Pleuroparenchymal Fibroelastosis: Its Pathological Characteristics

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Abstract: Pleuroparenchymal fibroelastosis (PPFE) is a distinct pattern of pulmonary fibrosis which often runs a rapidly progressive course with a poor prognosis, and it is likely to be introduced as a separate entity in the new classification scheme of idiopathic interstitial pneumonias. It is characterised by pleural fibrosis and subpleural fibroelastosis, with an upper lobe predominance. In addition to cases following lung and bone marrow transplantation, familial and idiopathic cases have been described. The literature on PPFE is fragmented, however, and primarily consists of small case series, lacking a uniform methodology of clinical, radiological and histopathological description. In this review article, most previously published reports of PPFE in the English-language literature will be discussed and the salient clinical and histopathological data analysed to arrive at a working definition of PPFE in daily histopathological practice, and to aid the generation of a unifying hypothesis regarding its potential aetiologies and pathogenesis.

Keywords: Pleuroparenchymal fibroelastosis, pathological characteristics, histopathology.

INTRODUCTION

Amitani is widely credited to be the first to have described a pattern of idiopathic upper lobe fibrosis in the Japanese literature in 1992 [1], and subsequently this pattern of pulmonary fibrosis has frequently been referred to as 'Amitani disease'. However, in their case series in 2004, Frankel *et al.* [2] from the Interstitial Lung Disease Program at the National Jewish Medical and Research Center in Denver defined a similar pulmonary fibrotic syndrome as a 'unique idiopathic pleuroparenchymal lung disease that is characterized by upper lobe radiographic predominance and pathologic findings that do not fit with any of the currently defined interstitial pneumonias', and they believed this to be akin to a pattern of fibrosis seen in earlier case reports in the English and non-English (esp. Japanese) literature, the first of which appeared as early as the 1960s [3-8]. Thus, in a less eponymous fashion, the disease has also become known as 'idiopathic upper lobe fibrosis' (IPUF; esp. in the the Japanese literature [9-13]), or '(idiopathic) pleuroparen-chymal fibroelastosis' ((I)PPFE), which is currently the preferred term in the English-language literature, most likely due to its concise yet highly descriptive nature.

Since the early reports, a series of corroborative reports have been published, which have sought to uncover possible causative factors, and have established this rare pattern of fibrosis as a separate entity with definable, reproducible radiological and histopathological criteria that allow its recognition as a disease which is distinct from the other currently recognised patterns of idiopathic interstitial pneumonias [14]. While several possible associations have become apparent, including previous lung and bone marrow transplantation as well as chemotherapy, the aetiology of this disease remains largely enigmatic. In this paper, we have

therefore systematically reviewed the histopathology and the clinical characteristics of known cases of PPFE in the English-language literature (69 in total), to aid in the generation of a unifying hypothesis regarding its pathogenesis and underlying mechanisms, and to provide a framework for the classification and specific diagnosis of this disease within the spectrum of known (idiopathic) interstitial pneumonias.

THE CLINICAL AND HISTOLOGICAL SPECTRUM

The initial case series of PPFE in the English literature by Frankel *et al.* [2] included five cases (4 female, 1 male, aged 32-65 years), 2 of whom had undergone CMF (cyclo-phosphamide, methotrexate, fluorouracil) chemotherapy, and all non-smokers, who presented with a range of symptoms, most consistent of which were dyspnoea on exertion and cough. For 4 patients, high-resolution CT (HRCT) data were available, which showed intense pleural thickening with evidence of fibrosis, primarily affecting the upper lobes, sometimes accompanied by centrilobular nodularity. Histo-logically, this corresponded to marked fibrosis of the pleura and the subpleural parenchyma, with a homogeneous mix-ture of elastic tissue and dense collagen. There was a relatively abrupt border between the areas of fibrosis and the surrounding unaffected parenchyma with rare fibroblastic foci observed at the interface, accompanied by a varying amount of lymphocytic inflammation.

More recently, Becker *et al.* presented two cases (both female, 51 and 59 years old) of idiopathic biapical, pleural and subpleural fibrotic change, characterised histologically by predominantly elastic fibrosis of the visceral pleura with extension into the adjacent alveolar walls [15]. Again, the demarcation to normal parenchyma was sharp, with a few questionable fibroblastic foci at the interface, and some mild interstitial lymphocytic infiltrates. One of these women had undergone extensive chemotherapy (fludarabine, CHOP, rituximab and ibritumomab tiuxetan) in addition to autologous stem cell transplantation for follicular centre cell lymphoma.

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A further 2 cases (male, 28 and 60 years old) were added to the literature by Piciucchi *et al.* [16], with subpleural fibrosis of the upper lobes reminiscent of PPFE on both HRCT and histology. They also noted a sharp demarcation with the surrounding parenchyma, with some fibroblastic foci being present at the interface in both cases.

