The pathogenesis and pathology of idiopathic pleuroparenchymal fibroelastosis

Authors: Yoshiaki Kinoshita, Hiroshi Ishii, Kazuki Nabeshima and Kentato Watanabe

DOI: 10.14670/HH-18-289
Article type: REVIEW
Accepted: 2020-12-14
Epub ahead of print: 2020-12-14

This article has been peer reviewed and published immediately upon acceptance.
Articles in “Histology and Histopathology” are listed in Pubmed.
Pre-print author’s version
Reviews

The pathogenesis and pathology of idiopathic pleuroparenchymal fibroelastosis

Yoshiaki Kinoshita¹, Hiroshi Ishii¹, Kazuki Nabeshima², and Kentato Watanabe¹

¹Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, Fukuoka, Japan.

²Department of Pathology, Fukuoka University School of Medicine and Hospital, Fukuoka, Japan

³Department of Respiratory Medicine, Nishi Fukuoka Hospital, Fukuoka, Japan

Correspondence:

Yoshiaki Kinoshita

Department of Respiratory Medicine, Fukuoka University Chikushi Hospital, 1-1-1 Zokumyoin, Chikushino, Fukuoka 818-8502, Japan.

(Phone) +81–92–921–1011; (E–mail) y3kinoshitai@fukuoka-u.ac.jp

Keywords: elastofibrosis, elastic fiber, etiology, diagnostic criteria, histopathology

Short title: Pathogenesis of idiopathic pleuroparenchymal fibroelastosis
Abstract

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare subtype of idiopathic interstitial pneumonias that consists of elastofibrosis involving the lung parenchyma and pleural collagenous fibrosis predominantly located in the upper lobes. IPPFE has various distinct clinical and physiological characteristics, including platythorax and a marked decrease of forced vital capacity with an increased residual volume on a respiratory function test. The concept of IPPFE is now widely recognized and some diagnostic criteria have been proposed. In addition, the accumulation of cases has revealed the pathological features of IPPFE. However, little is known about the pathogenesis or the process of disease formation in IPPFE. This review article will provide a summary of the pathological features and previously reported hypotheses on disease formation in IPPFE, to discuss the potential etiologies and pathogenesis of IPPFE.
Introduction

Idiopathic pleuroparenchymal fibroelastosis (PPFE) is a rare subtype of idiopathic interstitial pneumonia (IIPs) that consists of elastofibrosis involving the lung parenchyma and pleural fibrosis predominantly located in the upper lobes (Amitani et al., 1992; Frankel et al., 2004; Travis et al., 2013). In 1992, Amitani et al. (Amitani et al., 1992) reported 13 cases of slowly progressive pulmonary fibrosis that were nearly confined to the upper lobes as "idiopathic pulmonary upper-lobe fibrosis". The concept of fibrosis has attracted attention because its clinicopathological features were distinctly different from those of any existing IIPs. With that fibrosis in mind, Frankel et al. (Frankel et al., 2004) reported 5 cases of pulmonary fibrosis with upper lobe predominance in 2004. They named the disease “pleuroparenchymal fibroelastosis”, representing the pathological features of increased elastic and collagen fibers in the subpleural area of the lungs with collagenous thickening of the visceral pleura. In 2013, IPPFE was added to the list of IIPs (Travis et al., 2013) as a result of the accumulation of a case series that elucidated the characteristics of IPPFE in considerable detail. Nakatani et al. (Nakatani et al., 2015) reported that IPPFE was found in 5.9 % of IIPs suggesting that the disease was not as rare as initially thought. However, little is known about the pathogenesis or the process of disease formation in IPPFE. This review article will explain the pathological features of
IPPFE and hypotheses regarding the formation of the disease.

Clinical features of IPPFE

The physical characteristics of IPPFE include slender build with progressive weight loss (Fuke et al., 1982; Amitani et al., 1992; Shiota et al., 1999; Morimoto et al., 2011; Watanabe et al., 2012; Nagashima et al., 2013; Suzuki et al., 2018; Kato et al., 2019), platythorax (Amitani et al., 1992; Camus et al., 2014; Harada et al., 2014; Ishii et al., 2018, 2019a; Watanabe et al., 2019), and the deepened suprasternal notch (Chua et al., 2019). Auscultation is normal; however, inspiratory crackles are sometimes audible when complicated by another interstitial lung disease (ILD) in the lower lobes. In particular, platythorax may be an innate characteristic of PPFE patients; however, it advances with the progression of the disease (Harada et al., 2014).

