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CASE REPORT

Pleuroparenchymal Fibroelastosis and Hypersensitivity Pneumonitis: A Clinical, Radiological and Pathological Overview

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ABSTRACT
Non-idiopathic pleuroparenchymal fibroelastosis (PPFE) has been increasingly reported in the literature. Little is known about the clinical relevance of PFFE and hypersensitivity pneumonitis (HP) overlap; therefore, we sought to investigate the clinical, radiological, and pathological features of patients with these two diseases. Five patients were identified, and the detailed characterization of these cases revealed a heterogeneous group in terms of clinical and treatment options. No mortality, acute exacerbations, or a significant decline in lung function were verified. Our cases seem to have a more "benign" disease behavior, contrary to previous idiopathic PPFE studies. More studies are needed to corroborate these findings and to better elucidate the clinical significance of PPFE and HP overlap.

Keywords: hypersensitivity pneumonitis, pleuroparenchymal fibroelastosis, idiopathic interstitial pneumonia

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is an interstitial lung disease (ILD) that was recently recognized as a specific idiopathic interstitial pneumonia (IIP) in the update of the international multidisciplinary classification of the IIPs.[1] It is characterized by fibroelastotic thickening of the pleural and subpleural lung parenchyma, mainly in the upper lobes. This condition can be classified as idiopathic or associated with other diseases, such as other ILDs (idiopathic pulmonary fibrosis [IPF][2-4], hypersensitivity pneumonitis [HP][2,5,6], and familiar forms of lung fibrosis[7]), connective tissue disease (CTD)[8-10], infections[8], hematopoietic stem-cell transplantation[8,11], chemotherapy[12], allograph dysfunction after lung transplantation[11], and others.[13-14]

Most published studies have focused on idiopathic PPFE (iPPFE). A recent review by Bonifazi *et al.*[15] stated that the increasing awareness of this condition among specialists has led to a more frequent identification of iPPFE, suggesting that it is not as rare as previously stated. While a definite diagnosis of iPPFE would ideally require a combination of radiological and morphological features, in some cases, histology is not obtained due to an unfavorable risk-effectiveness profile. Therefore, some authors have been proposing criteria for the diagnosis of iPFFE in the absence of a biopsy: a typical radiological pattern of PPFE in addition to other factors, such as the exclusion of secondary causes of PPFE, evidence of radiological disease progression, and some clinical variables (e.g., low body mass index that has been associated with PPFE).[15-17]

On the other hand, HP seems to be a consequence of an immune-mediated reaction secondary to repeated and prolonged specific antigens inhalation in a genetically susceptible individual.[18,19] The incidence and prevalence of HP are difficult to estimate accurately, mostly because of underdiagnosis, which might be partly explained by the absence of widely accepted diagnostic criteria.[18-22] Recently, Raghu *et al.*[20] have proposed a diagnostic algorithm based on antigen identification, bronchoalveolar lavage (BAL), and radiological and histopathological features. Avoiding exposure to the causal antigen(s) is the cornerstone of HP management and prognosis. However, identification of the responsible agent represents a major challenge, mostly because of the lack of standardized approach (including meticulous clinical history with exposure questionnaires, standardization of protocols for the serum specific IgGs measurements, and the specific inhalation challenge test performance).[19,20,23-24]

Non-idiopathic PPFE has been increasingly reported in the literature. However, little is known about its clinical relevance and impact on treatment or prognosis of other co-existent diseases, such as HP. Therefore, the authors aimed to characterize the clinical, functional, and prognostic variables of patients with the diagnosis of PPFE and HP overlap.

Methods

Patients with a histological diagnosis of PPFE were retrieved from the ILD outpatient clinic of Centro Hospitalar e Universitário de São João, Porto, Portugal. All cases had histological features of PPFE that were definitive or consistent with PPFE diagnosis, as described previously in the literature.[2] From this group, five patients were identified to have a concomitant diagnosis of HP by histological (n = 4) or clinical-radiological (n = 1) analysis.

All patients were discussed in an ILD multidisciplinary team (MDT), and the diagnosis of PPFE and HP was assumed. Each microscope slide and computer tomography (CT) scan were reviewed by two pathologists and two radiologists with experience in the ILD field, respectively.