More recently, our group published a study of 12 patients, all of whom had pleuroparenchymal thickening with subjacent fibrosis on CT imaging [17]. This was a selection of cases which had been identified as 'definite' or 'consistent with' PPFE by both histopathology and radiology, taken from a series of 30 patients with lung biopsy material in the archives of the Royal Brompton and Harefield NHS Foundation Trust (London, UK) which had been characterised by the terms 'intra-alveolar fibrosis', 'pleuroparenchymal' and 'fibroelastosis' in the original histopathology report. These patients had no significant drug history (except 1 case of immunosuppression following a renal transplant for ANCA-positive glomerunephritis), history of radiotherapy or bone marrow transplantation. Interestingly, 2 patients had first-degree relatives with interstitial lung disease (1 case of usual interstitial pneumonia (UIP) and 1 of non-specific interstitial pneumonia (NSIP)), and 4 of seven patients who reported recurrent infections had auto-antibodies in their serum. 5/12 had interstitial fibrosis in regions remote from the pleuroparenchymal changes, on HRCT being most reminiscent of NSIP / possible UIP (3), NSIP (1) and unclassifiable interstitial pneumonia (1) in the middle en lower zones. Histologically, all patients had intra-alveolar fibrosis with septal elastosis (IAFE), with 11 out of 12 also showing fibrosis of the pleura. Other upper lobe changes included perilobular (6/12) and bronchocentric (10/12) IAFE. Also of note was partial stenosis of the pulmonary vasculature in 8/12 patients in the fibrotic areas.

Kusagaya *et al.* [18] have identified a further 5 archival cases of histologically proven PPFE. In line with previous studies, these patients showed progressive functional deterioration even in a relatively short time of follow-up. These patients were aged 67 to 74, and included 4 men and 1 woman. The histology showed a markedly thickened visceral pleura and prominent subpleural fibrosis characterised by both elastic tissue and dense collagen, with an abrupt transition to adjacent normal lung parenchyma. They observed rare fibroblastic foci and a variable amount of inflammation, consisting mainly of small aggregates of lymphocytes. There were no known associated disorders or presumed causes in this group and the cases were therefore classified as idiopathic PPFE, or 'IPPFE'.

Watanabe *et al*. [19] described a series of 9 patients (aged 43-81 years, 4 males and 5 females) with a pattern of upper lobe fibrosis on HRCT. In all patients, this corresponded to subpleural fibroelastosis on histology with a preserved alveolar structure and intra-alveolar collagen deposition, which in most patients was also accompanied by pleural thickening and fibrosis to a varying degree. Interestingly, while these findings were upper-lobe predominant in all patients, two of the cases developed bilateral reticular or honeycomb opacities during follow-up. The patients had a poor prognosis, with two-thirds having died during follow-up, 1.8 to 12.2 years after initial presentation. The authors defined this pattern as IPUF, but recognised it as part of a spectrum of upper-lobe subpleural fibrosis that encompasses both PPFE and IPUF.

In addition, there have been reports of changes reminiscent of PPFE in pulmonary disease following both lung and bone marrow transplantation. Thus, Konen *et al.* [20] and Pakhale *et al.* [21] have reported upper lobe fibrosis on CT imaging in 7 and 13 lung transplant recipients, respectively, which was corroborated in four patients by open lung biopsy in the latter series. The histological findings were of variably dense interstitial fibrosis, sometimes accompanied by obliterative bronchiolitis, organising pneumonia, and aspiration, although the typical pattern of fibroelastosis was not mentioned in their series. More recently, Hirota *et al.* [22] described a single case of a 30-year-old female who had undergone living-donor lung transplantation for idiopathic pulmonary arterial hypertension, who developed PPFE-like changes 20 months after transplantation, with on biopsy pleural fibrosis and subpleural elastosis. In addition, there was evidence of constrictive bronchiolitis with surrounding peribronchiolar intra-alveolar fibrosis. They suggested PPFE as a possible pathological phenotype of restrictive allograft dysfunction (RAS), and as a manifestation of chronic lung allograft dysfunction. This is a view shared by Ofek *et al.* [23], who identified 47 patients with RAS, 16 of whom had a lung biopsy. In 15 of these, a pattern of subpleural parenchymal fibroelastosis was noted, characterised by intra-alveolar deposition of hypocellular collagen with preservation and thickening of the alveolar elastic network. Again, there was a sharp transition to unaffected surrounding parenchyma, with fibroblastic foci found at the interface. This was accompanied by obliterative bronchiolitis in 14, and diffuse alveolar damage (DAD) in 13 patients. This led the authors to propose that DAD may precede and be causally related to the development of PPFE in RAS.

Our group has reported a series of 4 patients who had undergone bone marrow transplantation and subsequently developed pulmonary fibrosis with a classical pattern of PPFE, both on CT and histopathology [24]. The spectrum included pleural fibrosis, sharply demarcated subpleural and paraseptal intra-alveolar fibroelastosis and obliterative bronchiolitis. Of note were CT findings of pneumothoraces with or without a history of recurrent pneumothorax in all of these patients.

A possible familial propensity for the development of otherwise idiopathic PPFE was suggested by an earlier French report of three sisters with bilateral isolated apical pleural fibrosis, leading to death in two cases and bilateral lung transplantation in the third patient [25]. The women (all non-smokers) were aged 23-29 at time of presentation, with no evidence of auto-immune disease or relevant exposure history except drug treatment for previous pulmonary tuberculosis in one patient. Imaging revealed pleural and subpleural fibrosis, predominantly in the upper lobes in all three cases, which was confirmed by surgical lung biopsy in two, with a sharp demarcation towards normal more central lung parenchyma and a lack of significant inflammation. Two of the patients developed apical pneumothoraces.