The vast majority of IPPFE patients die of chronic respiratory failure (Suzuki et al., 2020), and the 5-year survival rate of IPPFE patients was reported to be 23.3–58.9% (Enomoto et al., 2017; Ishii et al., 2018; Fujisawa et al., 2019). As reported previously, the clinical course of IPPFE is heterogeneous and the annual decline in forced vital capacity (FVC) follows two patterns: a rapid decline in a short period or an insidious decline in a long period (Yoshida et al., 2016). In patients with IPPFE, the FVC might
decline gradually to a certain point, after which it begins to decline rapidly (Yoshida et al., 2016). Thus, IPPFE patients who show a rapidly declining FVC might simply pass the endpoint of the slow deterioration phase. Meanwhile, there might be a phenotype of rapid deterioration in IPPFE patients. The prognosis of IPPFE patients with interstitial pneumonia in the lower lobes might be poorer than that in patients without interstitial pneumonia (Oda et al., 2014; Enomoto et al., 2017; Khiroya et al., 2017; Ishii et al., 2018; Kato et al., 2019). Usual interstitial pneumonia (UIP) is the most common pattern of ILD, which occurs as a complicating disease in the lower lobes of IPPFE patients (Reddy et al., 2012; Oda et al., 2014; Enomoto et al., 2017). Some studies have reported that coexistent UIP predicts a poor outcome in IPPFE patients (Ishii et al., 2018; Kato et al., 2019; Kono et al., 2019); however, Enomoto et al. (Enomoto et al., 2017) showed that there was no significant difference in the prognosis between IPPFE patients with a UIP pattern and those with other fibrosis. Other possible prognostic factors that have been described include male sex (Khiroya et al., 2017; Suzuki et al., 2018, 2020), a lower FVC (Kono et al., 2019), a higher serum Krebs von Lungren-6 antigen (KL-6) level (Ishii et al., 2018), and a higher gender-age-physiology (GAP) index (Shioya et al., 2018).

Physiologically, patients with IPPFE show a restrictive ventilatory impairment with a marked decrease in FVC, relatively increased residual volume (RV),
and an increased RV/total lung capacity (TLC) ratio (RV/TLC) (Watanabe, 2013; Oda et al., 2014; Watanabe et al., 2015; Yoshida et al., 2016; Enomoto et al., 2017; Hayashi et al., 2017; Ishii et al., 2018; Kato et al., 2019). In particular, an increased RV/TLC ratio is a striking feature that is useful for the diagnosis of IPPFE because the feature is not common in other IIPs, such as idiopathic pulmonary fibrosis (IPF) (Watanabe et al., 2019). An arterial blood gas analysis shows an elevated partial pressure of carbon dioxide (PaCO$_2$) (Amitani et al., 1992; Kusagaya et al., 2012; Oda et al., 2014; Watanabe et al., 2015; Hayashi et al., 2017; Kato et al., 2019; Suzuki et al., 2018, 2020). This may reflect the severely reduced FVC, resulting in alveolar hypoventilation.

The imaging features of IPPFE include subpleural airspace consolidation with traction bronchiectasis in the upper lobes, a bilateral upward shift of hilar structures, volume loss of the upper lobes, and tracheal deviation (Fig. 1) (Amitani et al., 1992; Frankel et al., 2004; Travis et al., 2013; Ishii et al., 2019b; Watanabe et al., 2019). However, PPFE lesions are not necessarily confined to the upper lobes and sometimes progress to the lower lobes in the advanced stages of the disease (Watanabe et al., 2012; Rosenbaum et al., 2015; Yoshida et al., 2016). Yoshida et al. (Yoshida et al., 2016) previously showed that upper and lower lung fields were equally involved in one-third of patients with pulmonary fibrosis presenting with histologically PPFE. Meanwhile,
patients with PPFE lesions have sometimes been diagnosed with unclassifiable fibrosis or other interstitial pneumonia, complicated by other pulmonary fibrosis in the lower lobes. Yamauchi et al. (Yamauchi et al., 2020) reported a case of ILD in which the patient was diagnosed with IPPFE in the early stage, but then diagnosed with unclassifiable fibrosis in the advanced stage because the lower lobes were extensively occupied by non-PPFE or undiagnosable fibrosis. It is controversial whether a case in which the predominant site of fibrosis changes from the upper to the lower lobes over time should be diagnosed as PPFE or as unclassifiable interstitial pneumonia. However, the upper lobe predominance of fibrosis is essential for the diagnosis of IPPFE (Amitani et al., 1992; Frankel et al., 2004; Reddy et al., 2012; Travis et al., 2013; Enomoto et al., 2017; Watanabe et al., 2019).

