Case Report

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The dark side of pulmonary alveolar proteinosis

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ABSTRACT

Background: Pulmonary alveolar proteinosis (PAP) has an unpredictable clinical course. Although usually benign, an association with pulmonary fibrosis is described in literature, with troubling therapeutic and prognostic implications.

Clinical case: We report the case of a patient affected by autoimmune PAP who developed pleuro-parenchymal fibroelastosis (PPFE) after 6 years of disease and underwent bilateral lung transplantation due to end stage respiratory failure.

Conclusion: Punctual descriptions of pulmonary fibrosis in PAP are still lacking and no predictors of fibrotic evolution of PAP are known. It is necessary to ensure a strict follow up in order to promptly recognize signs of fibrotic evolution and early refer patients with evolutive disease to lung transplant center. Moreover, an extended genetic analysis by targeted next-generation sequencing could provide high-resolution information that may allow the identification of susceptible patients in a pre-fibrotic stage of disease.

Key words: Pulmonary Fibrosis, Pulmonary Alveolar Proteinosis, Alveolar surfactant, Lung Transplantation, pleuro-parenchymal fibroelastosis

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Introduction

Pulmonary alveolar proteinosis (PAP) is an ultra-rare syndrome whose clinical course is bizarre and unpredictable, ranging from spontaneous resolution to progressive deterioration with respiratory failure requiring Whole Lung Lavage (WLL)) or treatment with inhaled exogenous granulocyte-macrophage colony-stimulating

factor (GM-CSF). Although inhaled GM-CSF is recommended as first-line therapy for symptomatic patients with autoimmune PAP, as stated in the recent European Respiratory Society (ERS) guidelines [1, 2], in Italy this therapy is not yet approved and is currently available only within the context of clinical trials. PAP is usually benign, however pulmonary fibrosis represents a potential manifestation that is still poorly understood in terms of frequency of onset, aetiology and pathogenesis. It is still largely unknown if fibrosis is an expression of advanced stages of the disease or a distinct event. It may results from a combination of immune dysfunction, chronic inflammation, epithelial injury, and dysregulated repair, potentially enhanced by genetic predisposition or environmental triggers [3-5]. The fibrotic evolution of PAP poses major challenges for therapeutic management as it represents a rare and unexpected progression of the disease that falls beyond its usual clinical course and is not addressed by standard treatment protocols. In fact WLL and inhaled GM-CSF are effective in reducing the alveolar filling but but they don't offer benefit once the fibrotic remodeling occurs. Currently, there are no approved antifibrotic therapies specifically for the fibrotic forms of PAP and the role of antifibrotic agents in these cases remains unclear. When fibrosis becomes extensive, lung transplantation is often the only viable therapeutic option. Here we present a case of autoimmune PAP who developed pleuroparenchymal fibroelastosis (PPFE) and underwent successful bilateral lung transplant. One year later, PAP relapsed on the graft, the patient underwent statin therapy, and clinical-functional stability was maintained.

