Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

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ABSTRACT This perspective highlights some evidence that has hitherto been neglected, especially because it may not have been sufficiently explicated in the clinical respiratory medicine literature. Idiopathic pulmonary fibrosis (IPF) has appeared only in the second half of the 20th century and, like lung cancer and chronic obstructive pulmonary disease, may be a direct consequence of the cigarette smoking epidemic. It is a disease of lung ageing, with most affected patients being >70 years of age. The relationship between lung ageing and pulmonary fibrosis is further illustrated in the bleomycin mouse model, in which older males develop more fibrosis than young female mice.

Earlier diagnosis of IPF is a prerequisite for significant progress to be made in the long-term outcome and prognosis. We consider that only two different yet complementary and realistic approaches could lead to earlier diagnosis of IPF and possibly to allowing more efficient disease management: 1) investigating any patients with early Velcro crackles at lung auscultation through proactive education of, and commitment from, primary care physicians; and 2) using current large-scale lung cancer screening strategies with low-dose high-resolution computed tomography in smokers for the detection of subclinical interstitial lung disease and especially early IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, is characterised by extracellular matrix accumulation with progressive lung remodelling and, eventually, honeycomb changes [1]. Fibroblasts, especially myofibroblasts, play a major role in the production of the extracellular matrix, which mainly consists of collagen [1, 2].

IPF occurs particularly in males in their sixth and seventh decades, and carries a poor prognosis with a median survival of only 2.5–4 years from diagnosis [3, 4]. IPF accounts for ~20% of cases of interstitial lung disease (ILD) [5]. Evidence-based guidelines for the diagnosis and management have recently been published based on extensive literature review [6]. However, some evidence has been neglected so far and warrants more emphasis in the respiratory literature.

Here, we develop the circumstantial yet strong argument that IPF is a relatively recent disease linked to the tobacco smoking epidemic. We further emphasise that IPF is a disease of ageing, and that earlier diagnosis could be achieved by recognising the value of Velcro crackles at auscultation and by promoting screening for IPF as a by-product of low-dose chest computed tomography screening for lung cancer.

IPF is a recent disease

History of chronic pneumonia

William Osler has been credited for the description of ''chronic interstitial pneumonia'' more than a century ago [7]. However, interstitial pneumonia did not have the same meaning as it has now. In his book, Osler first stated in the paragraph on morbid anatomy that ''the disease is unilateral'' [8], and what he described was indeed the chronic evolution of acute infectious pneumonia rather than an idiopathic fibrotic process. Previous descriptions did not correspond to IPF either. Osler largely referred to Jean-Martin Charcot, who had studied chronic pneumonia in detail, with the sequence leading from acute pneumonia to ''pneumonic fibrous metamorphosis'' including many ''fusiform cells'' likely corresponding to (myo)fibroblasts [9, 10]. In 1871, Wilson Fox [11] comprehensively reviewed the literature on chronic pneumonia, and found that two thirds of cases occurred between the ages of 15 and 40 years, with acute onset in most cases, frequent haemoptysis, unilateral involvement with retraction of the chest, and fine crepitation at the acute stage that did not persist chronically. Therefore, most cases of chronic pneumonia probably corresponded to nonresolving acute infectious pneumonia, with probable tuberculosis in other cases (Robert Koch did not describe the eponymous bacillus until 1882). It is critical to notice that despite the careful auscultation of patients by well-trained physicians and the usual practice of autopsy in all large hospitals, there were no reports of a condition consistent with true IPF until the second half of the 20th century.

Onset of IPF in the second half of the 20th century

In the 1930s, Hamman and Rich reported a few patients with fatal ''acute diffuse interstitial fibrosis of the lung'' [12, 13], which was considered an entity close to IPF until the 1960s [14] but is now labelled acute interstitial pneumonia, thus differing from IPF [15]. It was only from the 1950s that cases of probable IPF were increasingly reported. However, the series reported under the heading of pulmonary fibrosis also included a variety of other ILD, in patients of all ages (including children) [16–19].

In 1968, Averill Liebow proposed a pathologic classification of the interstitial pneumonias that included usual interstitial pneumonia (UIP) [20], which he considered to result from diffuse alveolar damage with hyaline membranes, and further interstitial proliferation and honeycombing. The terminology of IPF especially developed in the 1970s. In 1978, Charles Carrington reported a series of 53 cases of UIP (collected over 25 years) [21], defined as a ''highly variegated structure often including the entire spectrum from normal alveolar walls to fibrotic, end-stage lesions in the same tissue sample; dense pleomorphic interstitial cellular infiltrate including many lymphocytes and monocytes but relatively few eosinophils''. Fibrosis and honeycombing were considered to be nonspecific features of both UIP and desquamative interstitial pneumonia [21]. In the following decade, the prevalent concept was that ''alveolar macrophages direct the alveolitis associated with IPF'', with limited, if any, role attributed to fibroblasts [22].