Salient demographic, clinical, and histological findings of the various case series have been collated in tabular format in Table **1**. The age range over the studies was 13-85

years with an average age of 49, with almost total parity of sex (M:F ratio 46:54). There was a bimodal distribution of presentation, with an early peak in the third, and a later peak in the sixth decade (Fig. **1A**), with a striking predominance of female cases in the earlier peak, especially after exclusion of post-transplantation cases (Fig. **1B**). As far as is apparent from these publications, there were no active smokers and few ex-smokers amongst the patients. The most common presenting complaints were dyspnoea and cough (79% and 52% resp.), with weight loss and pneumothorax also common (20% and 30% resp.). The relevant history included cases of lung transplantation (47%), bone marrow transplantation (6%), chemotherapy (10%, many of whom had also undergone bone marrow transplant), known exposure to allergens (4%), previously detected auto-antibodies (8%) and recurrent pulmonary infective episodes (14%). There was a family history of lung fibrosis in 9% of

cases, which were virtually exclusively female (just 1 male patient), with an average age of just 38 and all represented in the earlier peak of presentation (Fig. **1C**).

THE HISTOLOGICAL DIFFERENTIAL DIAGNOSIS OF PPFE

The accrual of data through the radiological findings and histological description of surgical lung biopsies obtained from the cases in the series discussed in the previous section, has enabled the delineation of criteria for the diagnosis of PPFE. Thus, we have previously defined radiological boundaries which can render a 'definite PPFE' or 'consistent with PPFE' diagnosis [17] (Table **2**). In their paper, Kusagaya *et al.* [18] used previous studies to define the histological criteria of typical idiopathic PPFE as (1) intense fibrosis of the visceral pleura; (2) prominent, homogenous,

Table 1.   Clinical Characteristics of PPFE Patients

	N	Age Range (Ave.)	Sex M:F (%)	Smoking Status (S/E/N)			Symptoms (D/C/W/PT) (%)				Relevant History (LTx/BMTx/CRx/All./AA/RI) (%)						Family Hx Pulmonary Fibrosis (%)
Azoulay *et al.* 1999 [24]	3	23-29 (27)	0:3	0	NK	3	2	2	0	2	0	0	0	0	NK	0	3 ***
Konen *et al.* 2003 [19]	7	13-67 (48)	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	5	7	NK	NK	NK	NK	NK	NK
Frankel *et al.* 2004 [2]	5	32-65 (50)	1:4	0	1	4	3	4	0	0	0	0	2	0	1 *	1	2 ****
Pakhale *et al.* 2005 [20]	13	24-73 (44)	7:6	NK	NK	NK	13	5	4	1	13	NK	NK	NK	NK	NK	NK
Becker *et al.* 2008 [15]	2	51-59 (55)	0:2	0	2	0	2	2	0	0	0	1	1	0	0	0	0
Piciucchi *et al.* 2011 [16]	2	28-60 (44)	2:0	0	NK	2	0	2	0	0	0	0	0	1	0	0	0
von der Thüsen *et al.* 2011 [23]	4	13-55 (31)	3:1	0	0	4	4	2	1	4	0	4	4	0	0	0	0
Kusagaya *et al.* 2012 [18]	5	67-74 (70)	4:1	0	1	4	4	1	4	0	0	0	1	0	NK	NK	0
Ofek *et al.* 2012 [22]	15	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	*NK*	15	NK	NK	NK	NK	NK	NK
Reddy *et al.* 2012 [17]	12	33-85 (53)	5:7	0	3	9	11	9	1	3	0	0	0	2	5 **	7	2 *****
Watanabe *et al.* 2012 [19]	9	43-81 (61)	4:5	0	2	7	4	2	1	7	1	0	0	0	0	0	0
Hirota *et al.* 2013 [21]	1	30 (30)	0:1	NK	NK	NK	1	0	0	0	1	0	0	0	0	0	0
Total	78	13-85 (49)	26:30 (46:54)	0	9	33	44 (79)	29 (52)	11 (20)	17 (30)	37 (47)	5 (6)	8 (10)	3 (4)	6 (8)	8 (14)	7 (9)