Clinical case

In 2011, a 44-year-old Caucasian female was referred to the pulmonology clinic due to progressively worsening exertional dyspnoea, dry cough, and chest discomfort developed over a 2-year period. She reported no fever, haemoptysis, or weight loss. She was an active smoker (20 pack/years), worked as a saleswoman, and had no environmental or occupational exposure to pneumotoxic agents. She had a positive familial history for interstitial lung disease (ILD) with her mother affected by pulmonary sarcoidosis, while patient's medical history included chronic sinusitis with post nasal drip and recurrent otitis. At the first evaluation chest auscultation revealed fine bibasilar end-inspiratory crackles no changed by cough. Remaining physical examination was normal. Blood tests, antinuclear antibodies (ANA) and Extractable Nuclear Antigens (ENA) were unremarkable. As expected in a PAP patient, Lactate dehydrogenase (LDH) was increased (580 mU/ml vs normal value <300 mU/ml). Chest high resolution computed tomography (HRCT) showed ground glass opacities delimited by interlobular septal thickening with "crazy paving" appearance (Figure 1 A, B, C). The fibrobronchoscopy revealed opaque, milky, periodic acid of Schiff (PAS)-positive lipoproteinaceous bronchoalveolar lavage fluid (BALf). Measurement of serum anti-granulocyte macrophage colony stimulating factor (GM-CSF) antibodies resulted abnormally high (277 mcg/ml vs normal value <5 mcg/ml), thus confirming the diagnosis of autoimmune PAP. Pulmonary function tests (PFTs) showed normal static and dynamic values with a mild reduction of diffusing capacity of the lungs for carbon monoxide (DL_{CO}) (Table 1). Due to the stability of lung function and gas exchanges, the patient did not require WLL and was followed up with half-yearly visits. In 2013, the patient reported increased breathlessness with progressive lung function decline (Table 1), an impaired exercise tolerance, associated with desaturation along with a more extensive radiographic involvement. She underwent WLL with 12 litres and 9 litres of warmed saline solution (left and the right lung, respectively). Consequently, symptoms relief with functional (Table 1) and tomographic improvement were reported. After a 4-year period of clinical benefit, a new worsening of respiratory conditions occured, with latent respiratory failure onset, tomographic evidence of diffuse ground glass opacities, crazy paving, and development of modest fibrotic retracting alterations in apical submantellar regions, bronchiectasis and bronchiolectasis. The patient was enrolled in a phase III, multicentre randomized clinical trial evaluating the efficacy and the safety of inhaled recombinant GM-CSF (rGM-CSF); she received rGM-CSF (300 mcg) administered once daily, for 48 weeks. Treatment was completed without adverse effects and was

