# Pleuroparenchymal fibroelastosis in association with connective tissue disease: a new interstitial pneumonia to be aware of

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## ABSTRACT

Pleuroparenchymal fibroelastosis (PPFE) is a rare and recently described interstitial pneumonia. It consists of progressive fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes, with defined and reproducible clinical, radiological and histopathological criteria. No effective treatment has yet been shown to modify the natural course of the disease, which vary greatly in the literature. Several conditions have been associated with PPFE, including connective tissue diseases (CTD). The authors present two cases of female patients with a CTD (rheumatoid arthritis and limited cutaneous systemic sclerosis, respectively) who presented with typical bilateral upper lobe thickening in chest High Resolution Computed Tomography (HRCT). In the first case, diagnosis was based on "definite" radiological and histopathological criteria for PPFE, while in the second case diagnosis was established on clinical grounds after discussion in a multidisciplinary team meeting. The authors present these cases of CTD-associated PPFE in order to raise awareness of this entity among clinicians.

**Keywords:** Interstitial lung disease; Connective tissue disease; Rheumatoid arthritis; Systemic sclerosis.

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## INTRODUCTION

Pleuroparenchymal fibroelastosis (PPFE) is a rare clinical–pathological entity[1]. It was officially described in 2004 by Frankel *et al.*[2] and is considered a specific entity within the group of interstitial lung diseases (ILD)[5]. The aetiology, pathophysiology and natural course of PPFE are unclear. A few associated conditions have been described[1], including connective tissue diseases (CTD) such as rheumatoid arthritis (RA)[1] and cutaneous systemic sclerosis (SSc)[3]. Although the association with RA has been pointed in some reports, they all refer to the same article from 1980 with description of progressive upper lobe fibrosis in patients with RA, whose histological features were similar to those of PPFE[4]. ILD is common in SSc and PPFE might be a rare additional pattern of ILD associated with this disease[3].

### CASE 1

59-year-old woman, non-smoker, with a 20-year diagnosis of RA. She was treated with Methotrexate for the first 5 years after diagnosis, which was switched to Adalimumab because of uncontrolled disease with a subsequent good response. She had no significant comorbidities and denied relevant occupational or environmental exposures.

In the beginning of 2014 she complained of dry cough and exertional dyspnoea, without arthralgias or other relevant symptoms. Laboratorial analysis showed an erythrocyte sedimentation rate of 97mm/h. High Resolution Computed Tomography (HRCT) of the chest revealed interlobular septal thickening in both lungs, with predominance in the periphery of the lower lobes, compatible with a Nonspecific Interstitial Pneumonia (NSIP) pattern. In addition, an irregular pleural and subpleural interstitial thickening in the upper lobes was also observed, predominantly in the apical segments (Figure 1-A). Lung function tests showed a re-