Abbreviations: N=number of patients; M=male; F=female; S=smoker; E=ex-smoker; N=never smoker; D=dyspnoea; C=cough; W=weight loss; PT=pneumothorax; LTx=lung transplant; BMTx=bone marrow transplant; CRx=chemotherapy; All.=exposure to allergens; AA=autoimmune serology positive; RI=recurrent infections.
*ANA, RF
**Incl. RF (rheumatoid factor), antiribosomal antibody, anti-CCP (cyclic citrullinated peptide), ANCA-positive glomerulonephritis with kidney transplant and immunosuppression, ANF-IF speckled nuclei, equivocal dsDNA antibody, cardiolipin IgM antibody
***Three sisters included in this study
****Two sisters included in this study
*****1 case of UIP; 1 case of UIP/NSIP
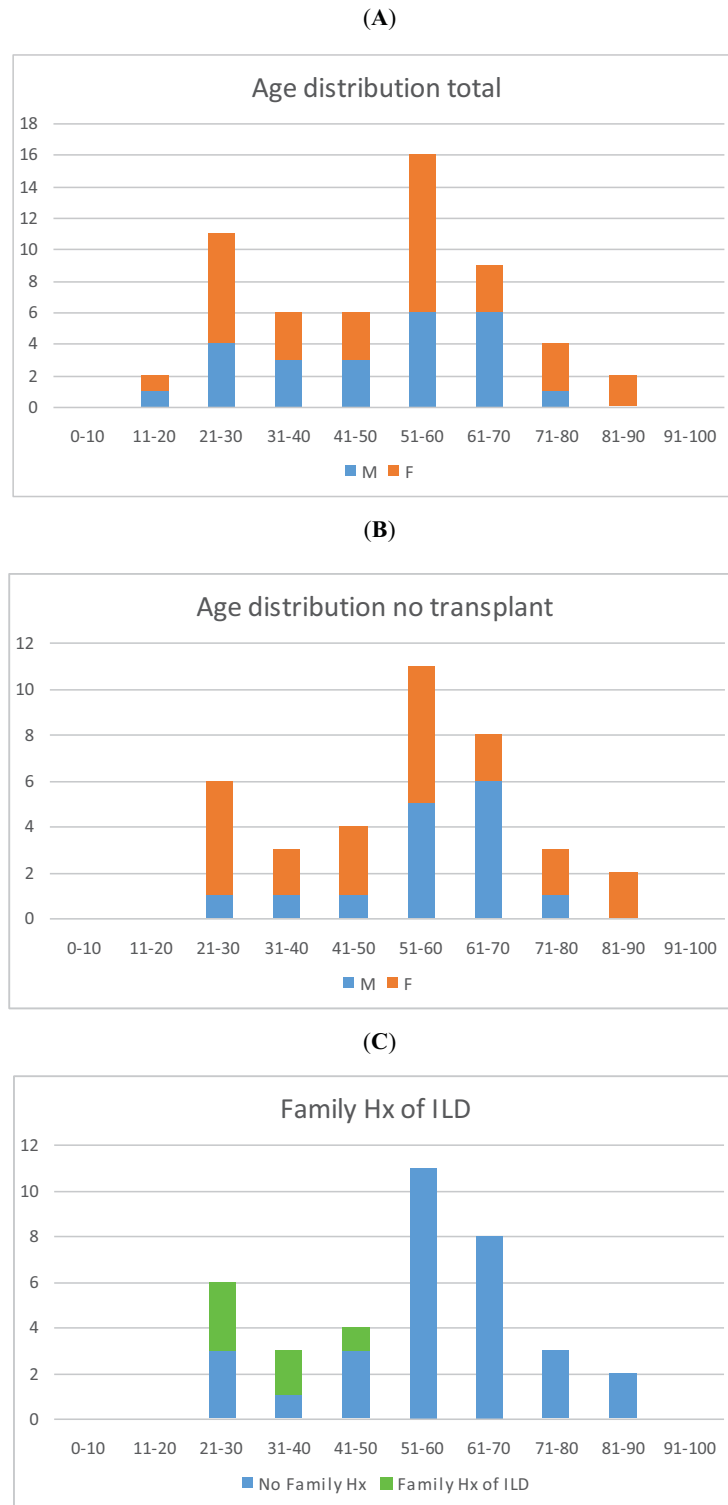Italics: excluded from analysis due to paucity of data.

(A)

(B)

(C)

Fig. (1). Age and sex distribution at age of presentation of patients in the studies included in Table **1** (**A**: total; **B**: after exclusion of transplant patients), with in **C**: age distribution according to presence or absence of a family history of lung fibrosis.

subpleural fibroelastosis; (3) sparing of the parenchyma distant from the pleura; (4) mild, patchy lymphoplasmocytic infiltrates; and (5) small numbers of fibroblastic foci present. A typical focus of pleural fibrosis and subpleural fibroelastosis in PPFE is shown in Fig. (**2A**, **B**). Our group has defined additional criteria to establish a diagnosis of a

pattern of fibrosis which is 'consistent with' PPFE, being intra-alveolar fibrosis as above, but (1) not associated with significant pleural fibrosis, or (2) not predominantly beneath the pleura, or (3) not in a upper lobe biopsy (Table **2**).

While tightening the histological definition, this method obviously still allows for a possible overlap in the

Table 2.   Criteria for the Diagnosis of PPFE

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 a upper lobe biopsy

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histological characteristics of PPFE with other known patterns of (idiopathic) pulmonary fibrosis. The two most prominent patterns of diffuse parenchymal lung disease in clinical practice today, are non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). NSIP will not easily be confused with PPFE due to its more diffuse involvement of the lung parenchyma with generally little pleural change (with the exception of connective tissue-related NSIP) and, on histology, an interstitial rather than intra-alveolar pattern of inflammation (as in cellular NSIP) and/or fibrosis (in fibrotic NSIP). In view of the subpleural predominance of the fibrosis of PPFE, however, the main radiological and histological differential diagnosis constitutes a pattern of UIP, be it in an idiopathic setting (i.e. idiopathic pulmonary fibrosis (IPF)) or secondary to known causes (e.g. drug effects, or chronic extrinsic allergic alveolitis (EAA)). IPF and a subset of PPFE patients also have a similarly poor prognosis, and familial cases have been described for both diseases [25, 26]. In contrast to the UIP pattern, however, PPFE has a typical upper zone predominance, while UIP, especially in the initial stages, primarily affects the lower lobes. Moreover, UIP leads to extensive remodelling of the lung parenchyma, eventually resulting in end-stage fibrosis with effacement of the original parenchymal architecture. These features are not characteristic of PPFE, as the pattern is of homogeneous intra-alveolar fibrosis with preserved alveolar structure and even accentuation of septal structures through elastosis, and a lack of cystic change with bronchiolisation; the latter equating to the radiological finding of honeycombing in UIP. Connective tissue stains which highlight elastic fibre deposition (such as an Elastica van Gieson stain) can therefore be highly valuable in solving this differential diagnosis. Also, the most important histological hallmark of UIP, which is temporal heterogeneity of fibrosis with the presence fibroblastic foci adjacent to areas of established

fibrosis, is not a feature of PPFE. Fibroblastic foci may be seen, but these should not exceed low numbers to permit a confident diagnosis of PPFE.