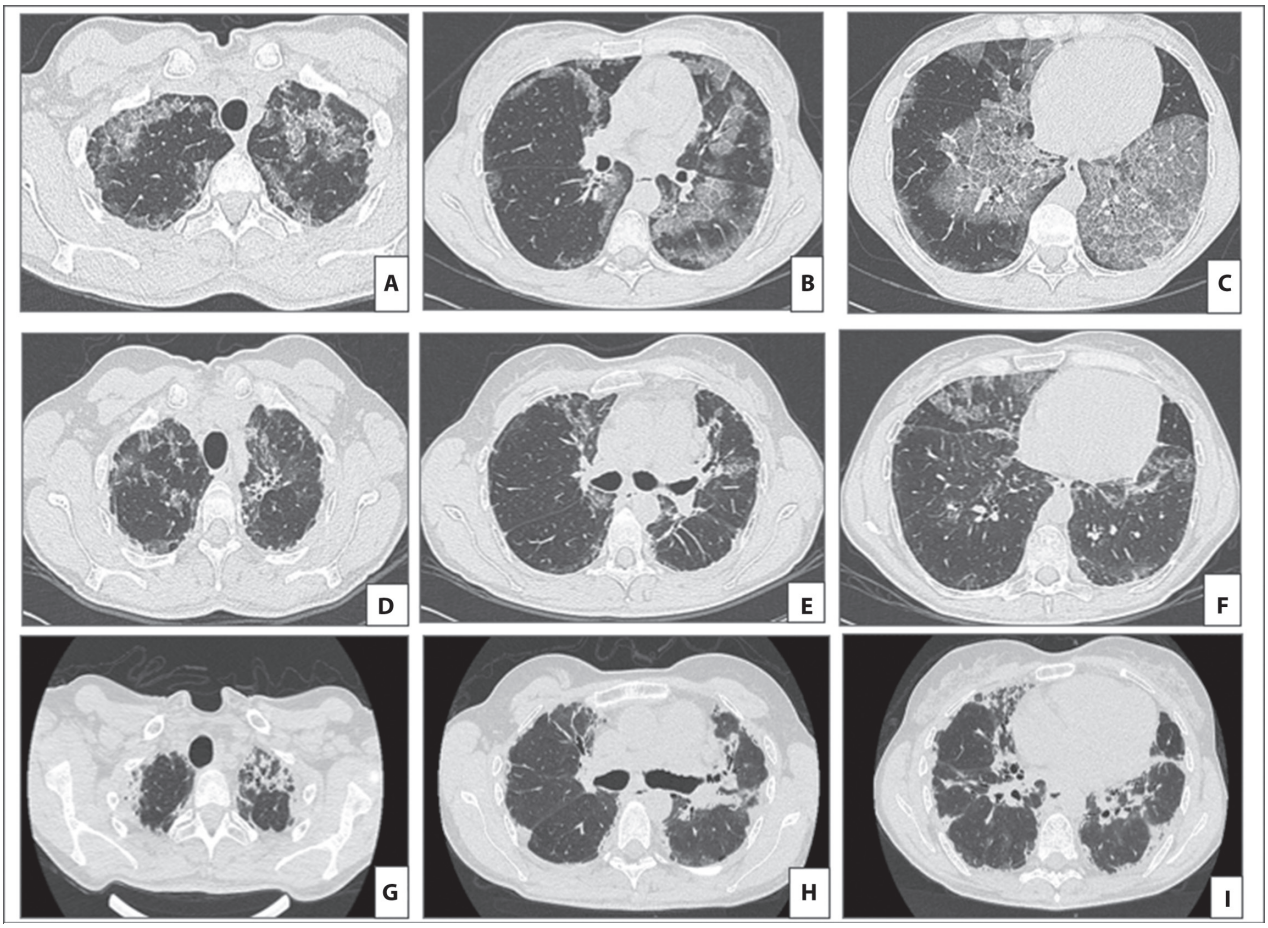

Figure 1. Axial high resolution computerized tomography scans of the chest at different time-points. A, B and C) images show the typical PAP appearance characterized by bilateral ground glass opacities with patchy distribution and thickened interlobar septa creating a "crazy paving" pattern. D, E and F) images show the reduced extent of the ground glass opacities after treatment with rGM-CSF; early signs of possible fibrotic evolution can be appreciated at the apical region of the left lung. G, H, and I) images correspond to the late phases of the disease, and show the features of PPFE, characterized by fibrotic subpleural thickening involving lung apices, upper lobes and apical segments of the lower lobes, a subsequent hypoexpansion of the involved pulmonary parenchyma and traction bronchiectasis and bronchiolectasis with distortion of the affected bronchial branches.

well tolerated and was associated to a reduction of crazy paving areas (Figure 1 D, E, F). In the 2019 patient was admitted to Pulmonology Unit for fatigue, dyspnoea and dry cough. Sicca syndrome and Raynaud phenomenon were reported. Chest HRCT revealed regression of ground glass opacities; however an evolution of parenchymal alterations with pleural thickening, bilateral subpleural fibrosis mainly involving the upper lobes, volume loss, traction bronchiectasis and bronchiolectasis was reported (Figure 1 G,H,I). A radiological diagnosis of pleuro-parenchimal fibroelastosis (PPFE) was achieved. The fibrobronchoscopy with BALF resulted no decisive, infections were excluded and the alveolar cytogram showed an increased cellularity with aspecific cell composition: 89% macrophages (of which 2% foamy), 5% lymphocytes and 6% neutrophils. PFTs revealed a severe restrictive ventilatory disorder and a severely impaired DL_{CO}, while a blood gas analysis on room air detected a normocapnic respiratory failure and the necessity of oxygen support (Table 1). LDH serum levels were normal (294 mU/ml), rheumatologic serum tests, sialometry, Schirmer's test and capillaroscopy resulted negative. Echocardiogram detected a patent foramen ovale causing a bidirectional shunt, not

Table 1. Pulmonary Function Tests at PAP onset, in pre-WLL phase, after 3 months from WLL, during early stage of PPFE and in late stage of PPFE.

