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Modern Concepts of Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic pulmonary fibrosis is a pathological process in the lungs characterized by refractory to therapy and high mortality rates, it is a heterogeneous group of disorders with progressive and irreversible destruction of the lung architectonics due to scarring, which ultimately leads to organ dysfunction, gas exchange disorders and death due to respiratory failure [D.V. Bestaev, 2014]. The article presents a review of the literature on modern concepts of idiopathic pulmonary fibrosis.

Keywords: pulmonary fibrosis, etiology, pneumonia, review.

Relevance. Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic lung disease characterized by progressive fibrosis of the lung tissue, an irreversible decline in lung function, and a fatal prognosis [1]. IPF is the most common form of idiopathic interstitial pneumonia (IIP). According to modern registries, IPF accounts for about 17–37% of all interstitial lung diseases (ILDs) [2, 3]. The prevalence of IPF varies from country to country, but is increasing in most cases. According to a study [4], conducted in the UK, the prevalence of IPF is 7.4 cases per 100,000 in 1 year. When analyzing these data, it can be noted that the prevalence and incidence of IPF is higher in men, these figures increase with increasing age, especially after 75 years. According to estimates based on the results of a survey conducted in large

Russian pulmonology centers, the prevalence of IPF in the Russian Federation is about 9–11 cases per 100,000 population [5]. IPF is a heterogeneous disease with varying individual rates of progression, but the prognosis is generally poor in patients with IPF, and 5-year survival is often worse than for many malignant tumors [6]. In order to improve the outcomes of IPF treatment and optimize costs, several international and national clinical guidelines have been developed, the main purpose of which is to offer the doctor the most rational strategy for managing a patient in a particular clinical situation, taking into account the current level of medical knowledge [1, 7–9]. The first clinical guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) Society for the diagnosis and management of patients with IPF appeared in 2000 [7]. ILF was defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring mainly in the elderly and limited to the lungs [7]. In 2011, the Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT) societies joined the collaboration in the development of clinical practice guidelines for the diagnosis and treatment of IPF for ATS and ERS [8]. This evidence-based guideline provides diagnostic criteria for IPF based on radiological and histological findings, but shows that diagnostic criteria (2011) have serious limitations in clinical practice. New ATS, ERS, JRS and ALAT recommendations (2018) are the result of a revision of diagnostic guidelines (2011) [9]. This guideline is intended to assist physicians in making an accurate diagnosis of IPF and to support the implementation of the recommended course of action in the context of the patient's individual values and preferences, especially when deciding whether to proceed with the intended scope of diagnostic interventions.

