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**Клинический случай идиопатической лёгочной артериальной гипертензии у пациента с сопутствующей ишемической болезнью сердца: ключевые этапы диагностики.**

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Несмотря на прогресс, достигнутый в развитии новых направлений в диагностике и лечении, идиопатическая лёгочная артериальная гипертензия остаётся одним из наиболее тяжелых и прогностически неблагоприятных заболеваний. В статье представлен клинический случай и описан алгоритм диагностики этого редкого заболевания соответственно процессу принятия решений в клинической практике. В данном наблюдении подчеркивается необходимость широкого проведения дифференциальной диагностики в случае выраженной одышки у возрастных пациентов, особенно когда интенсивность одышки непропорциональна тяжести основного заболевания сердца или легких, и если обычная терапия не проявляет ожидаемого эффекта. Ранняя диагностика идиопатической легочной артериальной гипертензии является жизненно важной для начала современной терапии с целью улучшения качества и продолжительности жизни таких пациентов.

**Ключевые слова:** легочная гипертензия; недостаточность правого желудочка; катетеризация правых отделов сердца; блокаторы кальциевых каналов; современная целевая терапия.

**A clinical case of idiopathic pulmonary arterial hypertension in patient with comorbid ischemic heart disease: the key stages of diagnosis.**

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**Summary.** Despite the progress achieved in the development of new directions in the diagnosis and treatment of idiopathic pulmonary arterial hypertension, it remains one of the most severe and prognostically unfavorable diseases. The article presents a clinical case and an algorithm for diagnosis of this rare disease, in respect to the decision-making in clinical practice. The present case underscores the need to consider a broad differential diagnosis for marked dyspnea in mature patients, especially when the intensity of dyspnea is out of proportion to the severity of underlying heart or lung diseases, or when symptoms fail to subside as expected in response to conventional therapy. Early diagnosis of idiopathic pulmonary arterial hypertension is vitally important for initiating modern therapy in order to improve the quality and duration of life in such patients.

**Key words:** pulmonary hypertension; right ventricle failure; right heart catheterization; calcium channel blockers; modern targeted therapy.

**Introduction.** The term “idiopathic pulmonary arterial hypertension” (IPAH) was used for the first time in 1951 by Dresdale. This clinical condition is characterized by the presence of pre-capillary PH, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases [1]. IPAH corresponds to sporadic disease; the lowest estimates of its prevalence are 5.9 cases/million in the adult population. IPAH affects women two times more often than men. The mean age of diagnosis making is 35 years. The disease has no family history of PH or known triggering factor [2]. However, specific gene mutations have been identified in such patients, including the bone morphogenetic protein receptor 2 gene, the activin receptor-like kinase type-1 gene and the endoglin gene [3, 4]. It is a severe chronic disease with an unfavorable prognosis. The symptoms of IPAH are caused by developing RV hypertrophy and failure. They are usually non-specific and include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension. In advanced cases symptoms such as jugular vein distension, hepatomegaly, peripheral oedema, and ascites might occur [5, 6]. In untreated patients with IPAH or heritable PAH, historical data showed a median survival of 6 months for WHO-FC (World Health Organization – Functional Class) IV, 2.5 years for WHO-FC III, and 6 years for WHO-FC I and II. The most common causes of death are terminal right ventricle failure and cardiac arrest [7].

**Case report.** The case patient, a 47-year-old man checked into Kharkiv Regional Hospital with marked dyspnea during minimal physical activity (walking up to 70 m, climbing half flight of stairs), paroxysms of nocturnal dyspnea, tachycardia, chest pain, fatigue, and episodic increases of blood pressure. Symptoms were typically absent at rest.

The described above symptoms of disease are nonspecific and may correspond to multiple clinical conditions, capable of provoking significant dyspnea, including heart diseases (systolic dysfunction, diastolic dysfunction, and valvular disease), lung diseases (chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, etc), systemic disorders, tumoral obstruction, connective tissue diseases and many others. Differential diagnosis is difficult.