	PAP onset	PAP pre-WLL	PAP post WLL phase	PPFE early phase	PPFE late
FEV_1 L/sec (% of pred)	2.78 (87%)	2.93 (80%)	2.32 (73%)	1.78 (61%)	1.21 (40%)
FVC L (% of pred)	3.44 (93%)	2.43 (77%)	2.83 (78%)	2.14 (63%)	1.9 (50%)
TLC L (% of pred)	4.84 (84%)	4.19 (73%)	4.33 (75%)	3.38 (61%)	2.01 (37%)
DLCO ml/min/mmHg (% of pred)	6.00 (64%)	4.1 (44%)	4.84 (52%)	2.8 (31%)	3.02 (39%)
PaO_2 mmHg	78.1	67.8	74.9	72.5	58.9
$PaCO_2$ mmHg	34.3	33.4	37.5	41.1	41.6
Metres on 6MWT Minimum	580	243	550	268	400 *
SpO_2% on 6MWT	96%	88%	93%	88%	90% *

*The last 6 MWT was conducted with support of oxygen (5 L/minute). FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DL_{CO}, diffusing capacity of the lung for carbon monoxide; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; 6MWT, 6 minutes walking test.

haemodinamically significant. Pulmonary arterial pressure was at the upper limit of normality.

We investigated genes related to surfactant abnormalities and fibrosis by performing targeted NGS on iSeq 100 Sequencing System (Illumina). The detected gene variants are reported in Table 2, with MUC5B and MUC2 being the most affected genes. Notably, the MUC2 rs41411848 variant is located in a splice region. These variants have not been previously described in the literature as being associated with ILDs.

In the attempt to slow down the progression of fibrosis and in absence of other therapeutic options, the patient received empirically a cycle of systemic corticosteroid therapy (prednisone 25 mg per day) that continued after discharge for two months with no beneficial effect. Due to further progressive clinical deterioration leading to end stage respiratory failure the patient was listened for lung transplantation. In December 2021, after about one-year waiting, she successfully underwent bilateral lung transplantation. Histological examination of explanted lungs confirmed the diagnosis of PPFE (Figure 2).

The post-operative course was regular. The only major event was reactivation of Cytomegalovirus, treated with Valganciclovir. However, about a year after lung transplantation, the patient developed cough, described as "strange and PAP-like". Chest CT showed multiple small areas of ground glass with associated intra- and interlobular septal thickening and predominantly peripheral/subpleural distribution with no signs of air-trapping (Figure 3 A, B, C). Routine pulmonary function tests showed no a functional graft decline: FEV_1 was 103% of best FEV_1 recorded after lung transplantation. No signs of infection were present. Therefore, on suspicion of allograft dysfunction, the patient underwent rigid bronchoscopy with broncholavage and transbronchial cryobiopsies, where PAS-positive amorphous finely granular endoalveolar material was found. Acute cell-mediated rejection was absent (A0, B0). No microbiological agents were isolated. The histological pattern was compatible with a recurrence of PAP. Based on emerging evidence supporting the role of statins in reducing intra-alveolar cholesterol accumulation [6-8], treatment with a low-dose statin (simvastatin 20 mg/day) was started. In addition to their potential therapeutic effect in PAP, statins may also offer collateral benefits in lung transplant recipients by mitigating the adverse metabolic effects of immunosuppressive therapies and potentially reducing

Table 2. Gene variant analysis.

Gene	Variant	Consequence	Zygosity	SIFT prediction	Polyphen prediction	Franklin prediction
MUC5B	rs2943502	missense	homozygous	tolerated	benign	benign
MUC5B	rs4963031	missense	homozygous	tolerated	benign	benign
MUC5B	rs2943527	missense	homozygous	tolerated	benign	benign
MUC5B	rs2672785	missense	heterozygous	tolerated	benign	benign
MUC5B	rs199518432	missense	heterozygous	tolerated	benign	likely benign
MUC5B	rs199736618	missense	heterozygous	tolerated	benign	benign
MUC5B	rs200110733	missense	heterozygous	tolerated	benign	likely benign
MUC5B	rs56159668	missense	heterozygous	tolerated	benign	benign
MUC5B	rs55856616	missense	heterozygous	tolerated	benign	benign
MUC5B	rs2943496	missense	heterozygous	deleterious	benign	benign
MUC5B	rs55693520	missense	heterozygous	deleterious	benign	benign
MUC2	rs2856111	missense	heterozygous	NA	Probably damaging	benign
MUC2	rs41411848	missense	heterozygous	tolerated	NA	benign
MUC2	rs57737240	missense	heterozygous	tolerated	NA	benign
TGFB1	rs1800472	missense	heterozygous	tolerated	benign	benign
TGFB1	rs1800470	missense	heterozygous	tolerated	possibly damaging	likely benign
SFTPC	rs1124	missense	heterozygous	tolerated	benign	benign
SFTPA2	rs201847938	missense	heterozygous	tolerated	NA	benign

