REVIEW

Idiopathic Pulmonary Fibrosis: Review of Current Knowledge

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Summary

Idiopathic pulmonary fibrosis (IPF) is a severe and currently incurable disease that is associated with irreversible fibrotic remodeling of the lung parenchyma. Pathological remodeling of the lung leads to damage of the alveolo-capillary barrier. There is a reduction in the diffusing capacity of the lungs for respiratory gases. Later, changes in the mechanical properties of lung tissue occur - their compliance decreases and respiratory work increases. Impaired respiratory gases exchange with restrictive ventilatory failure lead to tissue hypoxia and muscle weakness. Progressive respiratory insufficiency develops. The triggers of fibrotic remodeling of the lung are currently unknown, as are the pathomechanisms that keep this process active. IPF can only be slowed pharmacologically, not reversed. It is therefore very important to start its treatment as soon as possible. Early detection of IPF patients requires a multidisciplinary approach. Diagnosis, treatment initiation, and monitoring in specialized centers offer the best chance of slowing disease progression, enhancing quality of life, and extending patient survival. In addition to antifibrotic therapy, good lifestyle management, maintenance of physical fitness and treatment of associated chronic diseases such as diabetes and cardiac comorbidities are important. Lung transplantation is an option for some patients with IPF. This is a challenging treatment modality, requiring close collaboration with transplant centers and expert selection of suitable candidates, influenced, among other things, by the availability of suitable donor lungs. Our article aims to provide current information about IPF, focusing on its functional consequences and clinical manifestation. We discuss the molecular and cellular mechanisms potentially involved in IPF development, as well as the morphological changes observed in lung biopsies and high-resolution computed tomography (HRCT) images. Finally, we summarize the existing treatment options.

Key words

Idiopathic pulmonary fibrosis • Lung biopsy • HRCT • Antifibrotic therapy • Lung transplantation

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Introduction

IPF is a chronic lung disease associated with fibrous remodeling of the pulmonary interstitium. According to the American Lung Association, IPF is the most common form of idiopathic interstitial pneumonia and one of the most common interstitial lung diseases in general [1]. Globally, IPF affects approximately 5 million individuals, with around 200,000 in the United States. An estimated 110,000 people are affected in Europe [2]. In the Czech Republic, the incidence of IPF is estimated to 1/100,000 and the prevalence of IPF to 7/100 000 [3]. In the Slovak Republic, we estimate that there are

approximately 250 patients with IPF who have started antifibrotic therapy. In Slovakia there are seven pneumology centers authorized to indicate and monitor the treatment of patients with IPF. However, a unified registry is not yet established. We estimate that the incidence of IPF in Slovakia will be similar to that in the Czech Republic. The prevalence of IPF increases with age, with the majority of affected individuals being over 70 years of age. Men are more frequently affected.

Pathophysiology and clinical presentation of idiopathic pulmonary fibrosis

IPF primarily damages the alveolar-capillary barrier, leading to a concurrent restrictive ventilatory disorder. In patients with IPF, the initial manifestation often involves a respiratory gas exchange disorder between the lungs and the blood, quantifiable by assessing the reduced diffusing capacity of the lungs for carbon monoxide (DLCO). The proliferation of pulmonary interstitium and alterations in its physical properties, attributed partly to the substitution of elastin with collagen fibers, reduces lung compliance and increases the effort required for alveolar expansion [4,5]. Initially, an intrinsic restrictive ventilatory disorder develops, followed by progressive muscle weakness. Decreasing lung compliance and escalating muscle weakness diminishes both vital capacity and, subsequently, tidal volume. As the surface area available for respiratory gas exchange diminishes, the physiological dead space increases, leading to a rise in the ratio between physiological dead space and tidal volume (VD/VT) [6]. These factors lead to the development of progressive respiratory insufficiency. In the advanced stages of the disease, increasing resistance in the functional pulmonary circulation causes the development of pulmonary hypertension with subsequent secondary heart damage and the development of cor pulmonale [7].