The combination of both pleural and parenchymal fibrosis can also be seen in asbestosis, advanced fibrosing sarcoidosis, and radiation or drug-induced lung disease. A lack of a relevant history would obviously exclude the latter two, and histologically, none of these are characterized by the combination of intra-alveolar fibrosis and septal elastosis seen in PPFE. Thus, the archetypcal histological pattern of asbestos-related parenchymal fibrosis tends to display more advanced remodeling and architectural distortion than the intra-alveolar fibrosis seen in PPFE. Furthermore, in the case series included in this review, in only 3 patients [16, 17] exposure to potential (avian and fungal) allergens was noted, and only 1 patient was deemed to have significant asbestos exposure [16]. Several of the other studies specifically mention the absence of a history of inhalational exposure, and this therefore would not appear to support a major role in PPFE. Potentially, however, not all clinical assessments of the patients included were rigorous enough to completely exclude this as a possibility. In clinical practice, a confident diagnosis of PPFE should nonetheless only be made in the absence of (1) a relevant exposure history, and (2) significant numbers of asbestos bodies and sarcoid-type granulomas on histology if a surgical lung biopsy is performed.

Histomorphologically, the so-called 'apical cap', which is a localised lesion of subpleural fibrosis that predominantly occurs in the apices of the upper lobes, also enters the differential diagnosis of PPFE [27]. Several criteria can be used in combination, however, to prise these two entities apart. Firstly, apical caps tend to occur in older cigarette smokers and are typically asymptomatic and non-progressive (average age 65.6 years, age range 51-91 years), while PPFE also affects younger, non-smoking patients, who present with symptoms and often have a poor clinical outcome. Secondly, apical caps (as the name suggests) tend to be localised mass lesions in the upper lobe apices, and as such, they are often resected for a presumed diagnosis of carcinoma. PPFE, on the other hand, while displaying an upper lobe predominance, has a more diffuse subpleural distribution which can also affect basal portions and other lobes. Thirdly, histologically, apical caps are often associated with sclerotic pleural plaques and extensive alveolar collapse, which are not typically present in PPFE.

Akin to PPFE, (cryptogenic) organizing pneumonia ((C)OP) [28, 29] can lead to intra-alveolar fibrosis. OP is characterized by an initial phase, and a varying amount, of intra-alveolar fibrin deposition and inflammatory cell infiltration, followed by buds of intra-alveolar (myo) fibroblastic organization, the so-called Masson bodies. These foci of organization can be cleared with often complete resolution and restoration of normal lung structure. Alternatively, a progression to chronic fibrosis can occur, with incorporation of the foci into alveolar septa and irregular interstitial fibrosis. This does not result in the diffuse, homogeneous intra-alveolar fibrosis and alveolar septal elastosis typical of PPFE, however, and both radiologically and histologically, OP has a patchier, haphazard and frequently more peribronchial distribution than the predominant subpleural and paraseptal contiguous areas of fibrosis seen in PPFE.
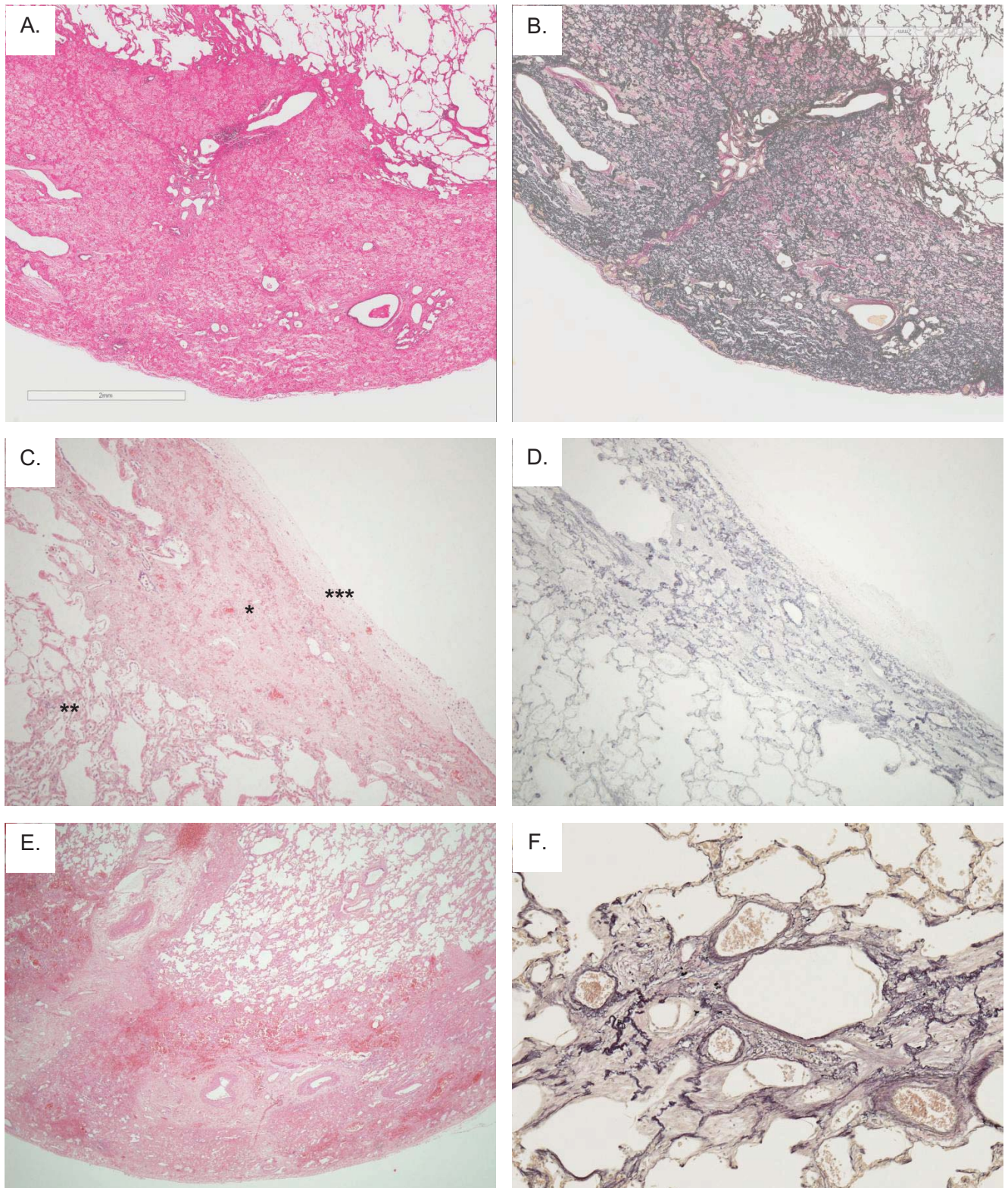
Fig. (2). Photomicrographs of salient features of PPFE. **A** (H&E stain) and **B** (Elastica van Gieson (EvG) stain) (both courtesy of Prof. Andrew Nicholson) show extensive subpleural intra-alveolar fibrosis with alveolar septal fibrosis (black stain in EvG). **C** (H&E stain) and **D** (EvG stain). Subpleural fibroelastosis (*) with adjacent fibrin deposition reminiscent of DAD (**) and overlying pleural fibrinous exudates (***). **E**. Intra-alveolar haemorrhage adjacent to area of subpleural fibroelastosis (H&E stain). **F**. End-stage alveolar duct fibrosis with adjacent blood vessel dilatation (H&E stain).