The advent of computed tomography contributed to a better characterisation of the phenotypes of the ILDs. Further clarification resulted from the individualisation of idiopathic nonspecific interstitial pneumonia (previously mixed with IPF) in the 1990s [23–27]; IPF was definitively acknowledged as a distinct entity only in 2008 [28].

IPF is presently established as a clearly defined entity with precise diagnostic criteria [6, 29], with a pathological pattern of UIP and characteristic high-resolution (HRCT) features including honeycombing. However, its cause(s) remains elusive.

IPF as a direct consequence of the cigarette smoking epidemic

The cigarette smoking epidemic started at the end of the 19th century and a turning point was the First World War, when cigarettes were provided to soldiers [30]. Although lung cancer was very rare during the first decades of the 20th century, statistics around 1930 reported that patients with lung cancer were often smokers. A strong relationship between tobacco smoking and lung cancer already existed and was four times higher for squamous cell cancer than for adenocarcinoma [31]. In 1954, the mortality of British doctors due to lung cancer was demonstrated to rise with the amount of tobacco smoked [32]; this landmark study has set the stage for the current era, in which lung cancer has become the most common cause of cancer death worldwide, and the link between tobacco smoking and lung cancer is no longer debated.

Although IPF is strongly linked to tobacco smoking [1, 6, 33–35], it has not yet been explicitly included in the list of tobacco-associated lung diseases together with lung cancer and chronic obstructive pulmonary disease (COPD) [36–39]. The increase in the prevalence of IPF paralleled, with some delay, that of lung cancer and COPD. Not all patients with IPF are smokers or ex-smokers; however, the majority are smokers with a frequency comparable to that found in lung cancer and COPD (*e.g.* 60–80%). Patients with IPF are significantly more likely than controls to report a smoking history (OR 1.58, 95% CI 1.27–1.97) [40], with a possible dose–response relationship between tobacco smoking and the risk of IPF [33]. Among first-degree relatives of individuals with familial interstitial pneumonia, older age, male sex and ever having smoked cigarettes are associated with the development of pulmonary fibrosis [41], suggesting that the development of ILD may result from an interaction between age, smoking and genetic factors. These studies were performed before the current international definition of IPF and may have underestimated the relative risk associated with tobacco smoking. Furthermore, disorders resulting from smoking may be associated in a given patient. The syndrome of combined pulmonary fibrosis and emphysema [42, 43] strikingly recapitulates the three major respiratory consequences of cigarette smoking, namely pulmonary fibrosis, emphysema and lung cancer.

The relationship between smoking and pulmonary fibrosis is further illustrated almost experimentally in rheumatoid arthritis. Indeed, tobacco smoking increases the citrullination of peptides *in vivo*, fosters the development of anti-cyclic citrullinated peptide antibodies, enhances the risk of developing rheumatoid arthritis with poor response to methotrexate therapy and increases the risk of developing ILD in the setting of rheumatoid arthritis. Interestingly, UIP is the most common pathological pattern of interstitial pneumonia in rheumatoid arthritis [44] and has a prognosis similar to that of IPF/UIP [45], further emphasising the links between tobacco smoking and lung fibrosis.

The fact that IPF developed only from the second half of the 20th century, coinciding with the development of cigarette smoking, strongly supports the hypothesis that IPF, like lung cancer and COPD, may directly result from the epidemic of smoking. Further epidemiological and pathophysiology studies should be carried on to confirm this.

IPF is a disease of ageing

Age of patients

The median age of patients with IPF is between 65 and 70 years in all series based on current criteria, with a range of 55–80 years [1]. In fact, older age (*e.g.* >70 years) is the most powerful clinical predictor of the probability of IPF in a patient with idiopathic ILD, while the probability of genuine IPF is extremely low before the age of 50 years [46]. Although a trend has been reported toward an increase in the incidence and prevalence of IPF, and in the mortality from IPF [47–49], large epidemiological studies based on precise diagnostic criteria for IPF are still awaited. It is likely that the increase in life expectancy in western countries partly contributes to the development of IPF in the ageing population; however, the rise in the burden of disease is not totally explained by this phenomenon [50, 51]. Specifically, ageing of the lung may contribute to modifications of the extracellular matrix, increase in the apoptosis of alveolar epithelial cells, accumulation of mesenchymal stem cells, telomerase dysfunction and shortening. and epigenetic changes [52, 53], collectively predisposing to IPF and COPD [54].