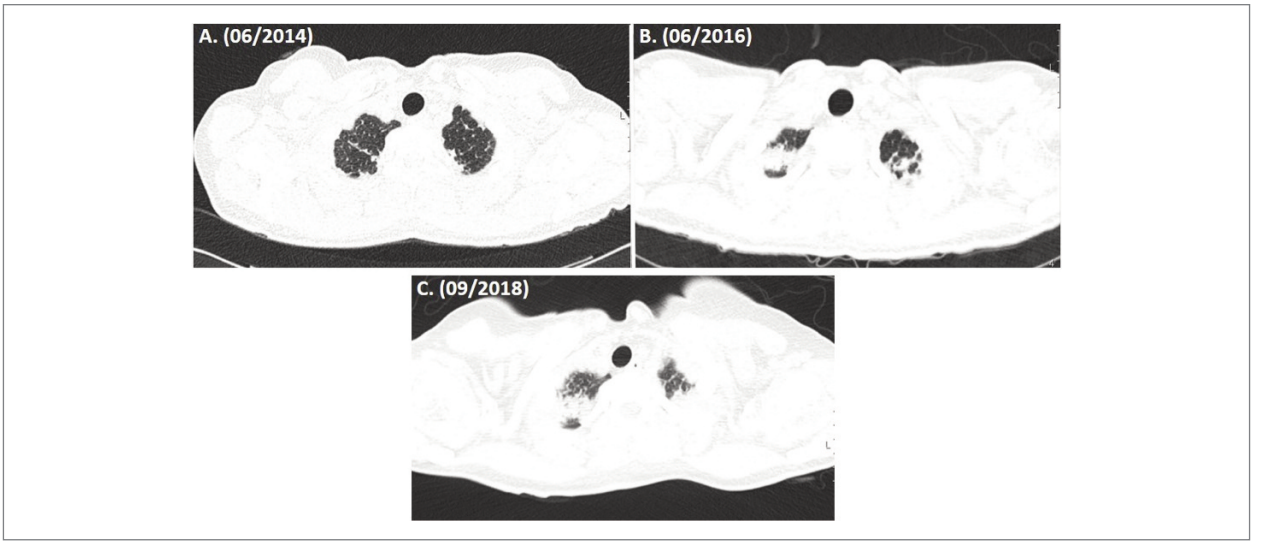


**FIGURE 1.** (A,B,C) – Evolution of High Resolution Computed Tomography (HRCT) thoracic imaging over time (axial images). Upper lobes pleural and subpleural parenchymal thickening representing fibrotic lesions are shown. Progression of fibrosis is seen over time.

duction in lung diffusing capacity for carbon-monoxide (DLCO, 68%), without other abnormalities. Blood gases were in the normal range. Flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed and a high lymphocytosis of 41.6% with CD4+ predominance was noticed in the total and differential cell count. She started oral prednisolone 40 mg/day. After 1 month of follow-up, a favourable clinical and analytical evolution was already evident and steroids were gradually tapered off and stopped.

In 2015 Adalimumab was stopped due to neutropenia and she was again given prednisolone for arthralgias. She remained without any relevant respiratory symptoms and had a stable lung function. After a rigorous haematologic evaluation, a diagnosis of medullary hypoplasia secondary to the rheumatic disease was established. Adalimumab was restarted in 2016. A follow-up chest HRCT performed at that time revealed worsening of subpleural and septal interstitial thickening, especially in both upper lobes (Figure 1-B). Due to persistent polyarticular flare, treatment was switched from Adalimumab to Rituximab.

A follow-up chest HRCT in 2018 showed similar imaging features, namely those previously described in the upper lobes. The analysis of the serial chest HRCT findings raised the suspicion of PPFE and the patient underwent percutaneous transthoracic lung biopsy, which revealed pleural fibrosis and prominent subpleural and parenchymal fibroelastosis (Figure 2). She is currently monitored in an ILD specialized centre and remains clinically and functionally stable, with no changes to prior medications.

## CASE 2

60-year-old woman, non-smoker, diagnosed with limited cutaneous systemic sclerosis since she was 22 years old comprising Raynaud's phenomenon, skin thick-

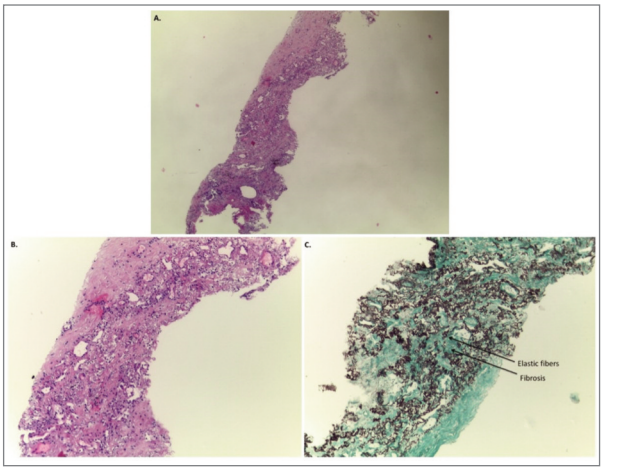


**FIGURE 2.** Section of upper lobe biopsy showing: (A, B) visceral pleura fibrosis and homogeneous dense subpleural fibrosis with prominent elastosis (C). Staining: A, B) haematoxylin and eosin; C) orcein staining. Magnification: A) 40×; B, C) 100×.

ening, digital ulcers, positive antinuclear antibodies at a 1:1000 titre with a centromere pattern and positive anti-centromere antibodies. She never developed any other specific organ involvement, had no significant comorbidities and denied relevant occupational or environmental exposures. Her usual treatment included only nifedipin 30 mg daily. A chest HRCT performed in 2012 had no other significant features than apparent residual upper lobes pleural and subpleural thickening (Figure 3-A). Serial transthoracic echocardiography showed no evidence suggestive of pulmonary artery hypertension. SSc remained stable over the years, without any signs of activity and no treatment adjustment was required.