Clinical, laboratory data, radiological patterns on high-resolution chest computed tomography (HRCT), and pulmonary function test (PFT) results at the time of diagnosis of the HP and PPFE overlap and after 1 year of follow-up were retrieved from the electronic database.

Results

The authors identified five patients with the overlap diagnosis of PPFE and HP. All patients were female, with a median age of 61 years (46–78 years), and the majority were non-smokers (4/5). No patient had a previous history of *Mycobacterium tuberculosis* infection. A positive nonspecific autoantibody was demonstrated in two patients (positive rheumatoid factor [RF] titer = 87.1 UI/mL; antinuclear antibodies [ANA] = 1:320; speckled pattern). Two patients had a family history of ILD: Patient Two and Patient Five had a first degree relative with IPF and sarcoidosis, respectively. Table 1 provides a detailed characterization of the patients.

Table 1 – Clinical and demographic characterization of patients with PPFE and HP overlap. (NF: missing data; PPFE: Pleuroparenchimal Fibroelastosis; HP: Hypersensitivity Pneumonitis; BAL: bronchoalveolar lavage; TTLB: transthoracic CT guided lung biopsy; SLB: surgical lung biopsy; TBLC: transbronchial lung cryobiopsy; MDT: multidisciplinary discussion)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	61	54	78	66	46
Smoking status	Former smoker	Non-smoker	Non-smoker	Non-smoker	Non-smoker
Body mass index (kg/m2)	19.75	26.02	20.78	20.00	22.66
Past comorbidities	Osteoporosis	No	Arterial hypertension, Dyslipidaemia, Diabetes mellitus, Hypothyroidism	Rhinosinusitis Gastroesophageal reflux Osteoporosis	Rhinosinusitis
Symptoms					
Exertional dyspnoea	Yes	Yes	No	Yes	Yes
Cough	Yes	Yes	No	Yes	Yes
Weight loss	Yes	Yes	No	Yes	No
Recurrent respiratory infections	Yes	No	No	Yes	Yes
Wheezing	No	No	No	Yes	No
Pleuritic pain	No	No	No	No	No
HP classification	Chronic	Chronic	Acute/Subacute	Chronic	Chronic
Known exposure	No	Yes, funghi	Yes, birds	Yes, birds	No
BAL lymphocytosis (%)	NF	14.4	43.6	NF	63.4
Diagnosis PPFE/HP	TTLB/SLB	TTLB/TBLC	TTLB/MDT	TTLB/SLB	SLB/SLB
Treatment	Vaccination Hydroxychloroquine	Exposure eviction Vaccination Corticosteroid + mofetil mycophenolate Azithromycin	Exposure eviction Vaccination	Exposure eviction Vaccination Corticosteroid	Vaccination Corticosteroid + azathioprine

Regarding symptoms, the most common complaints were exertional dyspnoea (4/5) and cough (4/5), followed by recurrent respiratory infections (3/5) and weight loss (3/5). No patient complained of pleuritic pain. Patient Three was asymptomatic at diagnosis.

Considering HP classification published by Vasakova *et al*,[19] four patients presented chronic HP characteristics, and acute/subacute HP was diagnosed in Patient Three. An antigen exposure was identified in three patients (birds in two patients and fungi in one). All patients were submitted to bronchoscopy with BAL, and an intense lymphocytosis (≥ 40%) was identified in two patients. No information was retrieved regarding the BAL results of Patient One and Patient Four, as both procedures were performed before the availability of a computer database and in one case, the procedure was performed in another hospital.

Regarding radiological patterns, all patients had evidence of upper lobe volume loss with apical pleural thickening and subpleural consolidations. Patient One presented almost exclusively with a nodular centrilobular pattern with extensive tree-in-bud. Patient Two presented with a pattern resembling radiological usual interstitial pneumonia (UIP), albeit with some scattered areas of ground-glass opacification. Patient Three and Patient Five showed mainly a mosaic attenuation pattern with scattered areas of ground-glass opacification, but without any features of lung fibrosis (apart from PPFE). Patient Four had evidence of small airways disease (mosaic attenuation pattern and centrilobular nodularity) and lung fibrosis with traction bronchiectasis and small foci of honeycombing. Additionally, bronchiectasis and esophageal dilation were identified in some patients, which might also contribute to facilitating respiratory infections (Table 2).