In 1988 the patient noticed increased blood pressure (BP) up to 160/100 mm Hg for the first time. His general condition was satisfactory, and therefore the man didn't seek any medical advice. Beginning in 2000 he began to experience undue dyspnea, chest pain and fatigue during ordinary physical activity. At this point, he started to take antihypertensive drugs episodically, only during significant increases of BP. In 2009 he suffered from myocardial infarction and was treated properly at a specialized regional center. Since the beginning of 2011 the patient has been experiencing significant deterioration of his general condition: marked limitation of physical activity due to progressive dyspnea, fatigue, angina as well as episodes of tachycardia, and unstable BP. The patient is

comfortable at rest, but sometimes has paroxysmal nocturnal dyspnea. Due to the severity of his condition, the patient was admitted to a local hospital with the diagnosis of coronary artery disease and arterial hypertension; however, there was no improvement as a result of treatment. In the beginning of 2012 the patient had a few episodes near syncope in addition to the previously mentioned complaints. He was hospitalized in a specialized regional center for additional diagnostic procedures and amendments of treatment.

As we know, the most common known causes for dyspnea are left side heart disease and lung diseases. At a first glance, the patient's medical history suggests a diagnosis of left side heart failure due to ischemic heart disease and arterial hypertension (especially when taking into consideration myocardial infarction in 2009). However, the first manifestation of undue dyspnea refers to 2000, when the patient was quite young and didn't have any symptoms other than rare moderate elevations of blood pressure. Besides, the ineffectiveness of in-hospital treatment for coronary artery disease in 2011 is a sufficient reason to re-check the patient's physical status.

The physical examination revealed left parasternal lift, an accentuated pulmonary component of second heart sound, a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency, and a right ventricle third sound. His blood pressure was 120/80 mm Hg, and his heartbeat rate was 102 beats per minute. The patient's lung sounds were normal, and his respiratory rate was 20 breaths per minute. Hepatomegaly was found, with no signs of ascites. A slight oedema of ankles and legs was revealed. His extremities were cool, especially wrists. His skin and mucosa were normal color. His BMI was 26,2 kg/m<sup>2</sup>.

According to the physical examination the patient has typical signs of pulmonary hypertension (PH), including signs of right ventricle overload, relative insufficiency of the tricuspid valve and increased blood pressure in the pulmonary artery. There is slight tachycardia and breathlessness. Hepatic congestion suggests further examinations to check the condition of his kidneys. Normal lung sounds assume the absence of chronic obstructive pulmonary disease, however further examinations should be performed to confirm this statement.

An electrocardiogram upon admission showed sinus rhythm, a heart rate of 96 beats per minute, right bundle-branch block, left posterior hemiblock, right ventricle hypertrophy and strain, and right atrial dilatation. The findings of the chest radiograph included central pulmonary arterial dilatation in contrast to the 'pruning' of the peripheral blood vessels, an enlarged right atrium and right ventricle. Transthoracic echocardiography confirmed the presence of marked dilatation of the right heart chambers (end-systolic dimension of right atrium 78 mm, lateromedial measurement; end-diastolic dimension of right ventricle 55 mm, short axis parasternal view) as well as dilation of pulmonary artery trunk (40 mm). The systolic pulmonary artery pressure was 101 mm Hg. There was fourth

grade tricuspid regurgitation, and the gradient of regurgitation was 86 mmHg. Concerning the left heart chambers, a moderate enlargement of the left atrium (end-systolic dimension 56 mm, anteroposterior measurement), and normal sizes of the left ventricle were revealed; the ejection fraction was 66% and systolic output was 52 ml. The thickness of the interventricular septum was 18 mm. Hypokinetic motion of the posterobasal segment of the left ventricle was detected. There were no signs of systolic dysfunction. No remarkable changes of the mitral and aortic valves were found, and there were no signs of pericardial effusion.

The results of the coronarography show initial signs of atherosclerosis in both the left and right coronary arteries without significant derangements of haemodynamics. As confirmed by clinical findings, the patient has pronounced PH, complicated by right heart dilatation and right bundle-branch block. A few factors favoring a diagnosis of left ventricular diastolic dysfunction in the presence of PH can be found in this patient: hypertension, coronary artery disease, left atrial enlargement, and left ventricle hypertrophy (mainly the interventricular septum). However, the ejection fraction and systolic output are normal. Coronary arteries are almost intact. The PH seems to be out of proportion to the severity of left side heart disease in this particular patient. The other causes for PH, starting with lung diseases, should be looked for. As chest X-ray didn't show any remarkable changes in the lungs, other noninvasive methods should be applied to assess lung structure and function.