In 2016 she developed persistent dry cough, with mild exertional dyspnoea and weight loss of 5kg over 6 months. She denied other constitutional symptoms. Laboratory blood tests were unremarkable. A new chest HRCT (01/2017) revealed stable pleural and subpleural thickening in the upper lobes and new patchy peripheral consolidations in the upper and middle lobes and scattered solid micronodules (Figure 3-B). Lung function tests showed small airway obstruction and decreased DLCO (62%); blood gases analysis was within the normal range. The BAL had no malignant cells or pathogenic microorganisms and total and differential cellular count showed mild neutrophilia (8,4%) and eosinophilia (2,0%). A percutaneous transthoracic lung biopsy was subsequently performed, with histologic findings of lymphoid interstitial pneumonia (LIP), without evidence of additional lesions. Serial chest HRCT showed discrete progression of the upper lobes pleural and subpleural thickening (Figure 3-C, D). The case was reviewed and discussed in an ILD multidisciplinary diagnosis meeting and a definitive diagnosis of LIP and PPFE in the SSc context was established. Since the patient remained clinically and functionally stable and the imaging extension was below 20%, no targeted therapy was prescribed. She is currently monitored in an ILD specialized centre.

## DISCUSSION

PPFE is a rare and recently described interstitial pneumonia[2,5-8]. It consists of progressive fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes[5,8], with a particular histopathologic pattern of visceral pleural thickening with collagenous fibrosis, subpleural elastosis and intra-alveolar collagenous fibrosis[2,9].

PPFE occurs mainly among non-smokers and has no gender predominance, with a median age of presentation of 46 to 57 years, according to different series[1,6,9,10]. In the depicted cases both patients were never smokers with an age of presentation within the

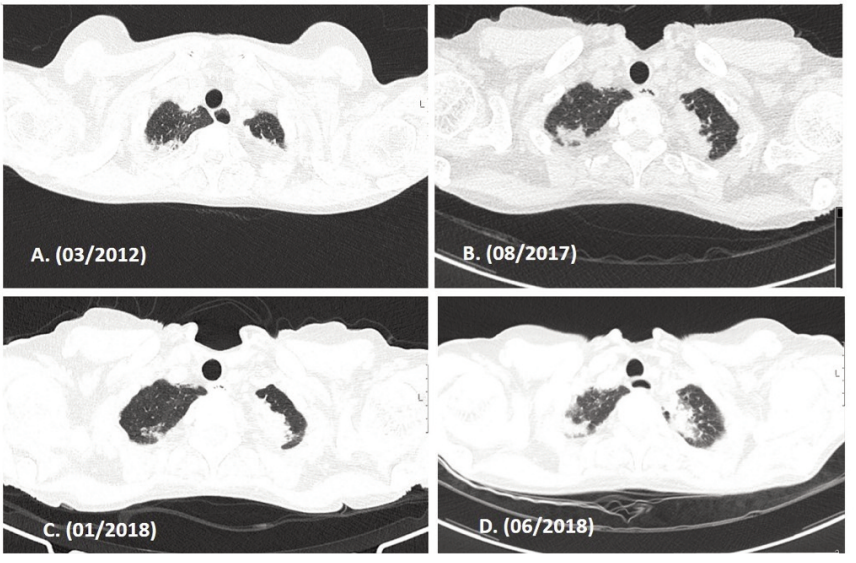


**FIGURE 3.** Evolution of thoracic imaging by High Resolution Computed Tomography (HRCT) over time (axial images). Upper lobes pleural and subpleural parenchymal thickening representing fibrotic lesions are shown. A slow progression of the fibrosis is seen over time.

range seen in literature.

Similarly to the reported cases, clinical presentation is not specific, with the most common symptoms consisting of exertional dyspnoea of insidious onset, dry cough and weight loss[1,8,9,10,11]. Chronic dull pleuritic pain[1,8,9,10], recurrent lung infections[8] and platythorax due to upper lobes fibrosis[1,9,10,12] may also occur. Spontaneous pneumothorax is a characteristic complication in the natural history of PPFE, being present in ~30% of patients[1,6,10], frequently with persistent air leak and poor reexpansion of the underlying lung[6, 10].

