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A clinical case of idiopathic pulmonary fibrosis against the background of comorbid pathology

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is one of the most common diseases in the group of interstitial lung diseases, which is characterized by persistent progression and poor prognosis. Over the past decade, experts have made significant progress in developing a diagnostic algorithm for IPF patients. This algorithm includes analysis of clinical, laboratory, and instrumental data, primarily the results of high-resolution computed tomography (HRCT). Precise adherence to the diagnostic algorithm and correct interpretation of HRCT data are prerequisites for IPF diagnosis.

Specialists of the Tomsk region have developed routing of patients with suspected IPF. The presented clinical case is a successful example of adhering to this algorithm. Wide implementation of modern diagnostic algorithms into diagnosis and treatment of IPF and quality improvement of imaging methods, primarily HRCT, carried out as a part of the differential diagnosis, open up prospects for early diagnosis of this pathology. A timely prescribed antifibrotic therapy (nintedanib, pirfenidone) in IPF allows to slow down pathological progression and improves the prognosis.

Key words: idiopathic pulmonary fibrosis, usual interstitial pneumonia, nintedanib, antifibrotic therapy, treatment.

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Клинический случай идиопатического легочного фиброза на фоне коморбидной патологии

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РЕЗЮМЕ

Идиопатический легочный фиброз (ИЛФ) относится к наиболее распространенным заболеваниям из группы интерстициальных заболеваний легких и характеризуется неуклонным прогрессированием и неблагоприятным прогнозом. В течение последнего десятилетия был достигнут значительный прогресс в разработке диагностического алгоритма для пациентов с ИЛФ, предполагающий анализ клинических, лабораторных и инструментальных данных, прежде всего, результатов компьютерной томографии высокого разрешения (КТВР). Точное следование алгоритму диагностики и правильная интерпретация данных КТВР являются необходимым условием для постановки диагноза ИЛФ.

В Томской области разработана маршрутизация больных с подозрением на ИЛФ. Примером успешного следования этому алгоритму является представленный клинический случай. Широкое внедрение в лечебно-диагностический процесс современных алгоритмов диагностики ИЛФ и повышение качества визуализационных методов, прежде всего КТВР, проводимые в рамках дифференциального диагноза, открывают перспективы ранней диагностики данного патологического процесса, а своевременно назначенная антифибротическая терапия (нинтеданиб, пирфенидон) при ИЛФ позволяет замедлить прогрессирование патологического процесса и улучшить прогноз.

Ключевые слова: идиопатический легочный фиброз, обычная интерстициальная пневмония, нинтеданиб, антифиброзная терапия, лечение.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

According to current data, interstitial lung disease (ILD) makes up 20% of all lung diseases. Common features of ILD are progressive shortness of breath, restrictive lung disease, and diffuse bilateral changes in X-ray and CT examinations. The diagnosis of ILD is still extremely unsatisfactory. Diagnostic errors account for up to 80%, and adequate specialized care is often provided to patients 1.5–2 years after the first manifestations of the disease. Such a depressing state of affairs is explained not only by the absence of pathognomonic signs (clinical, radiological, functional, laboratory and even morphological) in ILD, but

also by a lack of doctors' knowledge about this pathology and a wrong opinion about its low prevalence [1].

The most common disease in the ILD group is idiopathic pulmonary fibrosis (IPF). On average, IPF makes up 20–30% of all ILD cases. IPF is a specific form of chronic progressive idiopathic interstitial pneumonia of unknown origin. IPF occurs primarily in the elderly and affects only the lungs. It is associated with a histological and (or) radiological pattern of usual interstitial pneumonia (UIP) [2].

The most common clinical symptoms of IPF include slow progressive shortness of breath and nonproductive cough present in 80–90% of patients, crepitations (Velcro crackles) during the height of inspiration in the lower parts of the lungs, which in timbre resembles the sound of hook-and-loop fasteners on clothing, drumstick fingers, and watch-glass nails (in 25–50% of patients). It should be noted that the disease can be almost asymptomatic at early stages.

IPF is characterized by a progressive, malignant course with a high risk of developing an adverse outcome. Without treatment, the average life expectancy of patients is 3 years, and the five-year survival rate is about 30% [1]. High mortality rate of patients with this pathology is explained by the peculiarities of the disease pathogenesis – predominance of fibrosis and slight inflammatory changes. The main mechanism that leads to the development of progressive pulmonary fibrosis is persistent damage to the alveolar epithelium with subsequent impairment of its regeneration. It is followed by activation of fibroblasts and myofibroblasts and excessive deposition of extracellular matrix components. These changes determine the ineffectiveness of traditional immunosuppressive therapy in IPF patients [2].

