Pulmonary hypertension in chronic interstitial lung diseases

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ABSTRACT Pulmonary hypertension (PH) is a common complication of interstitial lung diseases (ILDs), particularly in idiopathic pulmonary fibrosis and ILD associated with connective tissue disease. However, other lung diseases, such as combined pulmonary fibrosis and emphysema syndrome, pulmonary Langerhans cell histiocytosis, and lymphangioleiomyomatosis, may also include PH in their clinical manifestations. In all of these diseases, PH is associated with reduced exercise capacity and poor prognosis. The degree of PH in ILDs is typically mild-to-moderate. However, some of these patients may develop a disproportionate increase in PH that cannot be justified solely by hypoxia and parenchymal injury: this condition has been termed ''out-of-proportion'' PH. The pathogenesis of PH in these diseases is various, incompletely understood and may be multifactorial. The clinical suspicion (*i.e.* increased dyspnoea, low diffusion capacity) and echocardiographic assessment are the first steps towards proper diagnosis of PH; however, right heart catheterisation remains the current gold standard for diagnosis of PH. At present, no specific therapies have been approved for the treatment of PH in patients with ILDs.

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PH is a common complication of ILDs, currently no specific therapies are approved for treatment of PH in these patients http://ow.ly/mRaGt

Introduction

Pulmonary hypertension (PH), defined as a resting mean pulmonary artery pressure (PAP) $\geqslant$25 mmHg, is an important complication of several interstitial lung diseases (ILDs) and can adversely affect patient outcome. Studies investigating the occurrence of PH in ILD have focused on specific population groups, such as lung transplant candidates with idiopathic pulmonary fibrosis (IPF) [1, 2] and patients with sarcoidosis [3, 4] or scleroderma-related ILD [5, 6]. The prevalence of PH in patients with ILD varies greatly according to the underlying disease, the severity of the disease and the diagnostic approach used to identify PH. In a recent study [7], 14% of 212 patients with mixed types of ILD, who were screened for PH by echocardiography at a tertiary referral centre in Denmark, were diagnosed with PH: 8% of them had mild PH (mean PAP $\geqslant$25 mmHg but $<$35 mmHg) and 6% of them had severe PH (mean PAP $\geqslant$35 mmHg), as confirmed by right heart catheterisation (RHC). The gold standard for diagnosis of PH is RHC [8]. Despite some limitations and inaccuracies [9, 10], echocardiography remains the best noninvasive screening tool for PH [11].

In this review we will focus on studies reporting data on frequency, diagnosis, prognosis and treatment of PH in patients with IPF; however, we will also briefly review the literature on patients with PH associated with other ILDs.

Received: May 05 2013 | Accepted after revision: May 27 2013

Conflict of interest: Disclosures can be found alongside the online version of this article at err.ersjournals.com

Provenance: Publication of this peer-reviewed article was supported by the World Scleroderma Foundation, Switzerland (principal sponsor, *European Respiratory Review* issue 129).

Prevalence of PH in IPF

IPF is defined as a chronic ILD of unknown aetiology, characterised by progressive and irreversible parenchymal fibrosis [12] and associated with poor prognosis, limited therapeutic options and reduced quality of life [13]. According to the Dana Point Classification, PH in IPF falls into the group III (''pulmonary hypertension due to lung diseases and/or hypoxemia'') classification of PH [8]. The prevalence of PH in IPF remains undefined, with estimates that vary widely between studies due to differences in patient populations, underlying disease severity and diagnostic modalities.

The epidemiology of PH in IPF is not well described due to several factors. First, IPF is an insidious disease, so PH is usually diagnosed at an advanced stage of the disease, thus making the incidence of PH in the setting of IPF difficult to study. Secondly, although the gold standard for the diagnosis of PH is RHC, which is an invasive and expensive test precluding longitudinal follow-up studies, a variety of assessment methods to diagnose PH and criteria for defining PH have been used in different studies [1, 14, 15]. Lastly, most of the data has been obtained from studies conducted on patients referred as candidates for lung transplant, probably because the diagnostic assessments for these patients always include RHC. Lung transplant candidates represent a specific patient population, which includes younger subjects, patients without significant medical comorbidities and with more severe disease. Therefore, the results from candidates for lung transplantation cannot be necessarily translated to all individuals with IPF [16].