Idiopathic pulmonary fibrosis (IPF) occupies an important place in the structure of interstitial lung diseases, which mainly occurs in middle-aged and elderly people [2]. Although the literature describes a case of IPF development in a 14-year-old girl [13]. IPF is a specific form of chronic fibrosing interstitial pneumonia [2]. The etiology of the disease has not been fully elucidated. However, many studies have shown an association of IPF with smoking, exposure to organic and inorganic dusts, infectious agents (Epstein-Barr virus, hepatitis), pharmacological therapy, type 2 diabetes mellitus (DM), gastroesophageal reflux disease, etc. [2,3] COVID-19 (COronaVIrus Disease 2019) may be contributing factors to the development of pulmonary fibrosis. At the end of 2019, cases of SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus 2) were first reported in Wuhan, Hubei Province, in central China. In a review study, Ilchenko L.Yu., Nikitina I.G. and Fedorova I.G. published in the journal "Archive of Internal Medicine", outlines the key points of the pathogenesis of COVID-19 [7]. Thus, SARS-CoV-2, infecting the vascular endothelium, interacts with the ACE2 receptor (angiotensin-converting enzyme 2), which is accompanied by the development of endothelial dysfunction, increased permeability, impaired microcirculation, development of vascular thrombophilia, and thrombosis [7,16]. Further progression of COVID-19 leads to diffuse alveolar damage with the formation of hyaline membranes and the development of pulmonary edema [7]. As the authors note, the histological picture of the lungs at autopsy is characterized by the organization of alveolar exudates and interstitial fibrosis, the formation of hyaline membranes, the presence of interstitial mononuclear inflammatory infiltrates, numerous fibrin microthrombi, severe edema, hyperplasia, and focal loss of type II alveolocytes with a significant content of macrophages with viral inclusions in alveolar exudate [7]. It is obvious that the lungs are the central organ affected by the negative effects of coronavirus, and a pronounced violation of the ventilation function of the lungs, as a rule, becomes the direct cause of fatal complications. On the other hand, post-covid changes in the structure of the lung tissue, late restoration of the alveolar epithelium in the form of impaired regeneration and microtraumatization, especially among people over 50 years of age, increases the risk of pulmonary fibrosis several times. In recent years, the hypothesis of the development of fibrosis in the lung tissue, as a result of a violation of the function and repair of the alveolar epithelium as a result of damage by an unknown agent, accompanied by the migration of myofibroblasts, as well as the loss of the regenerative capacity of the alveolar tissue, is recognized by all researchers [1,4,9,12]. A local increase in the number of myofibroblasts leads to an increased synthesis of extracellular matrix components and their deposition in the lung tissue. Slowly progressive dyspnea on exertion (at the onset of the disease), then at rest, nonproductive cough, bilateral inspiratory crepitus, drumsticks, weakness, fatigue, and weight loss in middle-aged and elderly patients should alert the physician to IPF [2,4,6]. The most important conditions for the diagnosis of IPF are clinical, radiological and morphological studies. High-resolution computed tomography determines the diagnostic accuracy of IPF. According to the literature data, the life expectancy of patients with IPF from the moment of diagnosis is 2–3 years, and the 5-year survival rate does not exceed 50% [2,15]. It is assumed that the survival of patients with IPF is worse than with many malignant tumors [6]. It is known that the therapeutic efficacy of anti-inflammatory and immunosuppressive therapy in IPF is low. In real clinical practice, in most cases, the treatment of IPF is symptomatic, less often pathogenetic [14]. The discovery of the pathogenetic mechanisms of the occurrence of fibrosis in the lung tissue and antifibrotic therapy remains the cornerstone of modern medicine. Non-drug therapy for IPF includes pulmonary rehabilitation, low-flow oxygen therapy, mechanical ventilation in severe respiratory failure, and lung transplantation [11]. According to the researchers, the use of glucocorticosteroids, as well as immunosuppressants in IPF, does not yet have a sufficient evidence base [3]. Meanwhile, in clinical practice, with the development of respiratory failure, or with exacerbation of IPF, glucocorticosteroid therapy comes to the fore. It is interesting to note that in real practice, 50-60% of patients diagnosed with IPF do not receive treatment immediately due to the late verification of the diagnosis of this formidable disease.

IPF is a specific form of chronic progressive fibrosing interstitial pneumonia of unknown etiology. The disease occurs predominantly in humans older age, affects only the lungs and is characterized by the morphological and / or radiological pattern of ordinary interstitial pneumonia (OIP). This disease should be considered in all adult patients with unexplained chronic dyspnea on exertion, cough, bilateral inspiratory crepitus in the basal parts of the lungs and / or deformity of the nail phalanges of the fingers in the form of "drumsticks" in the absence of congenital diseases and other symptoms of multiple organ damage. The incidence of IPF increases with age and is manifested by gradually increasing dyspnea in the 6th and 7th decades of life [11, 12]. Rarely, the first manifestation of IPF is an exacerbation with an inexplicable increase in dyspnea over several weeks and the appearance of new areas of "ground glass" against the background of fibrous changes in the lower parts of the lungs during high-resolution computed tomography (HRCT) [13]. In people younger than 50 years, IPF is rare; this age is typical for patients who subsequently develop signs of systemic connective tissue disease (CCTD), which had a subclinical course at the time of diagnosis of IPF [14], or for patients with familial IPF [15]. In men, IPF is diagnosed more often than in women; most patients are ex-smokers [16]. Other risk factors for IPF include gastroesophageal reflux [17–20], chronic viral infections such as Epstein-Barr virus [2–9], hepatitis C [3–6], and a family history of ILD. Many patients with IPF also have other comorbidities such as emphysema (combination of pulmonary fibrosis and pulmonary emphysema), lung cancer, pulmonary hypertension, sleep apnea, and coronary heart disease [7]. In some genetic forms, extrapulmonary manifestations are possible - bone marrow failure and liver disease [8, 9]. In some patients, blood relatives also suffer from IPF. At least 30% of patients with sporadic or familial cases of pulmonary fibrosis have genetic predisposing factors that increase the risk of pulmonary fibrosis [10–12]. However, known genetic factors associated with telomeres and telomerase may also occur in other ILDs [13–16].