Prominent intra-alveolar presence of fibrin on a background of OP is typical of acute fibrinous and organizing pneumonia (AFOP) [30, 31]. Again, AFOP tends to be a more patchy process than typical PPFE, with an average of 50% airspace involvement but less peribronchiolar accentuation than classical OP. It is generally more pronounced in the lung bases, in contrast to PPFE which has a predominant upper zone distribution. Based on the clinical characteristics, there is a potential aetiologic overlap with PPFE patients, as recently cases of AFOP in lung and bone marrow transplant patients have been described [32, 33]. AFOP can also occur as a non-specific secondary phenomenon, e.g. in the vicinity of tumours, foci of granulomatous disease, infarction of abscesses and in its primary form it has the same aetiologic differential as diffuse alveolar damage (DAD) (incl. infection, collagen vascular disease and drug reactions). It has indeed been speculated to be a possible variant of DAD, although intra-alveolar fibrin in AFOP is generally organized in 'balls' rather than the archetypal hyaline membranes in DAD. AFOP often resolves completely, and although it can run a fulminant course with rapid progression to death in as many as half of the patients, long-term sequelae with dense intra-alveolar or septal collagen deposition have not been described.

In some of the PPFE patients elements suggestive of DAD have been observed. Thus, as mentioned above, in the series of transplant-related PPFE in the context of restrictive allograft syndrome published by Ofek *et al.* [23] specimens obtained less than 1 year after onset of RAS typically showed features of DAD, with those obtained at a later date having less evidence of DAD. The authors thus suggested that there may be a temporal sequence of DAD preceding PPFE, especially as in some patients areas of DAD appeared to merge into areas of PPFE. This is also a phenomenon sometimes seen in our case series of bone marrow transplant-related PPFE, with foci of DAD-like fibrin deposition underlying areas of subpleural fibro-elastosis, pleural fibrosis and hypocellular pleural exudates (Fig. **2C**, **D**), infrequently accompanied by intra-alveolar haemorrhage (Fig. **2E**). In some patients, this may represent changes consistent with the previously described post-bone marrow transplant idiopathic pneumonia syndrome in the context of graft-versus-host disease, which has a high mortality rate (approx. 74%) and radiological and histological features of organizing pneumonia as well as DAD [34, 35]. Classically, DAD leads to a more interstitial pattern of initially myxoid-type, and later collagenous fibrosis, in contrast to the constantly denser, hypocellular intra-alveolar fibrosis in PPFE. Interestingly, however, when more central areas of intra-alveolar fibrosis are seen in PPFE patients, these often have an appearance reminiscent of the end-stage alveolar duct fibrosis with adjacent blood vessel dilatation first described in DAD by Pratt [36] (Fig. **2F**).