Several retrospective analyses indicate that PH in IPF may be frequent [1, 14, 15]. In patients with IPF a pulmonary arterial enlargement on computed tomography (CT) may occur even in the absence of PH, due to presence of fibrosis; therefore, it is an unreliable sign of PH in IPF patients (fig. 1) [17]. NADROUS *et al.* [15] observed that PH was frequent in advanced IPF, and correlated with both low diffusing capacity of the lung for carbon monoxide (*D*LCO) and low resting arterial oxygen tension (P_{aO_2}). However, these authors relied on echocardiography alone, which is known to overestimate or underestimate PAP in patients with ILD [11]. In a retrospective analysis of consecutive pre-transplant IPF patients undergoing RHC, LETTIERI *et al.* [1] found that PH was present in approximately a third of the study population and that even moderate increases of mean PAP (>25 mmHg) correlated with increased mortality. In another large retrospective analysis, SHORR *et al.* [2] confirmed that PH was common in IPF patients who were candidates for lung transplantation and was present in about 45% of these subjects; however, severe PH (mean PAP >35 mmHg) was relatively infrequent. In a prospective analysis of consecutive patients with early stage IPF undergoing initial workup with RHC and pulmonary function testing, HAMADA *et al.* [18] observed that the prevalence of PH in this patient population was as low as 8.1%.

Generally, the degree of PH in IPF patients is mild-to-moderate. ''Out-of-proportion'' PH is defined as an unjustified degree of PH that occurs in patients suffering from different types of parenchymal lung diseases (*e.g.* chronic obstructive pulmonary disease (COPD) and IPF). The pathological manifestations in patients with IPF and out-of-proportion PH are still quite unknown, and the prevalence of out-of-proportion PH is still matter of debate [19]. Intuitively, severity of fibrosis and the degree of restrictive physiology should correlate with the prevalence and degree of PH [20]. However, it appears that PH may not correlate with lung volumes (forced vital capacity (FVC) in particular) in patients with IPF [1, 2, 15]; suggesting factors

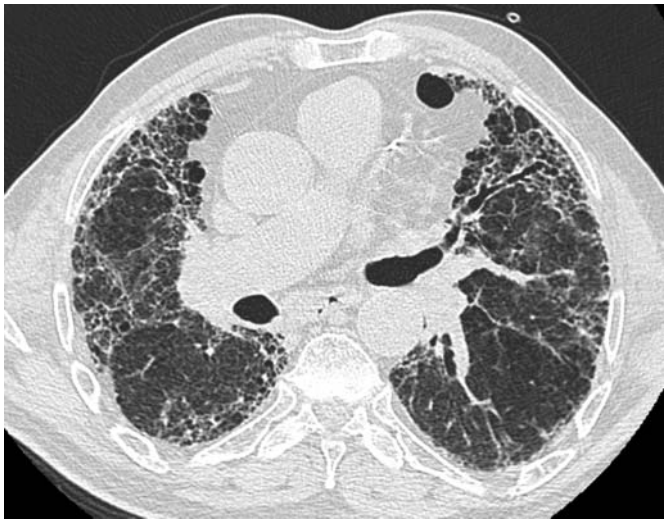

FIGURE 1 High-resolution computed tomography image showing a typical pattern of idiopathic pulmonary fibrosis. Main pulmonary artery and right pulmonary artery enlargement are present. The patient was a 73-year-old, male ex-smoker.

aside from progressive fibrosis are involved in the development of PH in IPF patients. Pulmonary artery remodelling might play a more relevant role than vasoconstriction, yet the two pathogenetic processes may be intimately interrelated.