Gene variants, their consequences, and associated predictions for each variant are summarized. Information includes the gene, variant, predicted consequence, zygosity status, as well as the in silico predictions from SIFT, PolyPhen, and Franklin for each variant.

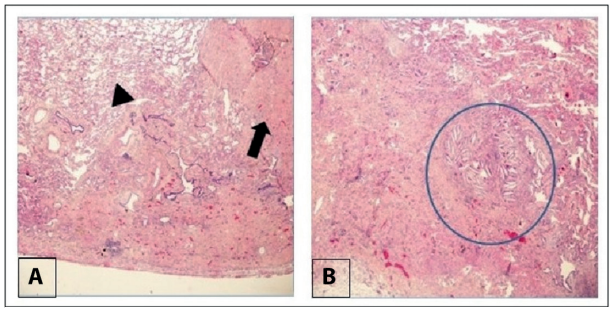

Figure 2. EE x 2. Prominent subpleural fibrosis (ARROW) with an abrupt transition to adjacent normal lung parenchyma (ARROWHEAD). A classic thickened visceral pleural feature. No fibroblastic foci were observed and only scanty inflammation is present. An area of giant cell reaction (blue circle) with cholesterol needles is present in the transition area between fibro-elastosis and normal parenchyma.

chronic allograft dysfunction [9]. After one year of therapy the chest CT scan showed overall reduction of the small ground-glass areas (Figure 3 D, E, F) and the pulmonary function was within normal limits: the FEV_1 was 111% of the best FEV_1 after lung trasnplantation and there was no desaturation at the 6 minute walking test, with the oxygen saturation ranging from 98% to 96% on room air and a covered distance of 540 m. Statin treatment is still ongoing, the patient's clinical condition is currently good, vital signs are stable, and graft function is preserved. The patient is on immunosuppressive therapy (triple regimen of tacrolimus, mycophenolate and prednisone 5 mg/day), trimethoprim/sulfamethoxazole therapy for infection prophylaxis, and periodic follow up visits.