THEORIES OF AETIOLOGY AND PATHOGENESIS

As the entity of PPFE is becoming more widely accepted, the number of cases reported in the literature is beginning to reach levels that allow for hypotheses of its aetiology and pathogenesis on the basis of the accumulated demographic data, clinical characteristics and histological features of these patients.

By far the strongest association appears to be preceding lung or bone marrow transplantation, with just over half of the patients included in this review having undergone either of these. The aetiology of PPFE in bone marrow transplantation patients remains elusive, although possible causes may include drugs (e.g. induction or chemotherapy regimens), radiation-induced effects or graft-versus host disease. Inflammation does not appear to be a dominant feature at the time of biopsy in these patients; however, an inflammatory component in earlier stages of the disease cannot be excluded. And although it is certainly conceivable that graft-versus host disease-related obliterative bronchiolitis could lead to a degree of subpleural atelectasis and collapse fibrosis, the pattern of fibrosis seen in PPFE is characterised more by alveolar filling with collagenous fibrosis with retention and accentuation of alveolar septal elastin. In the context of bone marrow transplantation, PPFE could also be a sequela of other known acute graft-versus host disease-related changes, such as the idiopathic pneumonia syndrome, with its characteristic histopatho-logical appearances of diffuse alveolar damage, organising or acute pneumonia and interstitial lymphocytosis. This syndrome tends to occur early after transplant (in the range of 1 to several weeks [37]), as opposed to pleuroparen-chymal fibroelastosis, which appears to be of relatively late onset in post-bone marrow transplant patients. It is conceiv-able that the intra-alveolar fibrosis in PPFE constitutes the result of an imbalance in the rate of deposition and clearance of fibrinoid material in these frequent DAD-like changes in the earlier stages after bone marrow transplantation, and/or an aberrant, relatively hypocellular and homogeneous fibrotic response to the presence of this material and its break-down products. Alternatively, PPFE could represent a consolidation of the intra-alveolar mixture of fibrin and fibroblastic plugs typical of (acute and fibrinous) organizing pneumonia [32], rather than the more common resolution or septal incorporation of these aggregates. Similarly, in lung transplantation patients who developed upper lobe fibrosis, this was in many cases accompanied by features of DAD, or (AF) OP, in addition to constrictive obliterative bronchiolitis [21, 23]. It is as yet unclear, whether a possible confirmation of the hypothesis of DAD/(AF)OP progressing to PPFE should be sought in disordered fibrin deposition, fibrinolysis, macrophage activity, fibroblastic response or pneumocyte homeostasis, or in a combination of these.

If this is a common final pathway shared by other, non-transplant related forms of PPFE, it is conceivable that any form of lung injury leading to an intra-alveolar fibrinous response could lead to fibrosis with a PPFE pattern. This could thus also serve as a mechanism for the PPFE cases with a history of recurrent infection, allergen exposure, previous chemotherapy, and positive autoimmune serology in the studies discussed in this paper, all of which have previously been shown to have the potential to lead to DAD/AFOP. Any such derangement in the balance of deposition and clearance of intra-alveolar fibrin / organisation could be due to environmental factors, or have a genetic basis, or be due to a combination of these.

This theory of post-DAD/(AF)OP PPFE is seemingly contradicted by the fact that the idiosyncratic pleural and subpleural localisation of fibrosis in PPFE does not conform to the typical radiological and histological pattern of changes in other bone marrow or lung transplant related lung pathology, which tends to have a more central and/or peribronchial distribution, especially when airway-related, such as is the case in constrictive or obliterative bronchiolitis. In transplant patients, and in some idiopathic cases, however, there also appears to be an additional (microscopic) bronchocentric component to the fibroelastosis [17], and it would therefore appear that this may be a self-limiting process in this location, whereas the fibrosis in the subpleural location is progressive and can continue unchecked. It is therefore likely that while fibrinous exudates and/or foci of intra-alveolar fibroblastic organisation may form the substrate for PPFE, other factors determine its eventual distribution. Thus, the correlation of idiopathic pneumonia syndrome with serositis, fibrosis and pneumothorax may be of particular interest, as the latter two are certainly also present in non-transplant cases of PPFE, and chronic serositis may have preceded the extensive pleuroparenchymal changes seen. Pleuritis in the context of systemic lupus erythematosus is known to have a potential to lead to pleural fibrosis in a minority of patients [38], as can drug-induced and rheumatoid pleuritis [39]. This could potentially also serve as a mechanism for the occurrence of PPFE in patients with known positive autoimmune serology in the various case reports, but (chronic) pleuritis does not appear to be a feature of PPFE once the patients reach the stage of clinical presentation. Scarring of a visceral pleural defect following pneumothorax could also lead to the occurrence of subpleural fibrosis, and pneumothoraces are a recognized association of transplant-related lung fibrosis as well as of idiopathic PPFE. However, in both instances foci of subpleural fibroelastosis are more likely to contribute to the development of pneumothoraces rather than being a result thereof, as pleural and subpleural scarring following a pneumothorax is generally characterized by more localised collagenous fibrosis and remodeling of the parenchyma in contrast to the diffuse intra-alveolar fibroelastosis of PPFE.