Diagnosis of PH in IPF

PH in IPF patients is more frequent when the underlying fibrosis is severe (*e.g.* secondary PH, due to parenchymal involvement). However, PH may also occur in milder disease. Since there may be key differences in pathogenesis and clinical implications of PH between the less severe forms of disease and advanced fibrosis, it has been proposed to distinguish between the two ''stages'' of PH in IPF: PH secondary to underlying lung disease; and disproportionate PH [21]. IPF patients should be evaluated for PH when: 1) symptoms are more severe than those expected based on lung function data (dyspnoea and fatigue are symptoms of IPF as well as PH); 2) signs of right heart failure develop; and 3) clinical deterioration is not matched by the decline in pulmonary function. Profound hypoxaemia and a low *D*LCO are indicators of possible PH [1].

In IPF patients without PH, pulmonary function tests play a key role in the assessment of severity and progression of the disease. The question is whether particular pulmonary function profiles can predict the presence of PH in IPF. Routine markers for disease severity assessments (such as FVC) are useless as a detection method for PH in these patients. *D*LCO is reduced both in vascular and fibrotic diseases. The findings of LETTIERI *et al.* [1] highlighted that *D*LCO was lower in patients with PH (determined by RHC) than in IPF patients without PH. The combination of *D*LCO <40% and a requirement for supplemental oxygen were specific, but not sensitive, for detecting PH in IPF patients undergoing evaluation for lung transplantation. Patients who met these criteria had an 87% chance of having PH. Nevertheless, patients who met none of these criteria still had an ~20% chance of having PH [1].

IPF patients often have functional limitations and a decreased exercise capacity, as evaluated by the 6-min walk test (6MWT). In IPF patients, the distance covered in the 6MWT is considered highly reproducible [22], and the minimal clinically important difference in 6-min walking distance is between 24 and 45 metres [23]. Several studies indicate that IPF patients with PH have a significantly lower 6-min walking distance [1, 7, 24–26]; however, the role and reliability of the 6MWT in this clinical situation is still very controversial.

Despite some limitations, related to inadequate visualisation of all segments of the right heart and operator dependency, echocardiography remains a reliable tool for noninvasive evaluation of PH and is currently the recommended screening modality for early detection of PH [8]. Tricuspid peak flow velocity recorded by Doppler correlates well with haemodynamic parameters [27] and systolic PAP is relatively sensitive and specific for the presence of PH [21, 28]. Systolic PAP cannot be measured in the absence of tricuspid regurgitation. Although the absence of tricuspid regurgitation is rarely a problem in severe PH, it may limit the utility of echocardiography as a tool for evaluation of mild-to-moderate PH. In a cross-sectional study of IPF patients, NATHAN *et al.* [10], found that echocardiographic assessment of systolic PAP was not a sufficiently accurate test for the assessment of PH, as nearly a third of patients with normal systolic PAP measured by echocardiography had PH, as diagnosed by RHC. A noninvasive tool that provides both high sensitivity and high specificity for detecting PH in IPF patients remains to be identified and validated. Measurements of serological markers, such as brain natriuretic peptide, might have a role in this regard, but have yet to be validated [29, 30]. At this time, RHC remains the gold standard test for evaluation of PH in IPF patients.

Prognostic significance of PH in IPF

PH is a negative prognostic factor for IPF and other ILDs. In the view of some authors, ILD patients affected by PH should be listed for lung transplantation without delay [31]. In a retrospective study, LETTIERI *et al.* [1] reported poor outcomes in patients with advanced IPF who were affected by PH (as diagnosed by RHC). In this study, the 1-year mortality rate in IPF patients complicated by PH was significantly higher than that observed in lung transplant candidates without PH [1]. PATEL *et al.* [16] observed that PH (mean PAP >25 mmHg) was an independent predictor of mortality in 376 patients with IPF referred for lung transplantation. In a recent study, KIMURA *et al.* [32] confirmed by multivariate analysis that a high mean PAP value measured at the initial evaluation of IPF patients undergoing RHC is an independent predictor of survival. Unlike many other studies [1, 33, 34], this retrospective analysis focused on IPF patients affected by milder disease (mean FVC 70.2%, and mean *D*LCO 47.9%) [32]. The study demonstrated the importance of the initial evaluation of PH and supported previous observations indicating that PH is not just a result of restrictive impairment in patients with IPF [1, 20, 35]. In the study by KIMURA *et al.* [32], higher mean PAP was an independent prognostic factor, comparable to FVC % predicted, a well-known prognostic indicator in IPF. In particular, the prognosis of patients with mean PAP between 21 and 25 mmHg and that of

DOI: 10.1183/09059180.00002713

patients with mean PAP >25 mmHg appeared to be very similar, underlining that even "borderline" PH may have prognostic relevance in IPF [32].