The characteristic symptoms of IPF include cough, decreasing exercise tolerance, fatigue and escalating, sometimes immobilizing dyspnea [8]. During a physical examination, a distinct sound resembling Velcro opening is often audible upon inspiration over the basal regions of the affected lungs. This sound occurs in more than 80 % of all IPF patients, serving as an important factor in the early recognition of the disease. Additionally, patients often exhibit clubbed fingers. There exists a close correlation between the functional condition of the lungs and the quality of life, often translating to psychological distress and subsequent tendency towards depression [9].

The rate of progression of pulmonary dysfunction varies. In some cases, the disease progresses relatively slowly, while in others, it progresses rapidly and leads to the development of fatal respiratory insufficiency and death within a short period. In the periodic course of the disease, with alternating periods of relatively stable pulmonary function and periods of increasing pulmonary dysfunction, episodes of deteriorated respiratory function are referred to as acute exacerbations. Acute exacerbations generally require patient hospitalization and are associated with high mortality. The median survival in acute exacerbation is reported to be 3–4 months [10]. In patients with a stable course of the disease, without antifibrotic treatment and lung transplantation, the median survival ranges between 3-4 years. Overall, the median survival after the diagnosis of IPF is reported to be between 2–5 years [11].

Etiology of idiopathic pulmonary fibrosis

The cause of IPF is unknown. The factors triggering the disease could include those causing chronic or recurrent microtraumas to the alveolar epithelium. Factors such as cigarette smoke, wood dust, metals, biological pollutants such as feces or infectious agents such as viruses are of concern [12]. An increased risk of IPF has been reported in patients with obstructive sleep apnea and in patients with diabetes mellitus [13,14].

Diabetes mellitus is an independent risk factor in the development of this disease. Several studies indicate a potential relationship between advanced glycation-end products (AGEs) and IPF. Increased accumulation of AGEs has been demonstrated in alveolar macrophages of patients with IPF, and inhibition of their formation in an animal model reduces the risk of pulmonary fibrosis.

Among viral pathogens, hepatitis C virus (HCV), adenoviruses, TT virus, and herpes viruses are at the forefront. IPF-like disease even occurs in some rare genetic conditions. Syndromes featuring short telomeres are often associated with pulmonary fibrosis. Familial forms of idiopathic pulmonary fibrosis manifest at a younger age [15].

IPF is considered a disease limited to the lung, but its risk factors are shared with a number of comorbidities (e.g., cardiovascular and degenerative diseases), that may play an important role in the course of the disease of patients with IPF [16].

Pathogenesis of idiopathic pulmonary fibrosis

Microtraumas to the alveolar epithelium result in aberrant activation and damage to cell populations within the pulmonary interstitium. This leads to modifications in the physiological interactions among endothelial cells, fibroblasts, and resident lung macrophages. Consequently, changes in the concentrations of chemokines, cytokines, and growth factors occur within the tissue microenvironment [17].

Molecular factors in IPF

Changes in cytokine and chemokine concentrations in bronchoalveolar lavage fluid (BALF) and tissue samples of patients with idiopathic pulmonary fibrosis suggest the potential profibrotic role of several of these molecules. The most significant molecules that likely play a role in the tissue microenvironment of developing fibrosis include TGF-β, IGF-1, PDGF, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, M-CSF, PGE2, HGF, HDGF, EGF, TGF-α, and many more [18].