Table 2 – Radiological and histopathological findings. (RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; TTLB: transthoracic CT guided lung biopsy; SLB: surgical lung biopsy; TBLC: transbronchial lung cryobiopsy; NA: non-applicable)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Radiological findings					
Involved lobes	5 (RUL, RML, RLL, LUL, LLL)	5 (RUL, RML, RLL, LUL, LLL)	4 (RUL, RLL, LUL, LLL)	5 (RUL, RML, RLL, LUL, LLL)	2 (RUL, LUL)
Centrilobular nodules	Yes (w/tree-in-bud)	No	Yes	Yes	Yes
Ground glass/mosaic attenuation	No	Yes	No	Yes	No
Traction bronchiectasis	No	Yes	No	Yes	No
Honeycombing	No	No	Central bronchiectasis	Yes	Esophageal dilatation
Other findings				Mild central bronchiectasis	
Pathological findings					
Type of biopsy performed	TTLB/SLB	TTLB/TBLC	TTLB	TTLB/SLB	SLB/SLB
Examined lobe(s)	RUL/RUL, RLL	RUL/LUL, LLL	RUL	RUL/RLL	LUL, LLL
Fibroblastic foci	No	Yes	NA	No	Yes
Lymphocytic infiltration	Yes	Yes	NA	Yes	Yes
Loose granulomas	Yes	Yes	NA	Yes	Yes
Bronchiolocentric inflammation	Yes	Yes	NA	Yes	Yes
Peribronchiolar metaplasia	Yes	Yes	NA	No	Yes
Fibrosis	No	Yes	NA	No	No
Other findings	No	Thickening of arterioles wall		No	Thickening of arterioles wall

All patients obtained a histopathologic confirmation of PPFE (transthoracic CT guided lung biopsy [TTLB] = 4; surgical lung biopsy [SLB] = 1), and four patients had a histologic diagnosis of HP (SLB = 3; transbronchial lung cryobiopsy [TBLC] = 1). The diagnosis of HP in Patient Three was based on clinical-radiological criteria in MDT: known exposure, typical HP radiological pattern, and high BAL lymphocytosis. The TBLC of Patient Two was complicated, with a pneumothorax with the necessity of drainage. No complications were reported with the other invasive procedures. Detailed characterization of the radiological and histopathological patterns is presented in Table 2 and Figures 1 and 2.