In most studies, PH is quantified using the mean PAP or systolic PAP, rather than pulmonary vascular resistance (PVR). A recent study, conducted on patients with advanced fibrosing lung disease undergoing RHC, demonstrated that PVR provided discriminatory prognostic information not provided by mean PAP levels [36]. Raised PVR strongly predicted mortality within 1-year, independent of disease severity or a specific diagnosis of IPF. PVR was superior to other measurements at RHC in predicting prognosis. These findings suggest that, in advanced lung diseases, RHC could provide prognostic information with important management implications [36].

Treatment

Unfortunately, there are no approved targeted therapies for PH in IPF. Supplemental oxygen is indicated for prevention and therapy of PH due to hypoxia; however, there are no data supporting the beneficial effect of oxygen on survival in this group of patients. There is no clear evidence that specific therapies utilised in pulmonary arterial hypertension (PAH) can be an effective treatment for PH in IPF patients, and well-designed prospective studies are needed before routine use of these agents can be recommended and a firm conclusion made [16, 37–43]. The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF study) [44] intended to evaluate the effects of sildenafil in a population with advanced IPF, defined by the severity of lung function abnormalities (D_{LCO} <35% predicted). The primary end-point of the study, the distance covered in the 6MWT, was not met. The study group presumably included patients with PH; however, the lack of RHC assessment before and after treatment precluded the possibility of determining whether the use of sildenafil contributed to the achievement of some benefit in secondary end-points (*e.g.* decreased dyspnoea, improved quality of life and improved gas transfer) for this group of patients. Thus, it can only be assumed that the positive changes observed for secondary end-points in this study could probably reflect some improvements in PH. The subset of STEP-IPF patients with baseline echocardiogram evaluation have been reviewed in a *post hoc* analysis. Sildenafil treatment in patients with IPF and increased systolic PAP results in better preservation of exercise capacity and quality of life as compared with placebo [45]. The effect of ambrisentan, an endothelin-1 receptor antagonist, was studied in a prospective, multicentre, randomised, double-blinded study in PH-IPF patients. The ambrisentan PH-IPF trial was interrupted prematurely because of a lack of superior activity of the experimental arm (unpublished data). There were some limitations in these two trials, which were also observed in other studies. In particular, the primary end-point, the 6MWT distance, is a nonvalidated and probably a misleading test, and its prognostic significance is still unknown [19]; therefore, this could have complicated the result's interpretation. Also, mild PH is frequently observed in advanced IPF, whereas moderate-to-severe PH is rarely observed. Patients with severe PH (out-of-proportion PH) have a completely different disease course and a very bad prognosis; therefore, these patients should be distinguished from other groups in clinical trials [19]. Another randomised, double-blind, placebo-controlled clinical trial conducted on IPF patients without PH was prematurely discontinued because patients treated with ambrisentan had higher incidence of disease progression (*i.e.* decline in respiratory function and respiratory hospitalisations) compared to patients receiving placebo [46]. The safety, tolerability and preliminary efficacy of riociguat