TGF-β potentiates extracellular matrix formation and deposition, affecting inflammatory cell distribution and mesenchymal cell differentiation. In humans with IPF, elevated concentrations of TGF-β were observed in bronchoalveolar lavage fluid, and overexpression of the TGF-β gene has been demonstrated in pulmonary fibroblasts, alveolar and bronchial epithelial cells, as well as alveolar macrophages. In lung biopsies of IPF patients, increased concentrations of insulin-like growth factor-1 (IGF-1), mainly produced by macrophages, lymphocytes and epithelial cells, have been reported. IGF-1 modulates cell migration and differentiation, epithelial regeneration, stimulates collagen synthesis by fibroblasts and inhibits apoptosis. PDGF is involved in the regulation of angiogenesis and has been detected in elevated concentrations in both bronchoalveolar lavage fluid and lung tissue samples in IPF. Elevated concentrations of TNF-α have been observed in a rat pulmonary fibrosis model. IL-1β is a pro-inflammatory cytokine and potentiates the differentiation of fibroblasts to myofibroblasts and extracellular matrix production, and increases the concentration of IL-6, TNF-α, TGF-β or PDGF in lung tissue. IL-6 has ambivalent effects in an animal model, suppressing fibroblast proliferation in healthy lung tissue and stimulating fibroblast proliferation in the pulmonary fibrosis environment. PGE2 is a regulator of fibroblast proliferation and differentiation. There are contradictory statements in the literature regarding its role in IPF. Some authors report increased concentrations of PGE2 in bronchoalveolar lavage fluid of IPF patients. However, some observations demonstrate that fibroblasts isolated from the lungs of IPF patients produce PGE2 to a lesser extent compared to healthy control groups after stimulation (e.g. with IL-1β, LPS and TGF-β) [19,20]. Another important substance is adenosine. The development of adenosine A2B receptor antagonists represent a possible starting point for the pharmacotherapy of IPF [21].

In IPF patients, increased concentrations of both M-CSF and CCL2 were found in bronchoalveolar lavage fluid. In an experimental model, mice with knockout mutations for M-CSF and CCL2 exhibited less intense lung fibrosis. Molecules affecting monocyte differentiation and migration, therefore, also play an important role in the development of fibrosis [22].

Protein glycation, oxidative stress, mitochondrial dysfunction and endoplasmic reticulum stress in IPF

Chronically elevated blood glucose levels lead to protein glycation. RAGE (Receptor for Advanced Glycation Endproducts) has a protective role, and its reduced expression is associated with the development of pulmonary fibrosis.

Oxidative stress increases the formation of reactive oxygen species (ROS). ROS stimulate epithelial cell apoptosis, suppress fibroblast apoptosis, and potentiate myofibroblast differentiation and extracellular matrix deposition. Oxidative stress by NF-kB activation leads to inflammation associated with activation and recruitment of immunocytes such as macrophages and T-cells. Inflammatory cells stimulate further production of free radicals, including hydroxyl radicals and superoxide radicals, leading to depletion of antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione. The use of antioxidants in IPF treatment is the subject of intense research [23]. The rise in ROS is a crucial consequence of mitochondrial dysfunction. Disorders in mitochondrial quality control (MQC) likely contribute significantly to the development of IPF [24,25]. Several metabolic disorders were observed in pneumocytes in fibrotic lung tissue. The modifications in lipid metabolism and impaired phospholipid and cholesterol synthesis translate into pulmonary surfactant synthesis disorder and subsequent damage to the alveolar epithelium. Endoplasmic reticulum damage alters protein synthesis and metabolism, referred to as endoplasmic

reticulum stress (ERS). The unfolded protein response (UPR) failure leads to the formation of defective proteins, a reduction in chaperone production and changes in the activity of the ubiquitin-proteasome system. Defective proteins activate the Bcl-2 signaling pathway, leading to programmed cell death [26]. An example of impaired endoplasmic reticulum function and proteosynthesis control is the formation of defective surfactant proteins SFTPA2 and SFTPC, which cannot be adequately secerned by a cell. Non-functional proteins accumulate in the cytoplasm of secretory pneumocytes, causing damage to these cells and destruction of alveolar epithelium [27].

Cell populations significant in the development of IPF

In the pathogenesis of IPF, cell populations that come to the forefront include fibroblasts, myofibroblasts, and alveolar epithelial cells – particularly secretory pneumocytes, endothelial cells and macrophages. Fibroblasts are considered effector cells of fibrogenesis. Dysfunction of secretory pneumocytes and alveolar epithelium is likely an initial change in the development of pulmonary fibrosis [28]. Mutations in genes specific to these cells are frequent in human interstitial pulmonary fibrosis. Type II alveolar epithelial hyperplasia is often observed near honeycomb areas, and these cells are also found in fibroblastic foci [29]. Macrophages are significant producers of biologically active molecules, the extensive effects of which have been described above. In addition, macrophages induce IL-1β, CCL18-mediated exacerbation of fibrosis. Fibrosis is also affected by macrophage metalloproteinases (MMPs), both in terms of suppression and stimulation [30,31]. The ambivalent behavior of macrophages in pulmonary fibrosis models is likely a consequence of the extreme phenotypic plasticity of these cells.