In this regard, appearance of two new antifibrotic medications for treatment of this pathology – pirfenidone and nintedanib – is essential. They were approved by the FDA in 2014 and registered in 2016–2017 in the Russian Federation. These medications have proven effective in IPF as they slow down the progression of the disease and reduction of lung volumes, improving the survival rate of patients [3, 4]. In May 2019 (SENSCIS trial, 600 patients), it was proved that nintedanib slows down the progression of the disease and the loss of the forced vital capacity (FVC) of the lungs decreases [5]. Moreover, it was revealed that nintedanib treatment slows down a decrease in FVC parameters regardless of their initial level. It gives grounds to recommend it both at the earliest stage of the disease, even before the development of clinically significant functional respiratory disorders, and in a significant decrease in the functional parameters of respiration [6, 7]. Thus, the appearance of medications that improve the prognosis of the disease determines the importance of early IPF diagnosis.

Over the past decade, significant progress has been made in the development of a diagnostic algorithm for patients with IPF, involving the analysis of clinical, laboratory, and instrumental data, primarily the results of high-resolution computed tomography (HRCT).

At the first stage, this algorithm requires thorough history taking to rule out other known IPD causes, for example, occupational and household exposures, connective tissue diseases, and drug toxicity. In addition, a differential diagnosis should be made with diseases that have similar clinical symptoms, for example, chronic heart failure: shortness of breath, fatigue, cough, crepitations in the lungs, and weight loss [2, 8].

The next step is to conduct HRCT and analyze the data. Improvement of modern diagnostic methods and introduction of HRCT into clinical practice made it possible to significantly expand verification of IPF diagnosis at the onset of the disease [9, 10]. Spiral computed tomography of the lungs is now a gold standard for IPF diagnosis. IPF is characterized by a HRCT pattern, which manifests itself as UIP and includes the following signs: reticular changes, honeycombing, and distribution of pathological changes mainly in the subpleural and posterior basal parts. The criteria for evaluating HRCT data are based on disease probability. The Fleischner Society identified four main radiological patterns of UIP: typical, probable, indeterminate, and not associated with IPF, characteristic of another ILD (not IPF) [11].

A typical UIP pattern in HRCT is characterized by the presence of honeycomb lung features, reticular changes, and peripheral traction bronchiectasis predominantly in the basal (less often diffuse) and subpleural segments. In the absence of honeycombing and in the presence of other signs, the X-ray pattern of UIP is probable. Signs that are atypical of UIP or exclude it are: pronounced frosted glass signs, areas of consolidation, single pulmonary nodules and dissemination, predominance of changes in the upper and middle segments of the lungs, peribronchovascular distribution of changes, pulmonary cysts in the extracortical areas, and bullous emphysema.

It is important to emphasize that the modern diagnostic algorithm for IPF offers a differentiated approach to the use of invasive diagnostic methods. Thus, a lung biopsy is not required to verify the di-

agnosis in the presence of clinical presentation of IPF and a CT pattern of typical or probable UIP. Surgical lung biopsy (SLB) is recommended in the presence of a CT pattern that is atypical of UIP. In such cases, the diagnosis is made on the grounds of the HRCT data combined with histological findings.

Therefore, precise adherence to the diagnostic algorithm and correct interpretation of the HRCT data are prerequisites for IPF diagnosis.

The Tomsk region has developed routing of patients with suspected IPF. If IPF is suspected, the following actions are carried out:

Planned admission to the Pulmonology Department of the Tomsk Regional Clinical Hospital.

At the Department, the patient is examined in accordance with the Federal clinical guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis (2016), excluding other interstitial lung lesions. The diagnosis is made after discussing all the data obtained by a council of doctors.

After the initial diagnosis of IPF, all documents (with the HRCT scans of the chest organs) are submitted to federal experts to confirm or exclude the diagnosis of IPF. They include patients in the registry of patients with IPF in the Russian Federation.

Once the diagnosis is confirmed, treatment is prescribed. It has become more accessible in the Russian Federation after the registration of new antifibrotic medications.

The presented clinical case is a successful example of adhering to this algorithm.

CLINICAL CASE

Patient K., 67 years old, first went to the Pulmonology Department of the Tomsk Regional Clinical Hospital in October 2015 with complaints of generalized weakness, heart failure, shortness of breath of a mixed nature when walking up to 10 meters and climbing 10 stairs (2 points on the MRC scale), episodic increases in the body temperature to 38.5 °C, and coughing up of gray phlegm up to 30 ml per day. According to the medical history, cough had been bothering the patient for the last 15 years, while shortness of breath of a mixed nature appeared 5 years ago.