**Diagnostic criteria for IPPFE**

The accumulation of cases uncovered the clinical features of IPPFE and led to the proposal of the diagnostic criteria. In 2012, Reddy et al. (Reddy et al., 2012) described the characteristics of PPFE as follows: upper lobe pleural thickening with associated subpleural fibrosis on chest computed tomography (CT) that is pathologically correlated with pleural fibrosis with subjacent intra-alveolar fibrosis accompanied by alveolar septal
elastosis. In 2017, Enomoto et al. (Enomoto et al., 2017) proposed the following diagnostic criteria for IPPFE: 1) a radiologic PPFE pattern consisting of bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or absent involvement of the lower lobes; 2) radiologic confirmation of disease progression; and 3) the exclusion of other lung diseases with identifiable etiologies. These criteria are significant in that the disease progression on chest imaging is included, and a histological diagnosis is not required. Suzuki et al. (Suzuki et al., 2020) recently showed that there was no difference in the clinical characteristics of pathologically diagnosed IPPFE and clinically diagnosed IPPFE. PPFE is occasionally complicated by refractory pneumothorax (Amitani et al., 1992; Azoulay et al., 1999; Shiota et al., 1999; Frankel et al., 2004; Becker et al., 2008; Reddy et al., 2012; Watanabe, 2013; Enomoto et al., 2017). There might be no clinical significance in performing a tissue biopsy for the diagnosis of patients at risk of pneumothorax.

In 2019, Watanabe et al. (Watanabe et al., 2019) proposed comprehensive diagnostic criteria for IPPFE with and without surgical lung biopsy (SLB). They classified suspected IPPFE patients into four categories: definite IPPFE with histological confirmation, radiologically and physiologically probable IPPFE, radiologically probable IPPFE, and radiologically possible IPPFE. The criteria of definite IPPFE, which requires
a histological diagnosis, are almost identical to the criteria described by Reddy et al. (Reddy et al., 2012). The diagnosis of IPPFE without SLB is classified based on the confidence of the diagnosis as follows: 1) “radiologically possible IPPFE”, consisting of subpleural airspace consolidation with traction bronchiectasis in the upper lobes; 2) “radiologically probable IPPFE”, consisting of i) respiratory symptoms, ii) the component of radiologically possible IPPFE and bilateral upward shift of the hilar structures and/or volume loss in the upper lobes, and iii) the exclusion of other lung diseases with identifiable etiologies; and 3) “radiologically and physiologically probable IPPFE”, consisting of the component of radiologically probable IPPFE and a physiologic component of i) percentage of the predicted values of RV/TLC (RV/TLC %pred.) > 115% or ii) body mass index < 20 kg/m² and RV/TLC %pred. > 80%. The criterion is significant because physiological parameters that are characteristic of PPFE are included in the criteria. The physiological criteria are based on the data from a review of 52 PPFE patients in Japan, which showed that the RV/TLC ratio was negatively correlated with BMI and FVC %pred., and positively correlated with GAP score (i.e., the RV/TLC ratio was strongly correlated with the disease severity of PPFE). Further studies are required to validate these diagnostic criteria.
Pathological features