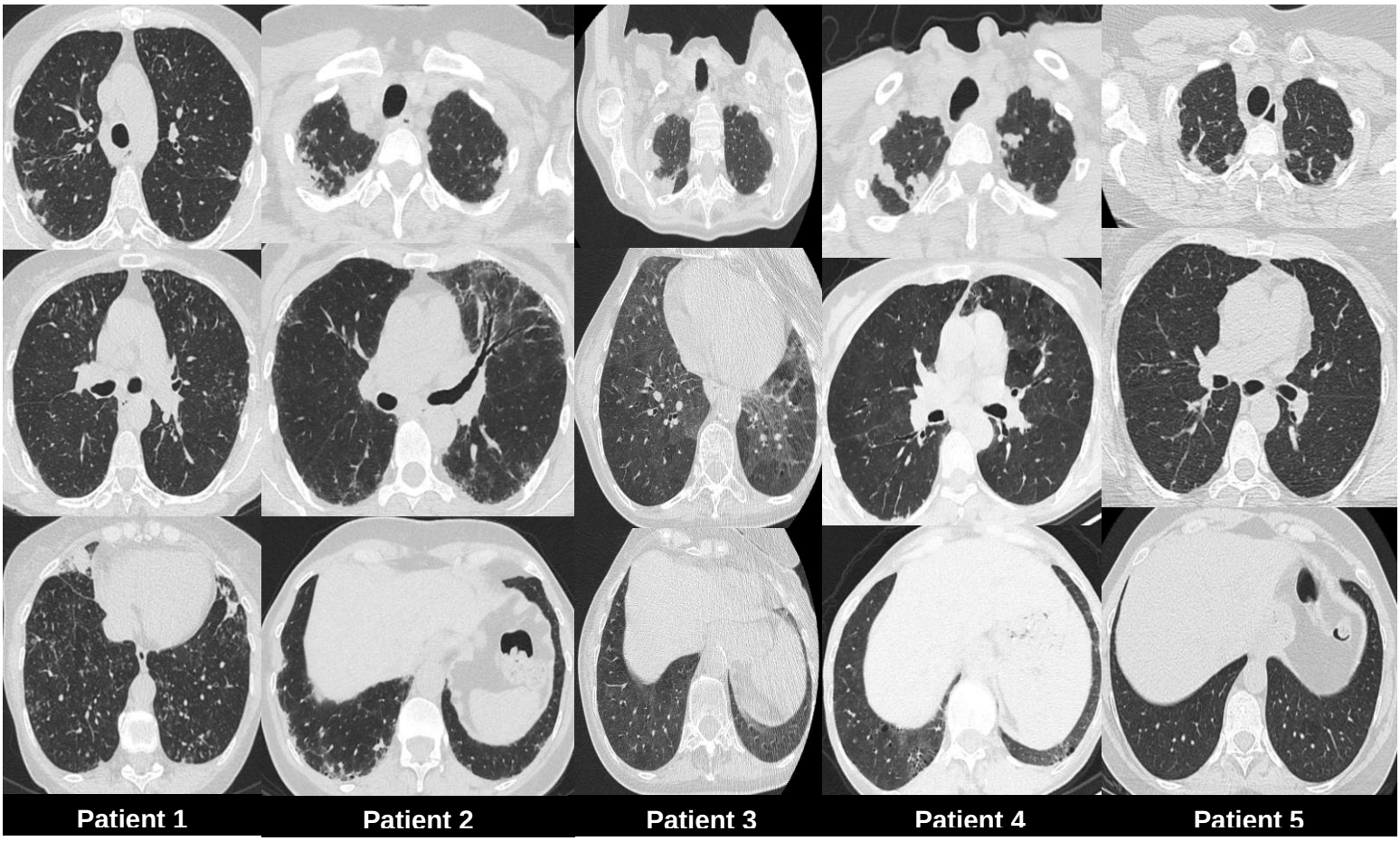

Figure 1- Chest HRCT findings of PPFE and HP overlap. All patients had evidence of upper lobe volume loss, apical pleural thickening and subpleural opacities in keeping with pleuroparenchymal fibroelastosis. Patient 4 had also a deepened suprasternal notch and reduced anteroposterior diameter of the thoracic inlet (platythorax) with retraction of the trachea. In Patient 1 a micronodular centrilobular pattern with extensive tree-in-bud is seen. Patient 2 presented with features of possible UIP with subpleural intralobular reticulation and traction bronchiectasis but no honeycombing. Some areas of peribronchovascular ground-glass opacification can also be seen in the LUL. Patients 3 and 5 presented mainly with features of small airways disease, with ground-glass opacities and mosaic attenuation pattern with scattered lobular areas of reduced attenuation and vascularity. Note also esophageal dilatation in Patient 5. Patient 4 presented with features of small airways disease and pulmonary fibrosis with subpleural traction bronchiolectasis and probable honeycombing in the lower lobes.