Tissue transitions, progenitor cell recruitment and changes in physical properties of the parenchyma in IPF

Epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndMT) are important mechanisms for mesenchymal cell proliferation and fibroblast foci formation. Tissue transitions are potentiated by cytokines and growth factors produced by inflammatory cells, such as macrophages, neutrophils, or eosinophils. The formation of fibroblastic foci in lung parenchyma damages capillaries, the alveolocapillary barrier and interalveolar septa [32,33]. In addition to tissue transitions, the recruitment of progenitor cells (circulating fibrocytes) from the bone marrow may play a role in the mesenchymal cell proliferation in the lung interstitium. Later, excessive stiffness of the lung interstitium itself is involved in signal transduction potentiating mesenchymal cell activity [34].

Genetic factors and cellular ageing in IPF

The significance of genetic factors in IPF is evidenced, for example, by the existence of its familial form or by the presence of IPF-like disease in the clinical picture of some rare genetic diseases. Genetic factors, for example, pulmonary surfactant production and metabolism disorders or genetically determined disorders of apoptosis induction and regulation are of concern [35,36]. Cellular and organism ageing also play asignificant role. The increased incidence of IPF associated with population ageing is reported by several authors. Ageing is linked to cell cycle control and division disorders, as well as with the accumulation of harmful environment influences (Fig. 1). Cells change their phenotype and secretome with age, referred to as SPRA (secretory phenotype related to ageing). In an animal model of pulmonary fibrosis, regression of fibrotic changes was achieved after the eradication of type II pneumocytes (AECs II) using a senolytic agent – navitoclax (ABT-263) [37].

Association of idiopathic pulmonary fibrosis with other diseases

Only about 10 % of patients with IPF have no comorbidities. Conversely, up to 60 % of patients have one to three associated comorbidities and around 30 % have more than three associated diseases [38]. The co-occurrence of IPF with other diseases significantly affects the quality of life and survival of affected individuals, and highlights possible common exogenous risk factors as well as genetic predisposition factors for IPF with these diseases.

The most important comorbidities coexisting with IPF include atherosclerosis and associated coronary artery disease, congestive heart failure, increased susceptibility to venous thrombosis and pulmonary embolism, osteoporosis, diabetes mellitus, hypothyroidism, pulmonary emphysema, pulmonary hypertension, lung cancer, GERD, obstructive sleep apnea, nutritional disorders, sarcopenia, and others.