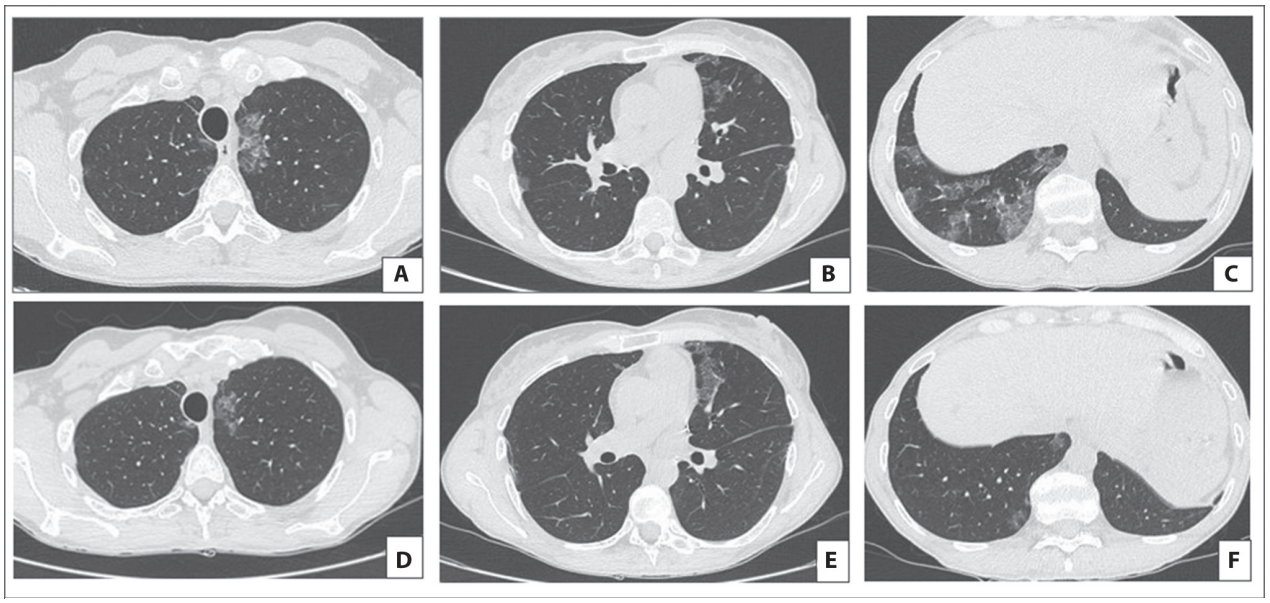

Figure 3. High-resolution axial computed tomography scans of the chest after lung transplantation. A, B, and C) images show the relapse of circumscribed areas of ground glass opacities, sharply demarcated by areas of unaffected parenchyma, one year after double lung transplant. D, E, and F) images refer to one year after the introduction of statins. They exhibit the overall reduction in extent of the multiple ground-glass opacities, especially in the basal segments of the right lower lobe.

Discussion

PAP is an ultra-rare syndrome characterized by progressive accumulation of amorphous, proteinaceous material due to a dysfunction in surfactant catabolism caused by the disruption of granulocyte-macrophage colony stimulating factor (GM-CSF) signaling [10]. It has an unpredictable course, from spontaneous resolution to death due to respiratory failure or infections [10,11]. An association between PAP and pulmonary fibrosis is described in few case reports or case series [3-5, 11-18], but it is largely unknown with regard to underlying mechanisms. It may represent a manifestation of advanced or end-stage disease [15] or, less probably, a treatment-related adverse effect of whole-lung lavage (WLL) or oxygen administration [18,19]. In fact, the presence of fibrosis in lungs and liver of GM-CSF-deficient mice, may suggest a relation with the disruption of GM-CSF signalling rather than a treatment-related toxicity [20]. A recent retrospective cohort study conducted in France and Belgium involving 61 PAP patients revealed that approximately 25% developed signs of pulmonary fibrosis over a median follow-up period of 3.6 years. Interestingly, dust exposure resulted a significant risk factor for the fibrotic progression, thus suggesting that repeated activation of inflammatory macrophages may ultimately damage the alveolar epithelium through multiple pathways, such as TGF-beta and interferon signalling [3].

Some genes involved in surfactant homeostasis regulation, such as ABCA3, SFTPA, SFTPC, and NKX21, are implicated in congenital PAP and in chronic interstitial lung disease, suggesting a possible involvement of surfactant dysfunction in the pathogenesis of pulmonary fibrosis also in autoimmune PAP [21]. A role of human mucins has been reported in PAP, and in particular MUC1 genotype has been correlated to severity of disease and disease outcome in PAP patients [22]; furthermore recent evidence identifies mucins as key effectors in cell growth and tissue remodelling processes observed in lung fibrosis. From this perspective, the principal genetic risk factor for idiopathic pulmonary fibrosis (IPF) is a gain of function MUC5B promoter variant which causes mucociliary dysfunction [23]. In our analysis we have also considered the genetic polymorphisms of TGF-β1 as it promotes the fibrotic process through

various signaling pathways, including the Smad pathway [24,25]. Moreover, it has been demonstrated that SP-A, obtained from patients with alveolar proteinosis, induced Smad dependent inhibition of T lymphocyte proliferation [26]. In this way, SP-A and TGF-β1 could act synergically in regulating TGF-β1-mediated inflammatory and fibrotic pathways in the lung.