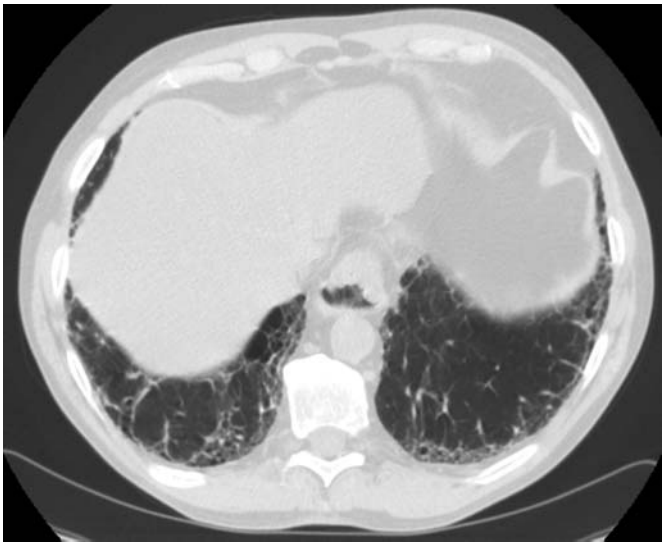

FIGURE 2 Subpleural intralobular interstitial thickening, reticulation, and traction bronchiectasis and initial honeycombing in a patient with systemic sclerosis. Oesophageal dilatation is present.

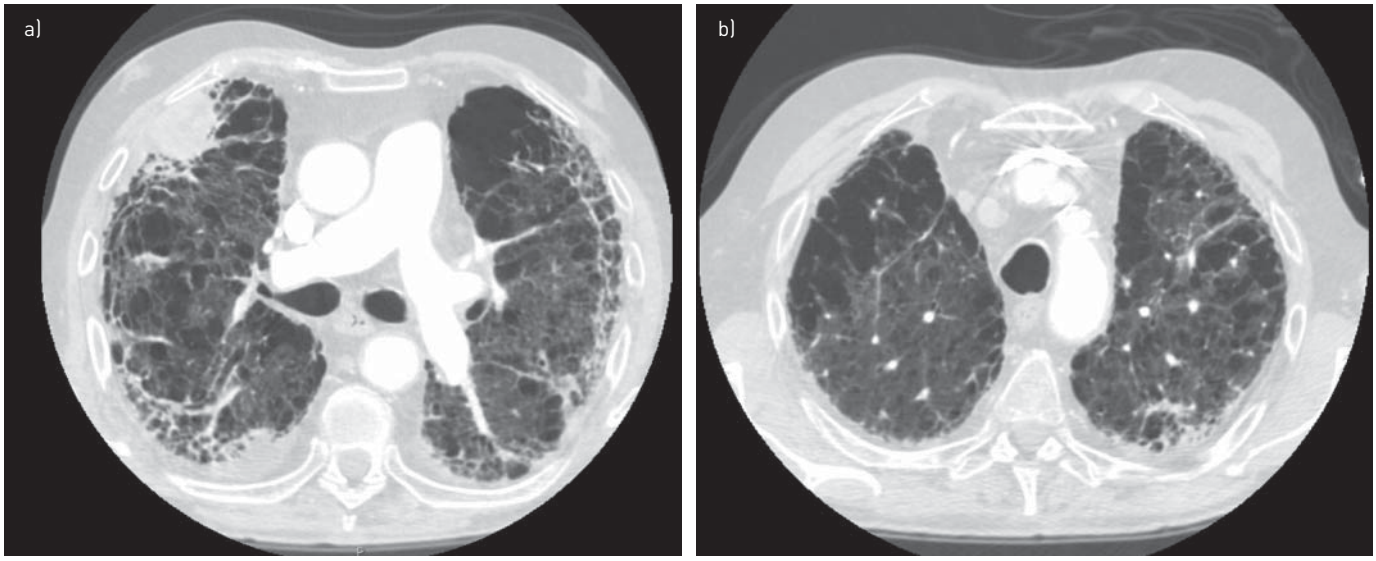

FIGURE 3 High-resolution computed tomography (HRCT) images from a 75-year-old, male ex-smoker with combined pulmonary fibrosis and emphysema syndrome (CPFE). a) HRCT image shows sub-pleural honeycombing in the middle lung, traction bronchiectasis and emphysema. On the right side a consolidation compatible with lung carcinoma is present, a frequent complication in CPFE syndrome. Echocardiography documented a pulmonary arterial pressure of 75 mmHg. b) Focal lucencies associated with paraseptal emphysema are more evident in the upper lobes in the same patient.