Of young mice and older men

Surprisingly, most animal models of pulmonary fibrosis used young mice to study a condition occurring especially in older males. Support for the concept that IPF may be a disease of lung ageing linked to male sex has recently come from experimental studies in rodents. In the past, most experimental studies have been conducted in rodents aged 6–12 weeks, the equivalent of about 10–12 years in humans [55]. A recent study was performed with bleomycin instilled intratracheally to young (8–12 weeks) and aged (52–54 weeks) male and female C57BL/6 mice [56]. In this model, aged male mice developed more severe lung disease with increased mortality compared to young mice [56] and young male mice developed more pulmonary fibrosis

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than young female mice [56, 57], demonstrating that both advanced age and male sex contribute to fibrotic pathophysiology in the animal model. Furthermore, mice prone to accelerated senescence are also more susceptible to bleomycin-induced pulmonary fibrosis compared to control mice [58]. These observations collectively suggest that older age and male sex predispose mice to a fibrotic response to alveolar injuries (including tobacco smoking) in a compatible genetic background.

Pulmonary fibrosis of genetic origin

In an apparent paradox, familial interstitial pneumonia predominantly occurs at a younger age as compared to nonfamilial IPF [41]. Some clues as to why this may happen have arisen from the recent description of germline mutations in the genes *hTERT* and *hTR* associated with the telomerase complex, a ribonucleoprotein holoenzyme that protects the tips of chromosomes from ''erosion'' during cell division, in patients with adult onset of pulmonary fibrosis [59, 60].

Mutations in telomerase and telomere genes characterise dyskeratosis congenita, a rare syndrome of premature ageing identified a century ago [61, 62]. About one in five patients with dyskeratosis congenita eventually develops pulmonary fibrosis and telomerase mutations may be found in ~15% of patients with familial pulmonary fibrosis [59, 60, 63]. Again, a history of tobacco smoking is present in over two thirds of affected patients with mutations [64]; current and former smokers have shorter telomeres than age-matched controls [65] including in the alveolar epithelium [66]; and sex hormones regulate telomerase activity [67], which may contribute to more frequent pulmonary fibrosis in males.

According to the current concept, mutations in telomerase and telomere components predispose to a broad spectrum of disease characterised in adults by pulmonary fibrosis, liver fibrosis and haematological features (reviewed in [68]), with age of onset and severity determined by telomere length. Although the exact pathophysiological mechanisms are not known, the loss of telomerase activity may contribute to pulmonary fibrosis through the suppression of fibroblast-to-myofibroblast differentiation [69] and through alveolar epithelial cell senescence limiting alveolar repair [60, 70]. Overall, syndromes of short telomeres represent archetypal premature ageing syndromes (as illustrated by premature hair greying or hair loss [68, 71, 72]) and are associated with pulmonary fibrosis and squamous cell cancers (especially of the skin, head and neck) [73].

Earlier diagnosis for earlier treatment of IPF

Whereas making an earlier diagnosis of IPF was not a priority in the absence of any effective drug therapy, it has become relevant since recent studies that demonstrated a reduction in the rate of decline of forced vital capacity using pirfenidone [74, 75] and nintedanib [76], with a further decrease in the risk of acute exacerbation of IPF for nintedanib [76].

Delayed diagnosis

With the exception of the few presenting with an acute exacerbation, patients with IPF usually follow a course of slowly progressive breathlessness and possible cough, which is underestimated for a long time by both the sedentary patient and the general practitioner.

The mean duration between first symptoms and referral to a tertiary care centre is >2 years, and is associated with a higher risk of death independent of disease severity [77]. Diagnosing IPF at an early stage is therefore an urgent challenge.

It is likely that some of the delay is due to less attention being paid to clinical examination over the last decades as a correlate to the increasing use of other efficient investigations. Both students and general physicians may further be spuriously discouraged from lung auscultation. The *British Medical Journal* recently published an article where the author wrote ''as a student I always agreed that I heard murmurs, crepitations, and rubs, even when I hadn't […] What I had been taught was highly unreliable […] basic auscultation may have value, but […] crepitation, and all other soft signs do not […] Definitive investigations should be organised on the basis of symptoms, irrespective of clinical findings'' [78]. We strongly disagree with such a provocative and dangerous statement regarding crepitations (crackles) that may contribute to further delay the diagnosis of IPF.

The value of Velcro crackles for early diagnosis

We consider that, presently, only two approaches could realistically allow an earlier diagnosis of IPF: 1) the assessment of Velcro crackles by lung auscultation [79]; and 2) screening using low-dose chest computed tomography.