The core pathological feature of IPPFE is subpleural fibroelastosis consisting of a band-like accumulation of elastic fibers and intra-alveolar fibrosis with septal elastosis (IAFE) (Fig. 2A, 2B) (Amitani et al., 1992; Kawabata and Matsuoka, 2003; Frankel et al., 2004; Reddy et al., 2012; Kobashi et al., 2013; Travis et al., 2013). Fibrous thickening of the visceral pleura (Fig. 2C) is not always recognized in pathological specimens because the presence of pleural fibrosis depends on the site from which the specimens are taken (Reddy et al., 2012; Watanabe et al., 2012). There is an abrupt transition between the affected lung and the non-affected lung (Fig. 2A), and fibroblastic foci are recognized at the boundary between them (Fig. 2D) (Amitani et al., 1992; Kawabata and Matsuoka, 2003; Frankel et al., 2004; Reddy et al., 2012; Kobashi et al., 2013; Travis et al., 2013). In the areas where the formation of an IAFE lesion is in progress, the alveolar walls are thickened by an increase in elastic fibers (Fig. 2D). However, the density of elastic fibers in the subpleural area is higher than that in the transition zone between the affected lung and non-affected lung (Fig. 2A) (Kawabata and Matsuoka, 2003; Morimoto et al., 2011; Kobashi et al., 2013). In the PPFE lesions just beneath the pleura, collagen fibers infrequently intervene between elastic fibers, and the elastic fibers are so dense that preexisting alveolar structures cannot be identified (Fig. 2C) (Kawabata and Matsuoka,
2003; Kobashi et al., 2013; Kinoshita et al., 2020a). However, even in these areas, the alveolar epithelial cells can be identified using appropriate immunostaining, indicating that the accumulation of elastic fibers is formed by alveolar collapse (Fig. 3) (Kawabata and Matsuoka, 2003; Kinoshita et al., 2018, 2020a; Watanabe et al., 2012, 2019).

Cystic lesions appear in the advanced stage of IPPFE (Kawabata and Matsuoka, 2003; Kobashi et al., 2013; Watanabe, 2013; Tanaka and Ishida, 2018). Cystic lesions may result from traction bronchiectasis (Fig. 4A and 4B) (Kawabata and Matsuoka, 2003; Kobashi et al., 2013; Watanabe, 2013; Tanaka and Ishida, 2018) or dissection of the fibroelastic interstitium (Kawabata and Matsuoka, 2003; Tanaka and Ishida, 2018), which could cause pneumothorax and allow *Aspergillus* infection (Ishii et al., 2019a). Cystic spaces caused by dissection of the fibroelastic interstitium may be filled with organized materials or remain cystic in PPFE (Kawabata and Matsuoka, 2003) (Fig. 4A and 4C). However, alveolar architectures are kept without destruction until the advanced stages of PPFE.

IPPFE patients often have coexisting non-PPFE fibrosis in the lower lobes. Several histological patterns of fibrosis in the lower lobes have been reported in IPPFE patients. The most common pattern is UIP, which is reported to be associated with 35–50% of case of PPFE (Becker et al., 2008; Reddy et al., 2012; Nakatani et al., 2015;
Enomoto et al., 2017; Kinoshita et al., 2017; Ishii et al., 2018). Other patterns of fibrosis include nonspecific interstitial pneumonia (NSIP) and unclassifiable fibrosis (Reddy et al., 2012; Nakatani et al., 2015; Enomoto et al., 2017; Kinoshita et al., 2017; Kato et al., 2019). The lower-lobe fibrosis progresses in the advanced stages of PPFE (Watanabe, 2013; Ishii et al., 2018).

Granulomas are present in 15–35% of IPPFE patients (Fig. 5) (Reddy et al., 2012; von der Thüsen, 2013; Cheng and Chuah, 2016; Khiroya et al., 2017; Oyama et al., 2017; Bargagli et al., 2018; Tanaka and Ishida, 2018; Chua et al., 2019). Granulomas typically result from a biological reaction to infectious or noninfectious antigens (Grunewald et al., 2015). There are several reports of Aspergillus or nontuberculous mycobacterium infection in patients with PPFE (Fuke et al., 1982; Kawabata and Matsuoka, 2003; Frankel et al., 2004; Piciucchi et al., 2011; Reddy et al., 2012; Yoshida et al., 2016; Khiroya et al., 2017). Thus, it has been suggested that a biological reaction to infectious or noninfectious antigens in a predisposed individual may be associated with granuloma formation in IPPFE (Reddy et al., 2012; Khiroya et al., 2017). It is unknown whether fibroelastic lesions in IPPFE are induced by these infections or whether IPPFE facilitates the development of these infections. Yoshida et al. (Yoshida et al., 2016) showed a case of PPFE in which Mycobacterium avium was isolated from
sputum during the early stages, and in which the infection progressed along with the progression of PPFE, indicating that these infections may be pathogenetic to PPFE, rather than simple comorbidities (Yoshida et al., 2016). Khiroya et al. (Khiroya et al., 2017) showed that the presence of granulomas was significantly associated with a better prognosis of PPFE. They hypothesized that, in some cases, PPFE might represent a progressive fibrosing immune-mediated response to infection or an inhaled antigen, and the presence of granulomas may be a marker of the reaction.