Medical history. In 2015, the patient was diagnosed with ischemic heart disease (IHD): paroxysmal atrial fibrillation, supraventricular extrasystoles, paroxysmal supraventricular tachycardia. Chronic heart failure, stage IIa. Stage 3 hypertension, class IV risk of cardiovascular complications. The patient constantly takes sotahexal 80 mg, ¼ tab 2 times a day and cardiomagnyl 75 mg 1 once a day. Strumectomy was performed in 1995 for diffuse toxic goiter, the patient constantly takes L-thyroxine 100 mg daily. The patient suffers from varicose veins of the lower extremities and has no bad habits.

Objective status. The condition is of moderate severity. Body temperature is 36.3 °C. Pulse – 100 BPM, respiratory rate – 20 breaths per minute, SpO_2 – 96%, blood pressure – 110 / 70 mm Hg. Consciousness is clear, the patient has full awareness. Skin is of moderate humidity with diffuse cyanosis. Drumstick fingers and watch-glass nails are noted. The tongue with a white and yellow coating is moist. The thorax is cylindrical. A box sound is heard in percussion. The lower border of the lungs is one rib higher. Breathing is hard with crepitations in the middle and lower parts on both sides. The heart tones are evenly weakened, the rhythm is normal. The liver edge is palpable along the costal margin. The abdomen is soft and painless. The spleen is not palpable. No peripheral edema is noted. Signs of varicose veins in the lower extremities are observed.

Spirography. Abnormal pulmonary ventilation of the 1st degree mainly according to the restrictive pattern. The HRCT data: the presentation corresponds to UIP. Taking into account the presence of clinical signs typical of IPF and a CT pattern of UIP, a lung biopsy was not performed.

The patient was diagnosed with IPF with a slowly progressive course with the formation of a "honeycomb lung". Upon discharge from the hospital, the patient was recommended follow-up examinations. The patient was advised to use only symptomatic therapy, since at that time antifibrotic medications with proven effectiveness in IPF (nintedanib (Vargatef) and pirfenidone (Esbriet)) were not available in the Russian Federation. Glucocorticoids and cytostatics used for many years to treat this disease were not recommended as a permanent therapy, since they negatively affect its course [2].

Repeated treatment and admission to the Pulmonology Department of the Tomsk Regional Clinical Hospital in February 2017 was caused by deterioration of the condition (progression of shortness of breath).

Objective status. No significant dynamic changes. The degree of oxygen saturation of the blood (SpO_2) decreased from 96 (2015) to 91%, which characterizes the presence of type I respiratory failure and indicates a downward trend in the disease. Spirography and body plethysmography parameters did not show significant changes.

Spirography of 27.02.2017. Vital capacity (VC) 85%, FVC 84%, forced expiratory volume in the first second (FEV1) 60%, FEV1 / FVC 76.4%.

Body plethysmography of 02.03.2017. The structure of the total lung capacity (TLC) is not altered. Bronchial resistance is normal. VC 93.5%; TLC 82.8%; residual volume (RV) 78.2%; R tot 43.1%.

Spiral CT of the chest of 25.03.2017 (Fig. 1–3). The chest is of usual shape and size. There are no destructive changes in the structure of the ribs, vertebrae, shoulder blades, and clavicles. Moderately pronounced reticular changes are detected in the lungs due to interstitial thickening. Frosted glass signs in the areas of reticular changes are determined. Traction bronchiectasis and honeycombing in the cortical regions are pronounced. The distribution of changes is cortical basal. The diaphragm is high, the volume of the lower lobes is reduced.

The lumina of large bronchi are not changed. The interstitial slits and sinuses are free, there is no fluid in the pleural cavities. The adipose tissue of the mediastinum has a homogeneous structure and increased volume (lipomatosis). The lymph nodes in the mediastinum and in the roots of the lungs are moderately enlarged and do not merge into conglomerates. The atria and ventricles of the heart are of normal size and shape. The aorta and its branches have signs of atherosclerosis, the superior vena cava is within the age norm. The esophagus is normally located, its walls are not thickened, the lumen is expanded, an esophageal hiatus hernia of the diaphragm is noted.

Conclusion: the CT pattern is characteristic of usual interstitial pneumonia.

The results of the spiral CT of the chest were sent for consideration to Igor E. Tyurin, chief freelance expert in radiology of the Ministry of Health of the Russian Federation. The answer was received in the electronic form in the IPF registries on 26.05.2017. Conclusion: the pattern of UIP.