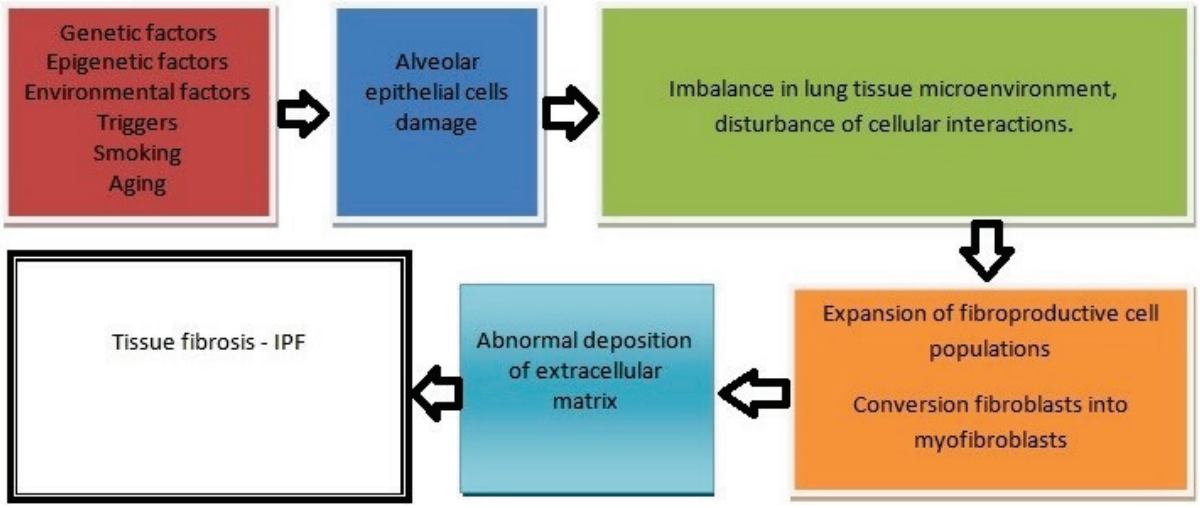

Fig. 1. Pathogenesis of idiopathic pulmonary fibrosis

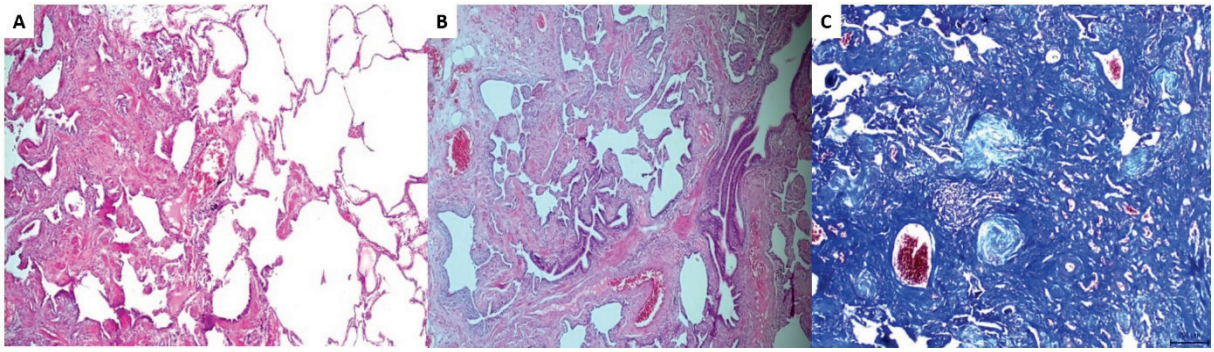

Fig. 2. Usual interstitial pneumonia (hematoxylin-eosin (**A**, **B**) and Masson trichrome (**C**), 50x) with evident heterogenity in the distribution of pathological changes, as well as areas of fibrosis at different maturity levels and with multiple fibroblastic foci. Department of Histology and Embryology, Faculty of Medicine, University of Ostrava, Ostrava

Diagnosis of idiopathic pulmonary fibrosis

Early diagnosis of IPF is crucial for the prompt initiation of treatment. However, it is challenging because the disease is idiopathic, and its manifestations are non-specific. In most patients, a period of more than a year with non-specific symptoms precedes the correct diagnosis. Establishing an IPF diagnosis requires, from the outset, the exclusion of other diseases associated with interstitial pulmonary fibrosis.

IPF, as a disease (nosological entity), is characterized, though not unequivocally defined, by a histological and HRCT pattern compatible with this condition. The histological pattern compatible with IPF is the microscopic image of usual interstitial pneumonia (UIP). However, these terms are not equal. IPF is a disease, and UIP is a microscopic pattern characterized by defined attributes. The UIP pattern can also be found in other diseases, such as non-specific interstitial pneumonia (NSIP), fibrotic hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease (CTD-ILD) or even sarcoidosis [39]. The UIP pattern also occurs in some cases of toxic lung damage. In terms of severity, however, the association of the UIP pattern with IPF stands out. Similarly, this applies to the HRCT pattern of UIP, which can also be found in other interstitial lung diseases. On the other hand, in IPF alone, the HRCT pattern may not have all the characteristic attributes.

Histological pattern compatible with idiopathic pulmonary fibrosis = microscopic UIP image

The fundamental attributes of UIP include the distribution of fibrosis and its spatial and temporal heterogeneity (Fig. 2). Often, there is a sharp demarcation between areas of advanced fibrosis and healthy lung tissue. Fibrosis typically develops in subpleural and paraseptal areas. The process begins in the periphery of secondary lung lobules and progresses centrally, especially along veins running in the interstitium between

these lobules (perivenular localization of fibrosis). Spatial heterogeneity represents the alternation of areas of fibrosis with regions of intact lung tissue. Different intensities and degrees of fibrosis maturity signify temporal heterogeneity.