Lung function tests may present a restrictive ventilatory impairment. An increased residual volume /total lung capacity ratio (RV/TLC) may be found due to compensatory hyperinflation of the lower lobes in response to upper lobe collapse. DLCO is typically reduced and DLCO/VA can be either normal or slightly reduced. Arterial hypoxaemia and hypercapnia may arise with disease progression[1, 9, 10]. In both cases patients had reduced DLCO with normal DLCO/VA but presented minor ventilatory changes. This may explain their pauci-symptomatic clinical picture.

Diagnostic criteria for PPFE were proposed in 2012 by Reddy *et al.*[8] HRCT imaging criteria for PPFE were divided in "definite" or "consistent with". "Definite" criteria consist of pleural thickening and subpleural fibrosis concentrated in the upper lobes, while the lower lobe involvement is less marked or absent[8, 9]. Histological criteria for PPFE were also divided in "definite" and "consistent with". "Definite" criteria include upper zone pleural fibrosis with subjacent intra-alveolar fibrosis, accompanied by alveolar septal elastosis[8,9] (Table I).

Despite that a definitive diagnosis of PPFE traditionally requires histological examination[11], a significant proportion of patients do not undergo lung biopsy due to reasons such as very advanced disease, risk of iatrogenic pneumothorax or the fact that the disease can be strongly suspected based on clinical and radiological features[10]. For those cases where no biopsy is available, a label of "consistent with PPFE" has been suggested[6,8,10] and a multidisciplinary diagnostic meeting is crucial to establish the diagnosis[8]. Recently Enomoto and colleagues[13] proposed a clinical diagnosis of PPFE based on a combination of radiological findings of "definite PPFE", radiologic confirmation of disease progression and exclusion of other lung diseases with identifiable aetiologies, with results supporting accuracy and confidence in clinical diagnosis. The second reported case is an example of this situation. The diagnosis of PPFE was established in a multidisciplinary diagnostic meeting, based only on clinical and radiological findings, with no need to pursue histological confirmation.

In addition to genetic predisposition[1,3,5,6,8,9,14-16], several conditions have been associated with PPFE, including previous lung and bone marrow transplantation, chemotherapy, recurrent infections and connective tissue diseases (CTD), such as rheumatoid arthritis or systemic sclerosis[1,3,5,6,8,9,15], as depicted above (Table II). Radiological and histological features like those of PPFE have been reported in CTD patients with apical fibrosis in earlier case reports, prior to the recognition of this entity[4, 6]. These are the only data sup-

**TABLE I. CRITERIA FOR THE DIAGNOSIS OF PLEUROPARENCHYMAL FIBROELASTOSIS**

**HRCT Imaging Criteria of PPFE**

*"Definite"*

- Upper lobe pleural thickening and subpleural fibrosis, and
- Lower lobe involvement less marked or absent

*"Consistent with"*

- Upper lobe pleural thickening and subpleural fibrosis, but
  - Distribution of changes not concentrated in upper lobes, or
  - Presence of features of coexistent disease elsewhere

**Histological Criteria of PPFE**

*"Definite"*

- Upper zone fibrosis of the visceral pleura, and
- Prominent, homogenous, subpleural intra-alveolar fibrosis with alveolar septal elastosis, and
- Sparing of the parenchyma distant from the pleura, and
- At most mild, patchy lymphoplasmocytic infiltrates, and
- At most small numbers of fibroblastic foci present

*"Consistent with"*

- Intra-alveolar fibrosis as above, but
  - Not associated with significant pleural fibrosis, or
  - Not predominantly beneath the pleura, or
  - Not in an upper lobe biopsy

Adapted from: Thusen J, Pleuroparenchymal Fibroelastosis: Its Pathological Characteristics[6]

**TABLE II. UNDERLYING DISEASES OR CONDITIONS THAT MAY BE ASSOCIATED WITH PLEUROPARENCHYMAL FIBROELASTOSIS (PPFE) UNDERLYING DISEASES OR CONDITIONS THAT MAY BE ASSOCIATED WITH PPFE**

| Underlying diseases or conditions that may be associated with PPFE |
|---|
| • Idiopathic PPFE |
| • Hereditary PPFE |
| – Family history of PPFE |
| – Observed association with mutations in telomere-related genes (TERT, TERC, RTEL1) |
| • Bone marrow or stem-cell transplantation |
| • Lung Transplantation |
| • Chemotherapy (alkylating agents) |
| • Radiotherapy |
| • Respiratory infections |
| – Recurrent bronchitis |
| – Aspergillus |
| – *Mycobacterium avium intracellulare* |
| • **Autoimmune diseases** |
| – Systemic sclerosis |
| – Rheumatoid arthritis |
| – Psoriasis |
| – Ankylosing spondylitis |
| – Ulcerative colitis |
| – Primary Sjögren syndrome |
| – Poly/dermatomyositis |
| • **Hypersensitivity pneumonitis** |
| • **Occupational dust exposure** |
| – Asbestos |
| – Aluminium |