The terminology of ''Velcro rale'' was coined in 1969 by the Mayo Clinic clinician Richard A. DeRemee [80], who found that ''the sound generated by tearing apart mated strips of Velcro adhesive, often used as fasteners on blood pressure cuffs, represents a striking reproduction of the rales of pulmonary fibrosis''. Anecdotally,

DeRemee later reported [81] the origin of the term Velcro (now a trade mark). The inventor of Velcro had noticed burrs caught in the beards of his goats when they came back from high-alpine Swiss pastures in the autumn. The hairs were soft as velvet and burdock (*Arctium lappa*) has little hooks when examined under the microscope, hence the word "vel-cro", from the French *velours* (velvet) and *crochet* (hook).

Crackles are almost constant in patients with IPF. Although found in other ILDs and not specific for IPF, Velcro crackles must prompt a thorough diagnostic process, including HRCT of the chest. Crackles may occasionally be heard in healthy individuals, especially elderly persons [82], individuals with congestive heart failure or those with bronchiectasis; however, only rarely are crackles in the latter conditions typical Velcro crackles. In most cases, older subjects with Velcro crackles are eventually diagnosed with IPF.

The early presence of crackles before patients are symptomatic and/or lung function is altered has also been reported in conditions where ILD may be expected to develop, namely asbestosis [83–85] and rheumatoid arthritis [86]. In the absence of honeycombing at HRCT, the diagnosis of IPF requires a lung biopsy [6]. This relatively invasive procedure may allow the diagnosis to be made before the disease is too advanced and lung function too altered for inclusion of the patient into clinical trials or consideration of specific IPF therapy. Therefore, we consider that lung auscultation remains a mandatory step in the diagnostic algorithm of any progressive dyspnoea or chronic dry cough, and contributes particularly to diagnosing IPF at an early stage, which is a prerequisite for earlier treatment and possible improvement of the long-term clinical outcome [79, 87, 88].

IPF screening as a by-product of cancer screening

Low-dose computed tomography of the chest was recently demonstrated to be effective for lung cancer screening [89]. Interestingly, low-dose computed tomography with a new computer-aided detection scheme may also detect early ILD [90]. Screening for ILD, especially UIP, has been analysed as a by-product in subjects (especially smokers) who underwent systematic low-dose computed tomography for lung cancer screening.

Interstitial changes were identified in 80 out of 3079 subjects screened for lung cancer, including seven with honeycombing and 14 with combined pulmonary fibrosis and emphysema [91]. In a cohort of 692 smokers included in a lung cancer screening trial, a UIP pattern or other chronic interstitial pneumonia patterns were identified by computed tomography in two and 26 patients, respectively [92]. In a large study of lung cancer screening, the opportunity to diagnose coronary calcification, which is highly predictive of cardiovascular events and overall mortality, has been mentioned as a by-product, yet surprisingly no reference to IPF was made [93]. In a subset cohort of the COPD-Gene study, the prevalence of a chest computed tomogram consistent with early ILD varied between 5% and 10%, with subjects with early ILD tending to have greater exposure to tobacco smoking than those without ILD [94]. The incidental finding of ILD at HRCT is also increasingly common [95], as is the identification of subclinical ILD in the setting of familial pulmonary fibrosis [87, 96], also contributing to the detection of IPF before subjects become symptomatic [79].

We thus consider that in terms of public health, ILD screening should be incorporated as a by-product of any lung cancer screening procedure warranted by a history of smoking.

Honeymoon before honeycombing

The current IPF guidelines [6] state that the diagnosis of IPF can be made without the need for lung biopsy in subjects with all four HRCT features of honeycombing (with or without traction bronchiectasis), subpleural, basal predominance, reticular abnormality, and absence of features inconsistent with UIP pattern [6].

Although honeycombing allows a confident diagnosis of IPF without biopsy, we nevertheless consider that it is unfortunately a sign of already advanced disease. Honeycombing at HRCT (*e.g.* typical UIP pattern at imaging) is indeed associated with an increased mortality rate as compared to patients with pathologic UIP but no honeycombing on HRCT [97, 98]. The development in the extent of honeycombing on serial computed tomography is associated with shorter survival [99]. We suspect that "waiting" for honeycombing to diagnose IPF when early nonspecific ILD is present at HRCT may be deleterious to patients who could have undergone a diagnostic lung biopsy earlier with limited risk and be treated before lung function is too impaired.

We suggest that a lung biopsy should be discussed during the "honeymoon" of early IPF, for example when crackles can already be heard at lung auscultation with only subtle subpleural reticulation at chest HRCT but lung function is normal or moderately impaired (subclinical ILD).

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Conclusion

The neglected evidence consists of facts or concepts based on substantial evidence that may be implicit for learned subspecialists but have not been explicitly formulated and made accessible to a wider audience. The latter was the objective of this perspective. Our final comment is that IPF is a misnomer, as it is mainly a consequence of smoking. A better future, neutral terminology could thus be usual pulmonary fibrosis (UPF), because IPF is not really idiopathic.

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