Taking into account the long-term use of drugs for the comorbid pathology, including L-thyroxine (100 mg)since 1995, a differential diagnosis was made between IPF and drug-induced fibrosing alveolitis. Therefore, the council decided to prescribe a trial therapy with prednisone *per os* 30 mg / day for a month, followed by a reduced maintenance dose (10 mg / day), which the patient took for a year (from 10.03.2017 to 01.03.2018) without improvements in the clinical presentation and CT findings.

Afterwards, the patient continued to undergo follow-up examinations. The principal diagnosis: idiopathic pulmonary fibrosis with a slowly progressive course with the formation of the "honeycomb lung". Complication: chronic pulmonary heart disease, compensation stage. Type I respiratory failure.

Concomitant diagnosis: IHD: paroxysmal atrial fibrillation. Supraventricular extrasystole, paroxysmal supraventricular tachycardia. Stage 1 chronic heart failure. Stage 3 hypertension, class IV risk of cardiovascular complications. Diffuse nodular goiter, condition after strumectomy in 1995, postoperative hypothyroidism. Varicose veins in the lower extremities, chronic venous insufficiency.

The condition progressively worsened, shortness of breath increased. In February 2019, due to the deterioration of the patient's condition (increased shortness of breath, an increase in the body temperature to 38 °C, a decrease in blood oxygen saturation to SpO_2 89%), she was admitted to the Tomsk Regional Clinical Hospital. Differential diagnosis was made between the exacerbation of IPF and community-acquired pneumonia. According to the current data, despite gradual progression of IPF, the course of the disease can be complicated by acute periods of worsening disease symptoms that are not associated with a respiratory tract infection, pulmonary embolism, decompensated heart failure, and other known factors. These episodes of acute deterioration of the IPF course are considered as IPF exacerbations. It is crucial to determine the cause of deterioration in IPF, since it is associated with the choice of therapy. Exacerbation of IPF, as a rule, requires more glucocorticoids (up to pulse therapy), while decompensation of concomitant pathology and pulmonary embolism require appropriate treatment. Respiratory tract infections require anti-infective therapy. For instance, the presence of community-acquired pneumonia requires mandatory prescription of antibiotics.

The analysis of the clinical presentation showed that the increased shortness of breath was not accompanied by an increase in other manifestations of heart failure. Echocardiography revealed signs of moderate pulmonary hypertension. No abnormal local contractility was detected. Global left ventricular function remained within normal limits.

The situation was regarded as a severe course of left-sided community-acquired multilobar pneumonia, caused by *Actinobacter boumonii*. Background diagnosis: idiopathic pulmonary fibrosis. Stage of the honeycomb lung, progressive course. The prescribed antibiotic therapy led to improvement in the clinical and radiological presentation and stabilized the condition.

On March 15, 2018, the patient was consulted by Professor Sergey N. Avdeev, chief freelance pulmonologist of the Ministry of Health of the Russian Federation. The diagnosis of IPF was confirmed. Palliative therapy with nintedanib (Vargatef) was recommended.

In February 2019, the patient started taking nintedanib (Vargatef) at 150 mg 2 times a day within the palliative care program. In December 2019, the patient had a planned admission (follow-up) to the Tomsk Regional Clinical Hospital. No deterioration of the condition during treatment with nintedanib (Vargatef) for 10 months was identified. No exacerbations of the disease were detected. The patient tolerated the therapy well. Parameters of arterial oxygen saturation were stable (SpO_2 91–92%). Spirography and body plethysmography parameters also did not reveal a downward trend.

Spirography of 13.12.2019: VC 87%; FVC 87%; FEV1 67%, FEV1 / FVC 84%. Bronchodilator test: negative.

Spiral CT of the chest of 18.12.2019 revealed no changes in comparison with the data of the previous CT examination (30.01.2020, Professor Igor E. Tyurin, a copy from the IPF registries, patient number 1759).

Therefore, treatment with nintedanib (Vargatef) leads to stabilization of the disease course, which is the main goal of IPF treatment.

CONCLUSION

IPF is a steadily progressing disease with an unfavorable prognosis. Its clinical manifestations, primarily shortness of breath on exertion and cough, mimic the symptoms of a number of other pathological conditions. Widespread implementation of modern algorithms for IPF diagnosis and quality improvement of imaging methods, primarily HRCT conducted in differential diagnosis, open up prospects for early diagnosis of this pathology. Timely prescribed antifibrotic therapy (nintedanib, pirfenidone) in IPF can slow down the progression of the pathological process and improve the prognosis.

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