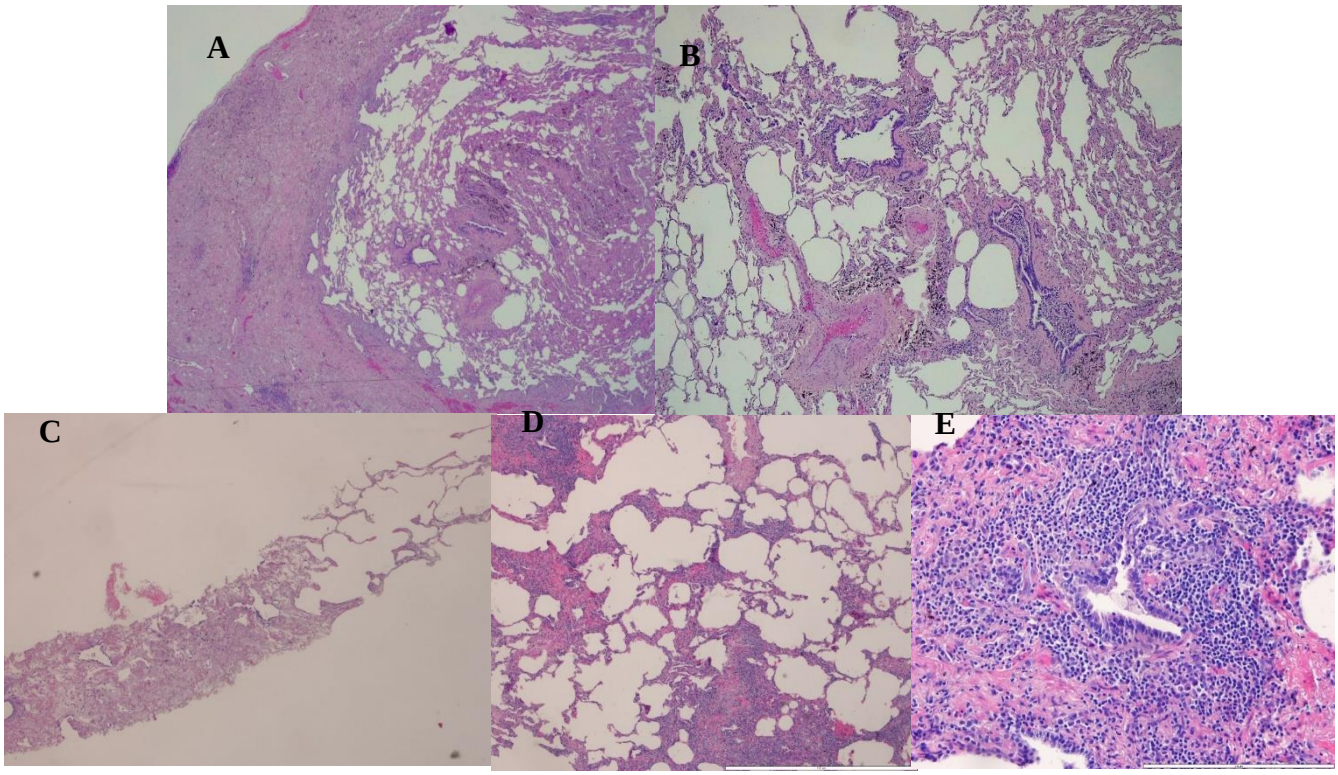

Figure 2: Histopathological findings of PPFE and HP. A - Pleural and subpleural parenchymal fibroelastosis (arrow) and B - Thickening of arteriole wall, small lymphocytic infiltrate and histocytes aggregates resembling loose granulomas (b) in the centrilobular area on surgical lung biopsy of patient 5. C – Pleuroparenchymal fibroelastosis on a transthoracic guided CT lung biopsy of patient 1. D – Lymphocytic infiltrates and E – Bronchiolocentric interstitial pneumonia in the surgical lung biopsy of patient.

The diagnosis of PPFE and HP was concomitant in three patients (Patient Two, Patient Three, and Patient Five), and in the other patients, the histological diagnosis of PPFE was posterior to the HP (Patient One = 2 years; Patient Four = 14 years). After reviewing the previous thoracic CTs, Patient One already presented areas of pleural thickening of the upper lobes, and a discrete radiological progression led to the investigation with TTLB. Considering Patient Four, we did not have access to the initial CT as the HP diagnosis was achieved in the early 2000s, and the PPFE was not a well-recognized entity at that time. The apical features of PPFE were initially assumed as mucous plugging and scars in 2008, and the patient stopped corticosteroids after 5 years of clinical stability. However, a clinical and radiological (apical and lower lobes features) deterioration in 2018 motivated the TTLB and the restart of treatment with corticosteroids.

Lung function and the 6-minute walking test (6MWT) evaluation over a 1-year period are presented in Table 3. Patient One showed an obstructive ventilatory defect, and four patients revealed a diminished monoxide carbon diffusion capacity (DLCO).