Several reports have shown that lymphatic proliferation is increased in fibroelastic lesions in IPPFE patients (Fig. 6) (Piciucchi et al., 2011; Sato et al., 2014; Cha et al., 2018; Kinoshita et al., 2018; von der Thüsen et al., 2018; Futatsuya et al., 2020). We have shown that the increase in the density and number of lymphatic vessels is a supportive histological characteristic that enables the differentiation of IPPFE from IPF and the pulmonary apical cap (Kinoshita et al., 2018). Interestingly, among IPPFE patients, the extent of the increase in lymphatic vessel density was correlated with a worsening of the physical and physiological parameters of IPPFE, such as the ratio of the anteroposterior diameter to the transverse diameter of the thoracic cage on CT and RV/TLC on a respiratory function test (Kinoshita et al., 2018). The lymphatic vessel density might be increased with the progression of PPFE lesions because the thoracic
cage becomes flattened and RV/TLC increases along with the progression of PPFE lesions (Harada et al., 2014; Ishii et al., 2018).

Pulmonary vascular involvement is a common histological feature in IPPFE, as it is in other forms of ILD (Reddy et al., 2012; Khiroya et al., 2017; Montero et al., 2017; Tanaka and Ishida, 2018; Kinoshita et al., 2020b). Both PPFE and IPF are occasionally complicated by pulmonary hypertension (Boerner et al., 2017; Khiroya et al., 2017; Kinoshita et al., 2020b). Khiroya et al. (Khiroya et al., 2017) reported that some remodeling of pulmonary vessels was found in 91% of PPFE patients. We have shown the histological changes of the pulmonary arteries in IPPFE patients, including thickening of the intima, media and adventitia, with subsequent luminal narrowing, medial elastotic thickening and adventitial collagenous thickening. Among them, medial elastotic thickening and adventitial collagenous thickening are unique in IPPFE patients, but uncommon in IPF patients (Fig. 7) (Kinoshita et al., 2020b). These changes could be histological manifestations in PPFE, as increased collagen and elastic fibers are in the alveolar lumens and septa. Other pathological findings seen in IPPFE patients include a varying amount of lymphocytic infiltration (Frankel et al., 2004; Reddy et al., 2012; von der Thüsen, 2013; Cheng and Chuah, 2016; Khiroya et al., 2017; Montero et al., 2017; Tanaka and Ishida, 2018), intra-alveolar fibroelastosis distant from the pleura (Reddy et
al., 2012; von der Thüsen, 2013), and airway-centered pleuroparenchymal fibroelastosis (Pradere et al., 2016; Bargagli et al., 2018; Kronborg-White et al., 2018; Tsubosaka et al., 2019; Minomo et al., 2020). The pathological features of IPPFE are summarized in Table 1.

**Hypotheses related to the pathogenesis and progression of IPPFE**

Various hypotheses have been proposed in relation to disease progression. Some investigators have hypothesized that diffuse alveolar damage (DAD) or organizing pneumonia occasionally precedes the formation of PPFE, and that PPFE is a late appearance of these conditions (von der Thüsen et al., 2011, 2018; Ofek et al., 2012; Kinoshita et al., 2019). Ofek et al. (Ofek et al., 2012) first described PPFE as a pathological phenotype of restrictive allograft syndrome following lung transplantation. They showed that PPFE was often associated with DAD, and a temporal sequence of DAD and PPFE was sometimes found in histological specimens of PPFE. Thüsen et al. (von der Thüsen et al., 2018) showed that half of the patients with chronic lung allograft dysfunction had histological PPFE lesions, and fibroelastotic lesions were frequently accompanied by fibrinous alveolar exudates. They hypothesized that IAFE in PPFE was induced by the intraluminal accumulation of fibrinoid substances due to acute lung injury.
and delayed excretion into the alveolar septum (von der Thüsen et al., 2018). This hypothesis was partly supported by molecular and morphological analyses of lung transplantation- or stem cell transplantation-related PPFE, which was conducted by Jonigk et al. (Jonigk et al., 2017). Intra-alveolar fibrosis could be attributed to the imbalance between the intraalveolar fibrin deposition and clearance (von der Thüsen, 2013), which may be caused by environmental factors, predisposing genetic factors, or a combination of these factors.