Tomographic features of pulmonary fibrosis in autoimmune PAP are not well defined or classified, unlike congenital forms of PAP, due to disorders of the surfactant system, which are associated to a variety of pulmonary phenotypes, age-dependent, such as non specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), less frequently usual interstitial pneumonia (UIP) or chronic hypersensitivity pneumonia (HP) or cystic alterations [27]. Recently, three cases of PAP (one autoimmune) as developed severe pulmonary fibrosis, have been reported: the patient with aPAP developed mixed NSIP/UIP patterns, confirmed by histopathology after lung transplantation; another died and autopsy revealed a combination of PAP with interstitial fibrosis, focal bronchopneumonia, and alveolar damage; the third patient developed new reticulation, bronchiectasis, and subpleural basal cysts in areas of previous crazy paving [28]. Similarly, in a small casistics of PAP patients undergoing transbronchial cryobiopsy, two cases of co-occurent fibrosis were found: one case presented bronchocentric fibrosis and granulomas, and received the diagnosis of fibrotic hypersensitivity pneumoniae and coexisting autoimmune PAP; the other case presented architectural distortion and fibroblastic foci at the histopathology, and was generically labeled as PAP-associated fibrosis [4].

We described the case of a patient affected by autoimmune PAP who developed PPFE after 6 years of PAP diagnosis and required lung transplantation for respiratory deterioration. Fibrotic interstitial evolution was associated to worsening of symptoms, gas exchanges and pulmonary function tests. No biomarkers able to predict PAP evolution to lung fibrosis are today available.

Although the genetic signature identified in our patient is not clearly described as pathogenic, most of the variants detected cause amino acid substitutions, in congruence with this we cannot exclude their ability to modify protein function and influence pathways involved in fibrogenesis.

In our case, PAP relapsed approximately one year after lung transplantation.

Lung transplantation is considered that a treatment for hereditary PAP, where recurrence of PAP after lung transplantation is exceptionally reported, due to the replacement of donor alveolar macrophages by recipient-derived, GM-CSF receptor-deficient cells [5,29,30]. Recurrence of PAP further complicates the therapeutic management. In this context, WLL or allogenic hematopoietic stem cell transplantation may be a potential strategy able to ameliorate symptoms and correct the genetic defect, respectively [31,32]. Also transplantation of human induced pluripotent stem cell derived macrophages has been hypothized, in order to restore macrophage function. However, immunological concerns remain and these approaches are today only experimental [5].

In contrast with hereditary PAP, there is a lack of data on transplantation as a treatment option for respiratory failure related to autoimmune PAP. To our knowledge, this is the first case of PAP recurrence after lung transplantation for PPFE in a patient with autoimmune PAP. After PAP recurrence, statin treatment was initiated, based on recent evidences of statins as novel pharmacotherapy approach to autoimmune PAP. Indeed, as demonstrated by pre-clinical models, statins are able to promote cholesterol efflux from alveolar macrophages, thereby reducing the imbalance of the cholesterol-phospholipids ratio in PAP alveolar macrophages [6]. Clinically, the introduction of statins has been associated with clinical, physiological, and radiological improvement in patients with autoimmune PAP [7,8].

Finally, PAP can emerge also as rare complication of lung transplants, with still unknown mechanisms [33,34], those proposed include the presence of alveolar macrophage injury linked to a pathogenic process specific to graft, an acquired impaired lymphatic drainage, the iatrogenic effect caused by mammalian target of rapamycin (mTOR) inhibitors used as immunosuppressive agents [35].

Conclusion

In conclusion, a precise description of the characteristics of the pulmonary fibrosis in PAP is still

lacking, as well as the knowledge of predictors of the fibrosing evolution of the disease. Moreover, there are no reports on the efficacy of therapeutic strategies used in PAP when the disease is complicated by pulmonary fibrosis. The role of antifibrotic drugs, already used in idiopathic pulmonary fibrosis, is unclear. Our case report highlights the necessity of a strict follow up to promptly recognize fibrotic evolution of PAP. Although chest CT is not required for routine follow up of PAP, it is recommended in case of unexplained clinical and/or functional worsening. Furthermore, early referral to lung transplant center is able to improve survival. Extended genetic analysis by targeted next-generation sequencing could provide high-resolution information useful to identify susceptibility or disease-modifying genes.

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