Table 3- Lung function and 6MWT parameters at baseline (diagnosis of overlap HP and PPFE) and at one-year follow-up. (FVC: forced vital capacity; FEV1= forced expiratory volume in the first second; TLC: total lung capacity; DLCO: carbon monoxide diffusing capacity; KCO: transfer coefficient of the lung for carbon monoxide; 6MWT: six-minute walking test; SpO2: peripheral oxygen saturation)

	At diagnosis of PPFE and HP overlap	1-year follow-up
FVC (L/% predicted)	2.1 ± 0.5 / 88.4 ± 14.3	2.2 ± 0.4 / 92.7 ± 11.1
FEV_1 (L/% predicted)	1.7 ± 0.4 / 87.5 ± 13.0	1.8 ± 0.5 / 88.8 ± 18.9
TLC (L/% predicted)	4.7 ± 0.5 / 105.0 ± 16.2	4.5 ± 0.2 / 101.8 ± 10.4
DLCO (% predicted)	61.0 ± 6.6	46.4 ± 3.8
KCO (%predicted)	72.0 ± 9.0	63.0 ± 9.3
Walking distance in 6MWT (m)	473.6 ± 76.5	480.0 ± 69.3
Baseline SpO_2 in 6MWT (%)	96.6 ± 1.3	96.0 ± 1.0
Minimal SpO_2 in 6MWT (%)	90.8 ± 2.8	91.3 ± 3.5

Most patients were treated with immunosuppressors and/or corticosteroids (Table 1). Moreover, exposure eviction and influenza and pneumococcal vaccination were recommended to all patients. Patient One was initially treated with corticosteroids. However, recurrent infections continued, so it was decided to start on hydroxychloroquine and to slowly taper the corticosteroids. Patient Two presented hepatotoxicity with azathioprine treatment and was initiated on mofetil mycophenolate. She started to complain of recurrent respiratory infections with the progressive increase of mofetil mycophenolate dosage. Consequently, it was decided by the MDT to taper corticosteroids, maintain MMF at 750 mg twice daily, and to initiate macrolide therapy after exclusion of atypical mycobacterial lung involvement. No other relevant changes in medication or adverse events occurred during follow-up.

During a median follow-up of 2 years (range, 1–5 years), no mortality, acute exacerbations, or a significant decline in lung function were verified in this case series.

Discussion

As previously stated, non-idiopathic PPFE has been increasingly reported in the literature. This report describes five cases in which clinical presentation, radiological, and histopathological features are compatible with the overlap diagnosis of PPFE and HP.

Some single reports of these diagnostic overlap have been described in the previous PPFE series. Recently, Jacob *et al.* [5] evaluated the prevalence and prognostic impact of PPFE in 233 patients with a previous diagnosis of HP. The authors identified that PPFE features were present in 40% (93 patients) of HP patients. However, only a minority had a pathological confirmation (20 patients = 22%). They observed that PPFE was independently linked to impaired lung function and mortality in HP. To our knowledge, this is one of the first studies attempting to characterize in detail patients with both diagnoses.

Considering clinical characteristics, we verified a female predominance, and patients' median age was similar to that reported by Jacob *et al.* [5], HP[23,24], and iPPFE cohorts.[2,15,27] By contrast, other contemporaneous reports have not identified a clear gender difference.[28,29] The absence of smoking habits in our cases is in line with previous reports and seems to be a common feature of these diseases.[15,30] In HP, the authors defended that the protective effect of smoking in these diseases might result from suppression of T-helper cell-1 immunity, but at a price in terms of other respiratory diseases.[30] Moreover, positive smoking history was also found to be protective against the development of PPFE in the Jacob *et al.* HP cohort.[5] However, the authors hypothesized that the lung damage caused by smoking might limit the development of PPFE in the visceral pleura.

PPFE pattern might be associated with a large variety of conditions, although a clear causative relationship has yet to be established. Regarding pathogenesis, HP seems to be a consequence of an immune-mediated reaction caused by recurrent exposure to environmental antigens in genetically predisposed individuals.[19,26] Most of the developed studies analyzed iPPFE cohorts, and its etiopathogenesis is not completely understood.[15,31] It has been suggested that acute or subacute lung injury, including diffuse alveolar damage (DAD), causing interstitial inflammation is central to the pathological cascade that culminates in PPFE.[29,32] Environmental factors, genetic predisposition, and immune dysregulation have also been identified as possible mechanisms for the development of iPPFE. In fact, in our cases, three patients complained of recurrent respiratory infections, which have been mentioned as a possible trigger for the development of PPFE. Furthermore, two patients revealed having a familiar history of ILDs, which might reflect a genetic susceptibility. Increased titers of serum autoantibodies were also present in two patients, possibly reflecting a pathogenetic role of immune dysregulation.[1,15]

Moreover, the immune dysregulation responsible for HP might also contribute to the development of the PPFE. In all our patients, the diagnosis of PPFE was posterior or concomitant with the diagnosis of HP. Therefore, the pathophysiology of these diseases, as well as the existence of a presumed smoking protective effect, is still unclear.