In the UIP image, the presence of fibroblastic foci is crucial. These lesions consist of fibroblasts and myofibroblasts and are covered by type II pneumocytes or metaplastic squamous epithelium. Collagen deposits are present in their proximity. Fibroblastic foci (Fig. 3) are observed more frequently at the interface between advanced fibrosis and intact lung tissue. Fibroblastic foci also occur in other fibrotic interstitial lung processes, but they tend to be more numerous in IPF, and their density correlates with the severity of functional lung impairment [40,41].

An important feature of UIP is the absence of signs contradicting this pattern, such as hyaline membranes, areas of organizing pneumonia, active inflammation, and the like.

During the progression of abnormal lung parenchyma remodeling, septa between the alveoli and the lung lobules thicken. Numerous cystic airspaces are formed, bordered by fibrous walls and surrounded by areas with completely suppressed normal lung tissue architecture. This is referred to as the "honeycombing" pattern.

The honeycombing pattern is an essential component of the microscopic UIP pattern in idiopathic pulmonary fibrosis, but it is non-specific and other lung diseases can lead to its formation.

Radiological pattern compatible with idiopathic pulmonary fibrosis = HRCT image of UIP

High-resolution computed tomography (HRCT) is a fundamental imaging examination in the diagnostic algorithm for IPF. The "HRCT image of UIP" is indicative of idiopathic pulmonary fibrosis in HRCT examination. The unequivocal attributes of the HRCT image of UIP are: 1) honeycombing, 2) traction bronchiectasis, 3) present but not predominant ground-glass opacity (GGO) areas, 4) reticular abnormalities, 5) subpleural basal predominance of pathological changes, and 6) absence of signs inconsistent with the UIP pattern (Fig. 4).

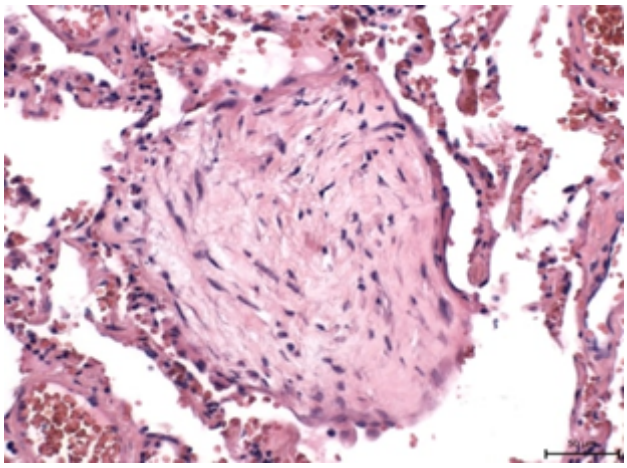

Fig. 3. Fibroblastic focus (hematoxylin-eosin, 200x), Department of Histology and Embryology, Faculty of Medicine, University of Ostrava, Ostrava.