(a soluble guanylate cyclase stimulator) has been evaluated in an open-label, uncontrolled pilot trial in patients with PH and ILDs with some positive results. Riociguat was well tolerated and was associated with an increase in cardiac output and decrease in PVR at RHC evaluation after 12 weeks of treatment; mean PAP was unchanged [47]. Riociguat shows the potential to improve exercise capacity in some patients (evaluated using 6MWT distance) [47]. More studies are needed to clarify the role of riociguat in the therapy of PH in ILDs [48].

With the advent of newer treatment options for PAH, coupled with the lack of effective therapies for IPF, targeting PH appears attractive; however, more adequate well-designed clinical trials should be performed [48]. Prior to this, it should be clarified whether mean PAP >35 mmHg is the appropriate cut-off value for diagnosing disproportionate PH, and if only patients with mild-to-moderate parenchymal involvement (and minor functional impairment) and moderate-to-severe PH should be considered for PH therapies.

Other ILDs associated with PH

PH is frequent in ILD associated with connective tissue disease (CTD), where the underlying pathology is usually a nonspecific interstitial pneumonia (NSIP) pattern. Data on the prevalence and clinical features of PH in idiopathic NSIP are sparse and basically unknown; in this setting, the level of PH is usually mild-to-moderate [49]. In an echocardiographic study, HANDA *et al.* [50] reported the incidence of PH to be 28% among 70 patients with idiopathic interstitial pneumonia, 11 of which had NSIP. The mean systolic PAP in this group was 30.2 mmHg. Severe PH has only rarely been described in idiopathic NSIP [51].

PH is a serious pulmonary complication in systemic sclerosis (SSc). Untreated SSc-PH usually results in right-sided heart failure and high risk of death. The average survival in SSc patients diagnosed with PH is 1–2 years [52, 53]. Patients with SSc-PH have a worse prognosis than most other PH patients, including those with PAH [54, 55]. PH may be an isolated manifestation of SSc or may be associated with interstitial lung involvement (fig. 2). The development of PH in patients with SSc and ILD is associated with a significantly poorer prognosis [6], even worse than that of patients with singular vascular involvement [56]. A recent study showed that PAH therapies in patients with SSc-related PH complicating ILD were not associated with any clear benefits [57].

Recently, the syndrome of combined pulmonary fibrosis and emphysema (CPFE) has been described [58]. Radiological findings of CPFE include upper lobe emphysema and lower lobe fibrosis (fig. 3). This syndrome typically occurs in male smokers and is characterised by severe dyspnoea at exercise, subnormal spirometry, severely impaired *D*LCO and poor prognosis [59]. CPFE has also been described as a distinct pulmonary manifestation within the spectrum of CTD-associated lung diseases, such as rheumatoid arthritis and SSc [60]. It appears that PH is rather frequent in patients with CPFE syndrome: in the study by COTTIN *et al.* [59] 47% of CPFE patients had systolic PAP ⩾45 mmHg, as estimated by echocardiography. PH seems to be more frequent in patients with CPFE than in IPF patients without emphysema [60]. PH is a

DOI: 10.1183/09059180.00002713

characteristic feature in the natural history of CPFE syndrome [59, 61] and the presence of PH is a determinant of prognosis in these patients [60]. In a recent study 68% of the patients with CPFE syndrome were found to have PH (mean PAP >35 mmHg as detected by RHC) that was disproportionate to the underlying parenchymal lung disease [62]. Therapeutic options for patients with CPFE are limited; oxygen therapy is only used to correct hypoxaemia. Therefore, these patients should have early evaluation for lung transplant candidacy, when appropriate [62]. COTTIN *et al.* [62] treated patients with CPFE, on an off-label basis, with bosentan, sildenafil or inhaled iloprost, after RHC, as a first-line therapy for PH. The evaluation performed at 3–6 months revealed that these treatments had no significant beneficial effects [62]. More adequate and well-designed prospective, randomised clinical studies are needed to evaluate the effect of these drugs in patients with PH and CPFE.