Few hypotheses in relation to the development of IPPFE have been proposed because of the rarity of the disease. We previously investigated three patients with IPPFE in which histological examinations were performed twice at intervals (Hirota et al., 2015). The histological diagnosis based on the first biopsies was acute lung injury or cellular interstitial pneumonia. In the second lung biopsy or autopsy, a histological diagnosis of PPFE was confirmed. The temporal changes in the histology suggest that some inflammatory or lung injury processes might be the first step in the occurrence and progression of PPFE, and that this is later replaced by densely packed aggregates of elastic fibers as a histological endpoint of PPFE (Hirota et al., 2015). Meanwhile, we recently demonstrated another possibility in relation to the development of PPFE. We classified subpleural fibroelastosis in IPPFE as three patterns: zonal elastosis (dense aggregates of
elastic fibers associated with alveolar collapse), intra-alveolar fibrosis with septal elastosis, and a two-layered pattern of these conditions (Fig. 8) (Kinoshita et al., 2020a).

In IPPFE patients, fibroelastosis appears to progress inward from the pleural side, because fibroblastic foci are present at the leading edge of intra-alveolar fibrosis with septal elastosis (Fig. 2D) (Kawabata and Matsuoka, 2003; Kobashi et al., 2013; Kinoshita et al., 2020a). We measured the thickness of each pattern of fibroelastosis using 10 patients with IPPFE to estimate the occurrence and development of IPPFE (Kinoshita et al., 2020a).

When the thickness of the subpleural fibroelastosis was <1 mm, the dominant pattern of fibroelastosis was zonal elastosis; meanwhile, when the thickness of the subpleural fibroelastosis was ≥1 mm, the dominant pattern of fibroelastosis was a two-layered pattern. Based on the thicker two-layered pattern of subpleural fibroelastosis and fibroblastic foci at the inner edge of the fibrosis, intra-alveolar collagenous fibrosis with septal elastosis could arise and grow adjacent to the pre-existing zonal elastosis in IPPFE patients (Kinoshita et al., 2020a).

The upper-lobe predominance of fibroelastosis is a fundamental characteristic of IPPFE (Amitani et al., 1992; Frankel et al., 2004; Travis et al., 2013).

Two hypotheses may explain the upper-lobe predominance of fibroelastosis in IPPFE patients. One hypothesis is that poor lymphatic drainage at the lung apex is responsible
for the disease formation of IPPFE (Kinoshita et al., 2018). The lymphatic vasculature plays a key role in tissue homeostasis of the lung, but reduces the function at the lung apex (El-Chemaly et al., 2009). The excess protein-rich fluid extravasated from the blood vessels returns to the blood circulation via the pleural or peri-bronchiolar lymphatics (Okada et al., 1979; El-Chemaly et al., 2009). We have previously shown that lymphatic proliferation is increased in lesions of intra-alveolar collagenosis, but decreased in the subpleural zonal elastotic lesions in patients with IPPFE (Kinoshita et al., 2018). The innate lymphatic drainage of the lung via the pleural lymphatics seems to be inhibited at the subpleural elastotic lesions with collapsed alveoli in IPPFE patients (Kinoshita et al., 2018, 2020a). Increased lymphatic proliferation in the areas of intra-alveolar collagenosis could be a compensatory mechanism against decreased drainage via the pleural lymphatics.

The predilection of fibroelastosis for the upper lobes could also be explained by ischemia at the lung apex (Pakhale et al., 2005; von der Thüsen, 2013; van der Oord et al., 2017). Van der Oord et al. (van der Oord et al., 2017) showed an autopsied case of IPPFE with prominent thromboembolic arteriopathy. They described that a higher number of thrombi were found in the upper lobes in comparison to the lower lobes. Meanwhile, ischemia has also been inferred as a possible etiology of pulmonary apical
cap, which presents an indistinguishable pathology from PPFE (Yousem, 2001; von der Thüsen, 2013; Lagstein, 2015). The clinical difference between PPFE and pulmonary apical cap is that PPFE is progressive with respiratory symptoms, whereas pulmonary apical cap is non-morbid and non-progressive in general population (Lagstein, 2015; Enomoto et al., 2017). Yousem et al. (Yousem, 2001) reported that thrombosis of pulmonary arteries and arterioles were identified in 11 of 13 (84.6%) cases of pulmonary apical cap. If the pathology and etiology are the same in both entities, it is possible that we see patients with a single disease but with different degrees of severity.