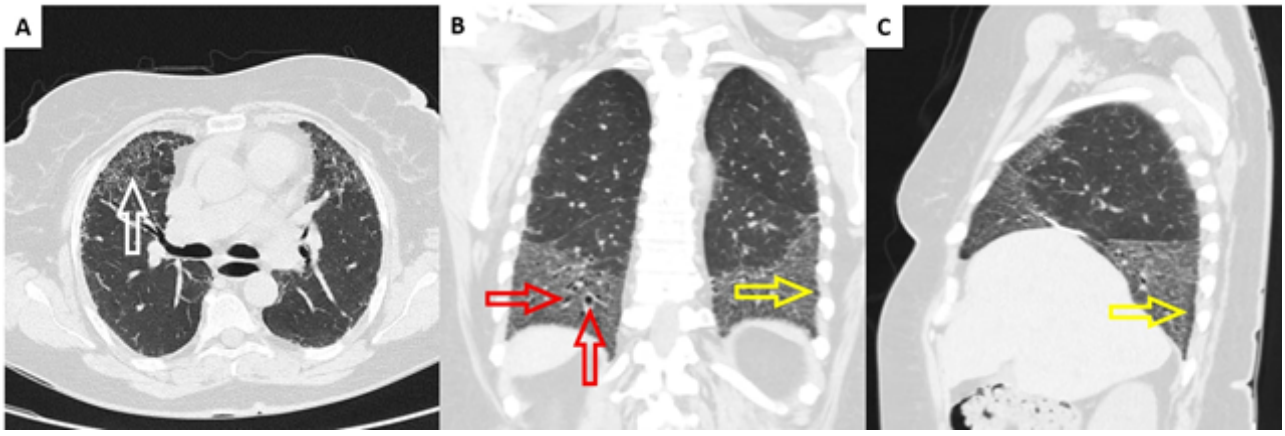

Fig. 4. HRCT of the lungs in a patient diagnosed with IPF with virtually all the attributes of the unequivocal HRCT image of UIP referred to in the text. (**A**) HRCT of pulmonary fibrosis demonstrating reticular opacities (white arrow) and predominant subpleural distribution. (**B** and **C**) demonstrate a basal predominance of fibrotic changes with traction bronchiectasis (red arrows) and honeycombing (yellow arrow). Department of Radiodiagnostics, National Institute for Tuberculosis, Lung Diseases and Thoracic Surgery in Vyšné Hágy, Slovakia.

If attribute 1 – honeycombing is absent in the evaluated HRCT examination, and all other attributes (2 to 6) are present, we speak of probable UIP. In the absence of the first two attributes, 1– honeycombing and 2 – traction bronchiectasis, and the concurrent presence of the remaining four attributes (3 to 6), we speak of a pattern indeterminate for UIP. The features inconsistent with IPF include predominance of pathological changes in the upper and middle lung regions, peribronchovascular distribution of changes, extensive areas of ground-glass opacity (GGO) – prevailing over reticular abnormalities, abundant nodular abnormalities, discrete cystic/cystoid changes localized outside the honeycombing areas (multiple, bilateral), diffuse areas of air-trapping, or consolidation in bronchopulmonary segments [42]. Also in HRCT imaging, honeycombing pattern emerges in an advanced stage of the disease. This pattern is characterized by clusters of cystic/cystoid air-filled spaces up to 1 cm in size, delimited by well-defined walls.

In dubious cases, when interpreting the HRCT, it is necessary to provide a differential diagnosis of the observed pattern with an expression of the probability of each relevant nosological entity.

Treatment of idiopathic pulmonary fibrosis

An essential part of the strategy to slow down pulmonary dysfunction is maintaining physical fitness, ensuring sufficient physical activity, and adopting adequate nutrition. For patients with significant respiratory insufficiency, home and portable oxygen therapy is available.

The optimal management of patients with IPF involves adequate treatment of comorbidities, particularly focusing on pulmonary comorbidities such as obstructive sleep apnoea, pulmonary hypertension, and similar conditions.

Currently, the process of fibrosis in the pulmonary interstitium in IPF can be affected by medication only to a limited extent. Antifibrotic drugs such as nintedanib and pirfenidone are used in pharmacotherapy. They slow down the deterioration of lung function, reduce the risk of disease exacerbations and prolong survival. Nintedanib is a small-molecule inhibitor of receptor tyrosine kinases of several growth factors. It inhibits the effect of PDGFRα, PDGFRβ, FGFR1, FGFR2, FGFR3 and VEGFR stimulation. Nintedanib restricts the fibroblast migration and proliferation [43]. Pirfenidone inhibits the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 and potentiates the production of anti-inflammatory cytokines such as IL-10, along with the anti-fibrotic effect of IFN-γ. In addition, pirfenidone inhibits the TGF-β production, suppressing fibroblast proliferation and extracellular matrix production [44,45]. However, the effect of both drugs is limited. IPF represents an obligatory irreversible disease that leads to fatal respiratory insufficiency with progressive deterioration of respiratory gas exchange.

