA decay pathway. According to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [6], this variation was classified as probably pathogenic (PVS1, PM2).

This report regards the “long and winding road” to the adulthood of a childhood ILD survivor affected by hPAP related to *CSF2RB* homozygous probably pathogenic variation c.631C>T p.(Arg211*) combined with pulmonary fibrosis, still surviving at the age of 47 years after lung transplantation.

hPAP related to *CSF2RB* mutations represents one of the rarest forms of the disease so far reported in three children: the first patient was homozygous for the c.812C>T, p.(Ser271Leu) variation; information about the variation was not available for the two remaining patients [3, 7, 8]. Survival into adulthood has been described only once, in a 36-year-old female patient carrier of the c.631del, p.(Arg211Glufs*54) homozygous variation with combined PAP and pulmonary fibrosis, who also received bilateral lung transplantation and survived a further 4 years. Autopsy confirmed recurrence of both PAP and fibrosis in the donor lungs [9, 10].

Recurrence of PAP represents an additional challenge in the management of combined hPAP and pulmonary fibrosis in patients undergoing lung transplantation and relates to the replacement of donor alveolar macrophages by the defective (*CSF2RB* mutated) recipient monocyte (bone marrow origin) alveolar macrophages [11]. Allogeneic haematopoietic stem cell transplantation has been attempted once in an 18-year-old lung-transplanted patient for end-stage hPAP related to *CSF2RA* mutation and pulmonary fibrosis, diagnosed at the age of 35 months [12, 13]; eventually, this option should also be taken into consideration in this case. Speculations about the late onset of hereditary *CSF2RB* mutation-related PAP include potential activation of multiple intracellular signalling pathways by GM-CSF binding to the GSF2RA alone [9]. However, scientific documentation through functional studies for such a rare disease is still missing, and therefore no recommendation for the use of inhaled GM-CSF can be made. Conversely, whole-lung lavage might be attempted in case of PAP reappearance, so far not detected in our patient at

1 year post lung transplantation [11, 14]. Pulmonary transplantation of human induced pluripotent stem cell derived macrophages might represent an alternative option, although its interference with the rejection process is unknown [15].

The eventual recurrence of fibrosis in the donor lungs is another concern in the future management of our patient. There is no established pathophysiological mechanism linking fibrogenesis and hereditary or autoimmune PAP; several mechanisms have been postulated, including surfactant homeostasis dysregulation and GM-CSF deficiency [16]. Antifibrotic treatment might be attempted based on the limited evidence for the management of progressive pulmonary fibrotic diseases overall. It seems that the development of pulmonary fibrosis in that case, although it occurs rarely, represents an event in the natural history of the disease, heralding the end of the "winding road" [17].

In this patient, an earlier diagnosis of hPAP might have contributed to an optimal application of precision medicine and hopefully a better outcome. This calls for genetic testing in all GM-CSF autoantibody negative and unclassifiable PAP patients.

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Author contributions: S.A. Papiris conceived the study, made a major contribution to the analysis and interpretation of data, and wrote the manuscript; C. Louvrier performed the genetic analysis of the SRG mutations, studied the *CSF2RB* pathogenic variation, made a major contribution to the analysis and interpretation of data,

and wrote part of the manuscript; A. Fabre performed the pathological examination of all biopsy samples, made a major contribution to the analysis and interpretation of data, and wrote part of the manuscript; L. Kaklamanis performed the pathological analysis of the explants, and made a substantial contribution to the analysis and interpretation of data; I. Tsangaris and F. Frantzeskaki made major contributions to the lung transplantation of the patient, substantial contributions to the analysis and interpretation of data, and wrote part of the manuscript; I.E. Dimeas made a major contribution in the management of the patient, and collection, analysis and interpretation of data; M-P. Debray performed the review of radiological images, contributed substantially to the critical interpretation of data and wrote part of the manuscript; F. Karakontaki, M. Kallieri, L. Kolilekas, Z. Daniil and A. Giatromanolaki made substantial contributions to the management of the patient during the past 25 years of his life, and to the collection and critical interpretation of data; C. Kannengiesser performed the genetic analysis of the TRG mutations, and made a substantial contribution to the analysis and interpretation of data; R. Borie, N. Nathan and M. Griese made major contributions to the analysis and interpretation of data, and revised this work critically for important intellectual content; and E.D. Manali conceived the study, made a major contribution to the acquisition, analysis and interpretation of data, supervised the accuracy and integrity of all parts of the work, coordinated the study team, and wrote the final version of the manuscript with S.A. Papiris. All authors read and approved of the final version of the submitted publication.

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