A small number of PPFE cases have been reported to occur in families (Azoulay et al., 1999; Kobayashi et al., 1999; Shiota et al., 1999; Frankel et al., 2004), and a genetic predisposition may be partly responsible for PPFE (Newton et al., 2016, 2017; Nunes et al., 2017). Newton et al. (Newton et al., 2016) found that telomere-related gene mutations were detected in patients with ILD. In their cohort, 8 of 77 ILD patients (10.4%) harboring telomere-related gene mutations were diagnosed with PPFE. Interestingly, some PPFE patients with telomere-related gene mutations had a familial background of ILD or suffered from severe hematological conditions, including leukopenia, thrombocytopenia, and aplastic anemia/myelodysplastic syndrome. Some investigators proposed other etiopathological hypotheses for PPFE. Enomoto et al.
(Enomoto et al., 2018) showed that podoplanin-positive fibroblasts were seen in PPFE, but not in UIP. They hypothesized that the podoplanin-positive myofibroblasts could be a pathological hallmark of PPFE. They speculated that mesothelial-to-mesenchymal transition may be a pathogenic mechanism of PPFE because podoplanin-positive mesothelial cells are identified as an origin of myofibroblasts (Enomoto et al., 2018). Oo et al. (Oo et al., 2019) showed the denudation of alveolar and bronchiolar lining epithelia scattered at the transition zone between the affected lung and non-affected lung from a patient with hematopoietic stem cell transplantation-related PPFE. They hypothesized that graft T cells attack epithelial cells and create erosion followed by a healing scar as fibrosis to develop IAFE. Various mechanisms might be associated with the development of histological PPFE.

**Future perspectives**

The concept of IPPFE is now widely recognized and some diagnostic criteria have been proposed. There will be more chances for us to diagnose IPPFE than ever before. IPPFE patients with a rapid progression have a poorer prognosis in comparison to IPF patients (Hayashi et al., 2017; Shioya et al., 2018; Fujisawa et al., 2019; Suzuki et al., 2020). However, we have no established strategies to prevent the disease progression of IPPFE.
Currently, anti-fibrotic agents have been shown to be effective for reducing the annual decline in FVC in patients with IPF (King et al., 2014; Richeldi et al., 2014), scleroderma-associated ILD (Distler et al., 2019), and progressive fibrosing ILD (Flaherty et al., 2019). However, the usefulness of these drugs in the treatment of IPPFE is questionable because the fundamental pathogenesis of IPPFE is a dominant increase in elastic fibers rather than collagen fibers. Although there are some common molecular pathways between collagen fiber formation and elastic fiber formation, it will also be necessary to explore specific therapeutic targets for elastogenesis in IPPFE patients. Recent evidence suggests that several molecules are involved in elastogenesis (Noda et al., 2013). We examined the protein levels of these molecules in lung tissues and serum samples from IPPFE patients. Latent transforming growth factor beta binding protein 4 (LTBP-4) was highly expressed in the lung tissues and serum of IPPFE patients in comparison to healthy subjects (Kinoshita et al., 2020c). In addition, we found that high serum LTBP-4 levels are associated with a poorer prognosis in IPPFE patients (Kinoshita et al., 2020c). In the future, it will be necessary to search for therapeutic targets for the upregulated elastogenesis in IPPFE patients.
Acknowledgement

**Declarations of interest:** none

**Funding information:** This work was supported in part by Grants-in-Aid for Scientific Research (#19K08638) from the Japanese Society for the Promotion of Science.

**Notation of prior abstract publication/presentation**

This research has not been presented or published elsewhere.
References


Res. Biol. 7, 197-203.
126, 2007-2013.