The predilection for the upper lobes of PPFE could also be another intriguing pointer towards its potential pathogenesis. In analogy with the apical cap [27], which is by some be presumed to be the end result of upper lobe subpleural infarction, PPFE can be accompanied by marked vascular changes, as shown in our recent case series [17], in which 8 out of 12 patients showed venous and arterial intimal fibrosis, which in 2 cases was sufficiently present to suggest vasculo-occlusive disease in the original reports. The peripheral localisation of PPFE with upper zone predominance may thus correlate with the relative hypoperfusion and ischaemia of these areas, although a mechanism for ischaemia leading to disordered fibrin and connective tissue homeostasis in these patients still needs to be established.

Pleural effusions could act as a marker of active pleural disease, and could potentially play a pathogenetic role in PPFE, for instance mediated by fibrin and its degradation products contained within the fluid [40]. At the time of presentation of PPFE, however, pleural effusion appears to be an extremely rare imaging finding. In fact, in the case series included in this review, only 1 case of unilateral pleural effusion was described, in the context of adjuvant chemotherapy following mastectomy for breast adenocarcinoma [2]. This pleural fluid was found to be negative for malignancy, and the paper is not informative as to whether the patient had undergone radiotherapy for breast carcinoma on the same side. Obviously, this does not exclude selective underreporting of pleural effusion in the other case series, and retrospective information regarding pleural effusion in earlier (subclinical) stages of PPFE is generally not available. Nonetheless, the lack of effusion as a consistent finding in the sizeable group of patients presented in this review, implies that its role as a feature in (the development of) this disease is probably negligible.

While there is a wide age range of presentation, the observed bimodal distribution, especially in the non-transplant cases, could be taken to suggest different aetiologies in the younger and the older age group. It is also of note that females are rather overrepresented in the first peak of presentation, with a relatively large number of these women having a family history of fibrosis, and also a generally poor prognosis. The publication of a set of 2 and 3 sisters, resp. by Frankel *et al.* [2] and Azoulay *et al.* [25], who all developed a pattern of fibrosis consistent with PPFE, provides strong support for the supposition that genetic variability may be an important, and at least contributory factor in its development and/or progression. Additional possible familial cases have been reviewed in the more extensive Japanese literature [9, 10]. As yet, however, it remains unclear as to what the underlying genetic aberration(s) and its/their mechanism could be.

CONCLUSION AND FUTURE PERSPECTIVES

In summary, PPFE is to be regarded as a distinct pattern of pulmonary fibrosis which is likely to be introduced as a separate entity in the new classification scheme of idiopathic interstitial pneumonias [14]. It often runs a rapidly progressive course with a poor prognosis, and can constitute a rare but reproducible response to a range of pulmonary insults. These are presumed to include factors related to lung and bone marrow transplantation, and possibly drugs, autoimmunity, and recurrent infective episodes. While the acute changes caused by these insults are likely to vary in distribution and morphology, the end result in PPFE patients is an upper zone predominant pattern of pleural fibrosis and subjacent diffuse intra-alveolar fibroelastosis, possibly due to a disorder of fibrinolytic and/or fibrogenic homeostasis following DAD or AFOP. Much remains to be understood about the potential triggers for PPFE (especially outside the setting of lung and bone marrow transplantation), however, and about the factors influencing an individual's predisposition to react to these insults with PPFE. Larger (and in view of the rarity of the disease, international) studies are therefore required to provide a clearer picture of possible clinical associations, delineate the natural history of the disease, and identify specific risk factors in patient characteristics.

Genetic linkage in combination with exposure studies involving familial cases of PPFE may prove indispensable not only for unravelling potential familial genetic defects leading to the development of PPFE, but after their

identification also those of possible sporadic genetic cases, and even of environmental factors which could influence the processes controlled by the genes involved.

In due course, animal studies could be employed to test theories of aetiology and pathogenesis, and eventually of candidate therapies for PPFE. Thus, while models which faithfully reproduce all of the characteristics of PPFE are not yet available, a transgenic mouse model has been developed which expresses transforming growth factor-α (TGF-α) in the distal lung under control of the surfactant protein C (SP-C) promoter which recapitulates some of the features of PPFE with pleural and subpleural fibrosis [41, 42].

Notwithstanding ongoing research into the causes and potential treatments for PPFE, it will continue to be important to raise awareness PPFE as a separate entity in the spectrum of rare fibrotic lung diseases amongst clinicians, radiologists and pathologists involved in the management of lung fibrosis patients, as specific radiological and histological features have now been identified which enable its diagnosis with some confidence. This holds particular poignancy for those patients with symptoms and signs of lung fibrosis following lung and bone marrow transplantation, and for cases of otherwise idiopathic fibrosis in young women, especially in those with a positive family history.

ABBREVIATIONS

AFOP   =   Acute fibrinous and organizing pneumonia

COP   =   Cryptogenic organizing pneumonia

CT   =   Computed tomography

DAD   =   Diffuse alveolar damage

EAA   =   Extrinsic allergic alveolitis

HRCT   =   High-resolution computed tomography

IAFE   =   Intra-alveolar fibroelastosis

IPF   =   Idiopathic pulmonary fibrosis

IPPFE   =   Idiopathic pleuroparenchymal fibroelastosis

IPUF   =   Idiopathic upper lobe fibrosis

NSIP   =   Non-specific interstitial pneumonia

OP   =   Organizing pneumonia

PPFE   =   Pleuroparenchymal fibroelastosis

RAS   =   Restrictive allograft syndrome

UIP   =   Usual interstitial pneumonia

CONFLICT OF INTEREST

The author confirms that this article content has no conflicts of interest.

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