Portillo K et al, Pleuroparenchymal Fibroelastosis: Is it Also an Idiopathic Entity?1; Watanabe K, Pleuroparenchymal Fibroelastosis: Its Clinical Characteristics[9]; Newton CH et al, Pleuroparenchymal Fibroelastosis Associated with TERT Mutations[14]; Newton CA et al, Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive1[6]

porting a definitive diagnosis of PPFE in patients with RA found by the authors[4]. In a recent study of patients with CTD associated with ILD[17], radiologic PPFE lesions were detected in 19% of patients. From these, 43% had SSc, 29% primary Sjogren syndrome, 11% poly/dermatomyositis, 6% RA and 28% overlapping CTDs. In this study the presence of PPFE lesions was identified as an independent risk factor of poor prognosis[17]. An idiopathic form of PPFE has also been reported and has been included in the latest international classification of idiopathic interstitial pneumonias[1,3,5,6,8,9].

An aetiological theory developed by Thusen in 2013[6] proposes that fibrosis with a PPFE pattern may be the common final pathway shared by any form of lung injury leading to an intra-alveolar fibrinous response.

Although PPFE may occur isolated within the lung, there is a high prevalence of coexistent ILD in patients with PPFE of the upper lobes[8,12,15,17] reaching 75% in one series[12], mainly UIP pattern[8,9,20]. In these cases PPFE may either represent or not the predominant abnormality (on HRCT and/or histology). It is essential to determine the predominant abnormality because it may have different therapeutic and prognostic implications. In the presented cases, both patients with PPFE had a coexisting ILD: NSIP in the first case and LIP in the second case.

No treatment has yet been shown to modify the natural course of PPFE[1,7] and management of this disease is based on limited evidence, mainly from the experience of specialized centres[7,18]. A treatment approach proposed by Brompton's interstitial lung disease unit[18] suggests introduction of a macrolide (azithromycin or clarithromycin 3 times/week) in patients presenting with recurrent infections due to its immunomodulatory effects. Patients with progressive or severe disease should be given corticosteroids at a moderate or low dose, with or without hydroxychloroquine[18]. If there is no improvement, immunosuppressants such as azathioprine or mycophenolate mofetil may be considered. Nevertheless, immunosuppressive drugs should be started with caution, since previous studies showed worse outcomes in idiopathic disease with intense immunosuppression[18]. In advanced stages lung transplantation should be considered in suitable patients[1,7,8,9,18,19].

Since parenchymal fibrosis is an important histological feature of PPFE, some case reports evaluated the potential efficacy of antifibrotic agents in preventing lung function decline, with promising results[15,19,20].

The clinical course of PPFE vary greatly in the literature: some describe a slowly progressive disease over 10-20 years after presentation, and it may take years before patients become symptomatic; while others describe a rapid clinical deterioration despite treatment[1,8,12]. Once PPFE becomes symptomatic, patients may remain stable for a long period of time or progress inexorably to hypercapnic respiratory failure, with a 40–66% mortality rate in a few years with or without

an identifiable abrupt exacerbation[6,8,10].

In conclusion, the authors present two cases of CTD-associated PPFE to raise awareness of this entity among clinicians. Imaging features of PPFE are very suggestive, if not pathognomonic[10] and a clinical diagnosis is possible with multidisciplinary diagnostic meetings. Histopathological confirmation is often unnecessary and is reserved for cases of ILD with uncertain diagnosis or suspicion of underlying neoplasm. Despite only recently recognized, case reports with radiological and histological features of PPFE in patients with CTD from as early as the 1960s[12]. This entity is well-documented among patients with CTD, occurring alone or in association with other ILDs and the evidence suggests that the presence of PPFE harbours a worse prognosis (the words "in these patients" were eliminated). It may also require a specific treatment and affect the choice of immunosuppressive therapy in a particular patient since one needs to be cautious with immunosuppression in PPFE.

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