Harada T., Yoshida Y., Kitasato Y., Tsuruta N., Wakamatsu K., Hirota T., Tanaka M.,


Ishii H., Kinoshita Y., Kushima H., Ogura T. and Watanabe K. (2019b). The upward shift


King T.E., Bradford W.Z., Castro-Bernardini S., Fagan E.A., Glaspole I., Glassberg M.K.,


Kronborg-White S., Ravaglia C., Dubini A., Piciucchi S., Tomassetti S., Bendstrup E., and Poletti V. (2018). Cryobiopsies are diagnostic in pleuroparenchymal and airway-


Nagashima O., Matsuno K., Tominaga S. and Takahashi K. (2013). Esophageal
diverticulum with idiopathic pulmonary upper lobe fibrosis. Intern. Med. 52, 159.


Shioya M., Otsuka M., Yamada G., Umeda Y., Ikeda K., Nishikiori H., Kuronuma K.,


pleuroparenchymal fibroelastosis. Respir. Investig. 54, 162-169.

### Tables

**Table 1. The histological features of IPPFE**

<table>
<thead>
<tr>
<th>Key histological findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural distribution of elastofibrosis</td>
<td></td>
</tr>
<tr>
<td>Dense accumulation of elastic fibers with collapsed alveoli</td>
<td></td>
</tr>
<tr>
<td>Intra-alveolar collagenous fibrosis with septal elastosis</td>
<td></td>
</tr>
<tr>
<td>Collagenous thickening of visceral pleura</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial elastofibrosis</td>
<td></td>
</tr>
<tr>
<td>Medial elastotic thickening</td>
<td></td>
</tr>
<tr>
<td>Adventitial collagenous thickening</td>
<td></td>
</tr>
<tr>
<td>Increased lymphatic proliferation in the fibroelastotic areas</td>
<td></td>
</tr>
<tr>
<td>Intra-alveolar fibrosis distant from the subpleural fibroelastosis</td>
<td></td>
</tr>
<tr>
<td>Airway-centered elastofibrosis</td>
<td></td>
</tr>
<tr>
<td>Cystic lesions in the advanced stage</td>
<td></td>
</tr>
<tr>
<td>Fibroblastic foci in the leading edge of the fibrosis</td>
<td></td>
</tr>
<tr>
<td>Lower lobe non-PPFE fibrosis (UIP, NSIP or unclassifiable)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less common findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Granuloma</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic inflammation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pertinent negative finding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant non-PPFE fibrosis in the lower lobes</td>
<td></td>
</tr>
</tbody>
</table>

NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia
**Figure legends**

Fig. 1

A 64-year-old man with IPPFE showing subpleural airspace consolidation with traction bronchiectasis in the upper lobes, a bilateral upward shift of the hilar structures, volume loss of the upper lobes, and a flattened thoracic cage.

Fig. 2

An Elastica van Gieson stained section (A-D) from a patient with IPPFE showing subpleural fibroelastosis consisting of a band-like accumulation of elastic fibers (A) and intra-alveolar fibrosis with septal elastosis (B [inset of A]), and the collagenous thickening of the visceral pleura (A and C [inset of A]). In areas where intra-alveolar fibrosis is in progress, some fibroblastic foci (arrows) are recognized and the alveolar walls have already been thickened by the increase of elastic fibers (D [inset of A]).

Fig. 3

An Elastica van Gieson stained section (A) and a corresponding CK AE1/AE3-immunostained section (B) from a patient with IPPFE showing some lining of the alveolar epithelium in a dense elastotic lesion.
Fig. 4

An Elastica van Gieson stained section (A-C) from a patient with IPPFE. A and B [inset of A] show traction bronchiectasis. Some cystic spaces are occupied by mature collagen (A and C [inset of A]).

Fig. 5

A hematoxylin and eosin stained section from a patient with IPPFE showing multinucleated giant cells with cholesterol clefts.

Fig. 6

A double-stained section with Elastica van Gieson staining and podoplanin immunostaining from a patient with IPPFE showing that dilated lymphatic vessels were frequently observed in the area of intra-alveolar collagenous fibrosis.

Fig. 7

Elastica van Gieson-stained sections of pulmonary arteries from a patient with IPF (A) and IPPFE (B-C). (B) shows a pulmonary artery with severe medial elastosis and
adventitial collagenous thickening, and (C) shows a pulmonary artery with severe adventitial collagenous thickening.

Fig. 8

An Elastica van Gieson-stained section from a patient with IPPFE showing a two-layered pattern of fibroelastosis involving zonal elastosis (arrows) and intra-alveolar fibrosis with septal elastosis.