PH has been studied in rare pulmonary cystic diseases such as lymphangioleiomyomatosis (LAM) and pulmonary Langerhans cell histiocytosis (PLCH). LAM typically occurs in young and middle aged females (fig. 4) [63–65]. PH may occur in a small subset of LAM patients and is usually mild; in a recent study, only 20% of LAM patients had mean PAP >35 mmHg (out-of-proportion PH) as detected by RHC [66]. LAM patients with PH had mildly and severely impaired lung function, and most of them had respiratory failure requiring supplemental oxygen therapy. However, mean PAP and PVR did not correlate with P_{aO_2}, indicating that factors other than hypoxaemia could be involved in the development of PH [66]. A specific off-label therapy for PAH with bosentan or sildenafil in a subgroup of six patients significantly improved pulmonary haemodynamics without a significant difference in exercise capacity or dyspnoea [66]. These are the results of an observational and uncontrolled study with a small number of treated patients (due to rarity of the disease) and more prospective, well-designed studies are needed before definitive conclusions can be drawn.

PLCH is a smoking-related interstitial lung disease; it is commonly associated with hyperinflation and/or obstructive defects on pulmonary functional testing, and is characterised by a bronchiolocentric granulomatous inflammation (fig. 5) [67]. The course of the disease is unpredictable, as it may regress, either spontaneously or after steroid therapy and/or smoking cessation, or progress to pulmonary fibrosis and honeycombing leading to chronic respiratory failure that requires lung transplantation as the only life-sustaining option [68, 69]. PH is frequent in patients with advanced PLCH [70], and is related to an intrinsic pulmonary vascular disease in which the pulmonary circulation is involved independent of small airway and lung parenchyma injury [71]. In the study of DAURIAT *et al.* [72], PH as diagnosed by RHC, was present in 92% of the 39 patients with PLCH referred for lung transplantation and was moderate-to-severe (mean PAP ⩾35 mmHg) in 72.5% of cases. However, PH may not occur only in end-stage PLCH patients [73]. Despite similar hypoxaemia and less severe functional limitation, PH appears to be more frequent and more severe in PLCH than in other diseases, such as IPF and COPD, due to the intrinsic pulmonary vascular disease involving arterioles and venules leading to a variable degree of luminal obstruction, vascular remodelling and inflammation [71]. The prognosis of patients with PLCH and PH is still not well known. LE PAVEC *et al.* [74] recently reported that the use of PAH-specific therapies was associated with a significant improvement in haemodynamics, which remained persistently improved over time, without oxygen worsening or pulmonary oedema. A possible development of pulmonary oedema has been reported by other authors, due to the presence of pathological aspects of pulmonary veno-occlusive disease [71]; the possible occurrence of such a treatment-related complication remains a controversial topic.

PH is a rare complication of another lung granulomatous disease, sarcoidosis [75–77]. Although this complication is rare in absolute terms, it is not uncommon in patients with advanced disease, particularly in patients with stage III and IV disease [4]. PH in sarcoidosis is not related to the degree of lung fibrosis and

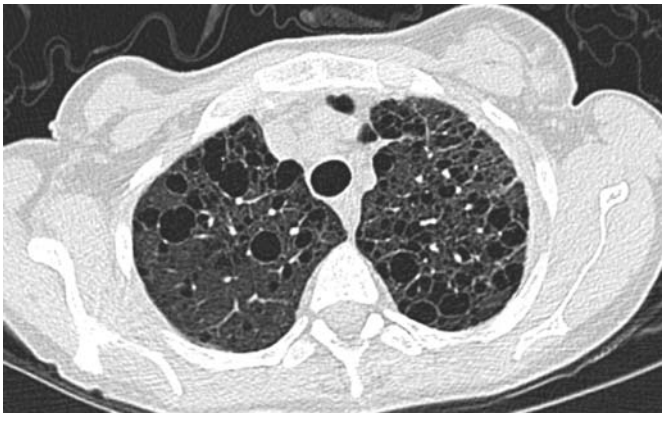

FIGURE 4 High-resolution computed tomography from a 63-year-old, female nonsmoker with lymphangioleiomyomatosis showing diffuse thin-walled lung cysts.