Experimentally, there is evidence for an anti-fibrotic effect of thalidomide against bleomycin-induced lung fibrosis in mice, where this drug suppressed IL-6 and TGB-β-potentiated collagen deposition in the lung interstitium. Thalidomide also suppresses TGF-β1-mediated epithelial-mesenchymal transition in tissue cultures of rat lung epithelia CCL-149. Its protective effect against the development of lung emphysema in mice exposed to cigarette smoke is also documented. The antitussive effect of thalidomide in patients with IPF was also investigated and demonstrated a benefit of this drug, but ultimately thalidomide was not recommended as a drug suitable for cough control in patients with IPF. Later, the investigation of the possible effect of thalidomide was not pursued further, probably also because of the historically known bad experience with this drug [46].

Immunosuppressants such as cyclophosphamide and mycophenolate have shown no benefit in IPF clinical trials and are currently considered inappropriate for IPF, while steroids are still used in the acute exacerbation stage of IPF.

Once the indication criteria are met, lung transplantation is possible for patients with idiopathic pulmonary fibrosis. The number of patients transplanted for IPF is increasing year by year, but waiting times are still relatively long. The average survival time after lung transplantation is 4 to 6 years, with approximately 80 % of patients surviving the first year post-transplantation [47,48]. Overall 5-year survival after transplantation is approximately 50 %. Lung transplant may be either unilateral or bilateral. Benefits of unilateral transplant are the shorter wait times, easier procedure with lower perioperative complication rate, and the potential to improve the health of two patients from one donor. Potentially better survival is seen in patients after bilateral lung transplantation, which is favored by certain institutions. A recent meta-analysis found no survival

advantage with bilateral lung transplant but did document better pulmonary function [49].

One potential starting point in the treatment of IPF is the use of mesenchymal stem cells (MSC). In the AETHER trial, bone marrow-derived MSCs were administered intravenously to patients with rapidly progressive IPF who were not taking antifibrotic drugs. The study demonstrated promising results, safety and tolerability of this treatment [50,51]. Another study, Human Autologous Lung Stem Cell Transplant for IPF (HALT-IPF) (NCT04262167), is currently ongoing.

Currently, the possibilities of treatment of IPF using human recombinant pentraxin PRM-151, as well as human recombinant antibodies against connective tissue growth factor (CTGF) - Pamrevlumab, Autotaxin (ATX) or Galectin-3 are being investigated.

Conclusion

IPF is a severe and rapidly progressing interstitial lung disease associated with the development of fatal respiratory insufficiency. Both the etiology and pathogenesis of this disease are complex and still poorly understood. In this article, we highlight several molecules, growth factors, cellular organelle dysfunctions, as well as cellular interactions and tissue transitions that likely play a crucial role in the development of IPF. Phenotypic changes in cells play a crucial role in the development of this disease. It is worth mentioning the IPF Cell Atlas, which aims to make available single-cell sequencing data from multiple cell types present in the lung with the possibility to compare the transcriptomes of control and IPF cells. It has also led to the description of aberrant basaloid cells, which are thought to be key in the pathogenesis of IPF but also other fibrotic lung diseases and which could be promising therapeutic targets.

The initially subtle and non-specific clinical manifestations of IPF often complicate and delay the correct diagnosis. Diagnosing and managing patients with IPF necessitate concentrated attention in specialized healthcare centers, promoting close and flexible cooperation among pulmonologists and radiologists. Collaboration with thoracic surgeons and pathologists may also be necessary in many cases. Pharmacological intervention in the disease is limited, and despite significant progress, lung transplantation remains a challenging process associated with waiting times that limit accessibility for a large group of IPF patients.

Given these facts, it is essential to deliberately consider IPF in patients with interstitial lung disease, centralizing their care, and focusing on maximizing achievable benefits through accurate diagnosis and treatment.

Our article aims to provide the basic information about IPF, emphasizing morphological changes in histological and HRCT images that are characteristic of the disease. Given the serious consequences and limited management options, we consider IPF an important target for research.

Publication ethics

The photographs of human materials and human tissues used in the study were obtained in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki Declaration, revised in 2013. Informed consent was obtained from all individual participants included in the study. Patients provided signed informed consent for the publication of their data and photographs.

Conflict of Interest

There is no conflict of interest.

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