Pathological features of the pattern of common interstitial pneumonia

A distinctive morphological feature and the main diagnostic criterion for AIP are areas of dense fibrosis, which are visible at low magnification, and also: • cause remodeling of the lung architectonics; • often lead to the formation of a "honeycomb lung"; • alternates with areas of less affected lung parenchyma. These morphological changes are usually most pronounced in the subpleural and paraseptal areas of the lung parenchyma. Inflammation is usually minimal and is a mosaic interstitial infiltration of lymphocytes and plasma cells in combination with hyperplasia of type 2 alveolocytes and bronchiolar epithelium. Areas of fibrosis consist mainly of dense collagen with diffuse subepithelial rounded foci with proliferating fibroblasts and myofibroblasts (so-called fibroblastic foci). Microscopically, the "honeycomb lung" is a cystic-fibrous area, often lined with bronchiolar epithelium and filled with mucus and inflammatory cells. In areas of fibrosis and "honeycomb lung" metaplasia of the smooth muscles of the interstitium is usually observed. Morphological diagnosis

AIP is considered confirmed if all of the features described are present, especially honeycombing. However, a definite diagnosis of AIP can be made even in the absence of a "honeycomb" if all other features are present. Characteristic morphological features can help rule out alternative diagnoses such as hypersensitivity pneumonitis (bronchiolocentric distribution of changes with marked lymphocytic bronchiolitis, severe peribronchiolar metaplasia, ill-defined nonnecrotizing granulomas in the peribronchiolar interstitium), exacerbation of IPF or acute interstitial pneumonia (hyaline membranes), cicatricial variants of cryptogenic organizing pneumonia (COP) with fibrosis (severe organizing pneumonia), pneumoconiosis (asbestos bodies, prominent dust accumulations and/or silicotic nodules), sarcoidosis (well-circumscribed non-necrotizing granulomas with perilymphatic distribution), interstitial fibrosis associated with smoking (common respiratory bronchiolitis (RB) and exclusively subpleural and/or peribronchiolar lean-cell dense eosinophilic collagen without disturbances in lung architectonics), and pleuroparenchymal fibroelastosis (pronounced subpleural intraalveolar fibrosis, elastosis and fibrosis of the visceral pleura, most pronounced in the upper lobes). The specificity of these features varies and depends on a putative alternative diagnosis, which

requires clarification in multidisciplinary discussion in conjunction with clinical, laboratory and radiographic findings, to an alternative diagnosis established with high probability.

Experts recommend subdividing the morphological patterns in IPF into AIP, probable AIP, indeterminate AIP, and an alternative diagnosis. The advantage of this approach is that the terminology is consistent with CT patterns (although the specificity of the alternative diagnosis will vary) and facilitates multidisciplinary discussion in the context of clinical data. This approach facilitates the definitive diagnosis, whether IPF is confirmed or not. In indeterminate AIP, biopsy specimens show a pattern of fibrosis that does not match either AIP or other fibrotic interstitial pneumonias, and in some cases may show signs of an alternative disease, while the possibility of technical defects in obtaining a biopsy in a patient who is ultimately confirmed by the diagnosis cannot be ruled out. ILF. In some patients with an asymptomatic course of IPF, the disease can manifest with an exacerbation, in which the patterns of AIP and diffuse alveolar damage are usually combined with the presence or absence of hyaline membranes.

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