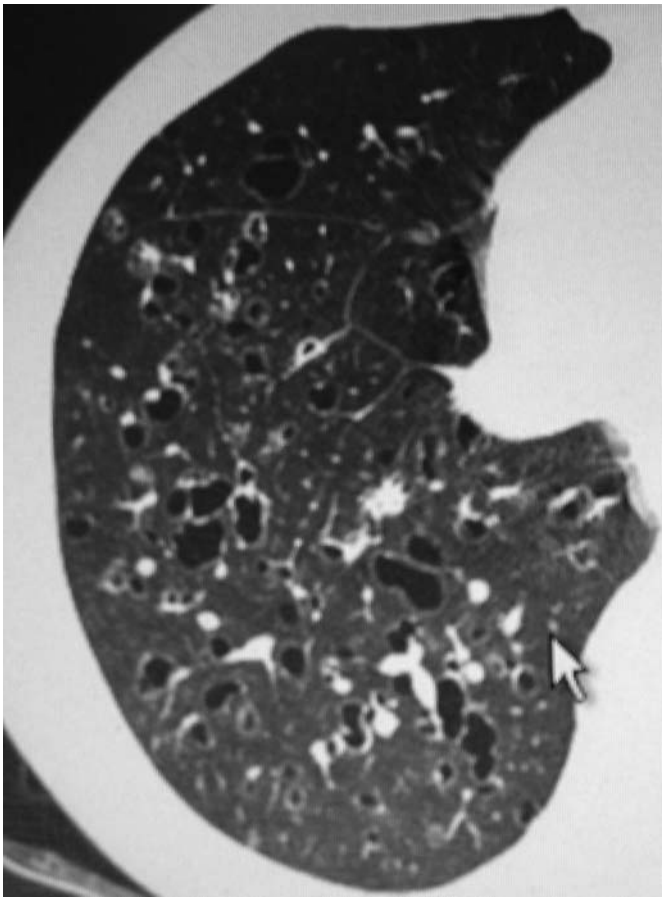

FIGURE 5 Irregular, thick- and thin-walled cysts and nodules in a patient with pulmonary Langerhans cell histiocytosis.

functional impairment [78]. NUNES *et al.* [78] reported that PH may develop in patients with sarcoidosis through several pathogenetic mechanisms: 1) fibrotic involvement and destruction of the capillary bed determining chronic hypoxaemia; 2) compression of large pulmonary arteries by mediastinal or hilar adenopathies or fibrosis; 3) specific granulomatous vasculitis; and 4) pulmonary vasoconstriction by release of vasoactive factors. The presence of PH in sarcoidosis is associated with poor outcomes [4]. In the absence of pulmonary fibrosis, corticosteroid therapy should be considered to treat PH complicating sarcoidosis, since it may sometime be efficacious. In patients with fibrotic disease, corticosteroids seem to be inactive and, when appropriate, these patients should have early referral for lung transplant evaluation [79, 80]. Caution should be used with vasodilator therapies in patients with PH in sarcoidosis due to the potential risk of developing pulmonary oedema [79, 80].

Conclusions

PH is a frequent and severe complication in IPF and other ILDs. PH should be suspected whenever hypoxaemia and *D*LCO are disproportionately low compared with functional and radiological impairment and patients show severe exercise desaturation. Echocardiographic evaluation is a preliminary step in the diagnostic work-up. RHC should always be performed in cases of suspected PH for diagnostic confirmation. The mechanisms for development of PH may, in part, be common to and in part specific to the different diseases. There are no effective treatments for PH in patients with IPF and other ILDs; supplemental oxygen should be prescribed according to standard guidelines. Lung transplantation, when indicated, is the only therapy that may improve survival in these patients; moreover, it is the best option in the advanced stages of disease. However, the presence of PH is a negative prognostic factor for lung transplantation. LAM and PLCH are the only ILDs complicated by the development of PH in which preliminary data suggest a possible effectiveness of PAH-specific therapies. Studies focused on targeted pulmonary vascular therapy, with long-term follow-up and clinically meaningful end-points (*e.g.* mortality and progression-free survival) are needed before a specific therapy can be recommended in these situations. Patients with ILD who are diagnosed with PH should be treated in a clinical trial setting whenever possible.

DOI: 10.1183/09059180.00002713

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