There is a certain variability of clinical presentation among the reported HP[19,20,26] and PPFE[2,15] cohorts. In a recently published series[2], the most frequent symptoms were exertional dyspnea and cough, which is concordant with the complaints reported in this paper. Another frequent complaint in PPFE is progressive weight loss that was verified in three of our patients. By contrast, none of our patients presented with chest pain or pneumothorax, as previously stated in the literature.[15,29]

Treatment management can be challenging, and a significant number of questions remain open: is PPFE secondary to HP? Should we direct therapy to HP as other secondary forms of ILDs? Or does PPFE needs a specific treatment? How relevant is infection prevention to the disease prognosis? Regarding iPPFE[15], patients have been empirically treated with corticosteroids and immunosuppressive agents in analogy with other ILDs. Concerns have been raised about the use of aggressive immunosuppression and the risk of recurrent infections as an adverse effect and its role in disease progression. Considering HP, some retrospective studies have demonstrated the efficacy of immunosuppressors usage.[32-35] However, to date, no treatment has yet been shown to modify the natural course of the disease, and there are no randomized controlled trials or case-control studies reporting the efficacy of the different immunosuppressive agents in PPFE or HP.[15,19,20,24,29]

In our described cases, most patients were treated with the previously stated strategy. In fact, two patients were under immunosuppressors for HP at the time of PFFE diagnosis, which limits any conclusions regarding disease-specific treatment. Considering the recurrent infections and their potential role in pathogenesis, all patients were submitted to influenza and pneumococcal vaccination. Prophylactic antibiotics and antifungal therapy have been hypothesized as possible effective treatments in PPFE, and one patient was treated with azithromycin.[30] A probable efficacy of antifibrotic therapy (pirfenidone) in preventing lung function decline has been suggested in a recent case-report of iPFFE.[37] Moreover, the INBUILD trial has recently demonstrated that patients who received nintedanib had a slower rate of forced vital capacity (FVC) decline versus placebo in progressive fibrotic ILDs (in which 26.1% were chronic HP).[38] Trials with pirfenidone for HP are occurring and will also bring relevant information concerning treatment (clinicaltrials.gov identifier: NCT02496182).

Prognosis has been reported as highly variable and largely unpredictable in both PPFE and HP. For example, limited data is available on iPPFE evolution, as in most of the studies, the overall survival was reported together for idiopathic and secondary forms. Moreover, it seems to be an increasing acknowledgment of a subgroup of patients who are prone to inexorably advancing disease in iPPFE and HP cohorts. So far, only one study addressed prognosis in patients with the diagnosis overlap. Jacob *et al*. had published that PPFE was associated with worse prognosis of HP patients.[5] Whilst several authors had demonstrated the same when PPFE was associated with UIP/IPF[3] or connective tissue disease related ILD[10], others have failed to demonstrate a negative prognostic impact[30]. In fact, our patients had a relatively stable disease behavior as no deaths or a significant decline in lung volumes was verified over the follow-up period. Despite these findings, a significant number of issues regarding PPFE and HP prognosis remain: should we regard the appearance of PPFE after the diagnosis of HP as a sign of progressive disease? Should it be an indication of treatment failure? Is the prognosis different if the diagnosis of these diseases is concomitant or sequential?

Conclusion

In conclusion, there are few studies published in the literature regarding PPFE and HP overlap. Despite being a small sample, the detailed characterization of these cases revealed a heterogeneous group in terms of clinical and treatment options. Furthermore, our cases seem to have a more "benign" disease behavior, contrary to previous studies. Therefore, the cases or series descriptions of PPFE and HP are important as they can contribute to improving diagnoses, therapeutic approach, and prognostic impact. Prospective studies with larger samples and follow-up periods are needed to corroborate these findings and to better elucidate the meaning of PPFE and HP association.

Conflicts of interest

The authors have no conflicts of interest to declare.

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