Pulmonary function tests showed moderate reduction of FEV and FVC1. High-resolution computed tomography showed pronounced dilatation of the pulmonary artery trunk as well as main, lobar and segmental arteries, and tortuosity of the arteries (Figure 1). The structure of the lungs and airways was normal; no signs of interstitial lung disease and emphysema were found. No signs of pulmonary embolism were detected.

The mild to moderate reduction of lung volume is typical for PH. It can also be seen in patients with chronic obstructive pulmonary disease, asthma, and other pulmonary diseases with mixed restrictive and obstructive patterns. As the patient didn't have symptoms, signs or history of chronic lung diseases and no pathognomonic findings were revealed by additional assessment, the diagnosis of lung disease as a possible cause for PH was rejected.

Laboratory studies revealed a red blood cell count of  $5.3 \cdot 10^{12}$  per cubic liter (normal range, 4.0 to 5.1), hemoglobin 168 grams per liter (normal range, 130 to 160), hematocrit 50.1%, and the erythrocyte sedimentation rate 29 mm per hour. Serum chemical profiles were notable for a blood urea level of 11.6 mmol per liter (normal range, 3.3 to 6.6), and serum uric acid 428 mmol per liter (normal range, 208 to 420).

It is not surprising to observe a secondary erythrocytosis in patients with pronounced PH. A compensatory mechanism of increased red cell production is being launched by hypoxia in case of heart failure. Increased levels of blood urea

and uric acid in the presence of unremarkable urine analysis suggest the presence of kidney congestion as the aftermath of congestive heart failure. Serum uric acid is also a marker of an impaired oxidative metabolism in the ischaemic peripheral tissue. High uric acid levels are known to relate to poor survival in patients with PH.

We performed a ventilation/perfusion lung scan in order to look for segmental perfusion defects as markers of less common diseases capable of provoking PH development.

The normal results of this scan helped us to exclude chronic thromboembolic pulmonary hypertension, pulmonary veno-occlusive disease, and pulmonary capillary haemangiomas as possible causes for the PH.

Next, we considered the possibility of other uncommon causes of PH, starting with pulmonary artery hypertension, and a decision to perform right heart catheterization (RHC) was made.

The data obtained by the RHC included: systolic pulmonary artery pressure = 92 mm Hg, diastolic pulmonary artery pressure = 35 mm Hg, mean pulmonary artery pressure (mPAP) = 52 mmHg, pulmonary wedge pressure (PWP) = 13 mm Hg, right atrial pressure = 18 mm, and cardiac output = 5.2 liters per minute. Pulmonary vascular resistance = 4.1 Wood Units. A vasoreactivity test with adenosine revealed a drop in mPAP of 16 mm Hg to the level of 36 mm Hg.

According to the findings of the RHC, the patient has pre-capillary PH. This statement fully denies the probability of PH as the result of left side heart disease. The good news is that the patient is a positive acute responder due to the results of the vasoreactivity test, so he may benefit from long-term therapy with calcium channel blockers (CCBs). A positive test is more often observed in patients with pulmonary artery hypertension (PAH): idiopathic or anorexigen associated. Nevertheless, other rare reasons for PAH should be considered.

When looking at connective tissue disease as a possible cause of PAH we were mainly concerned with systemic sclerosis, as it is the most common systemic disease PAH is associated with. As the patient was complaining of cold wrists, especially when exposed to a cold environment, and physical examination also revealed that they were pale and cold as a result of palpation, we suspected the presence of Raynaud's phenomenon, which can be one of the symptoms of systemic sclerosis.

An antinuclear antibody test and an anti-centromere antibody test were both negative. A nailfold capillaroscopy test was normal. Thermography with cold challenge showed a slight lowering of all indexes.

Limited cutaneous systemic sclerosis (LCSS) may have slow onset and symptoms may be relatively unnoticed until internal complications occur. An anti-centromere antibody test seen almost only in patients with LCSS was essential for our patient, because it is associated with increased risk of PH. As the patient didn't have any other clinical signs of systemic sclerosis, autoantibody tests were negative, and the nailfold capillaroscopy test was normal, we

diagnosed primary Raynaud's phenomenon. However, the origin of PAH still needed to be specified.

The patient reported no history suggestive of HIV or hepatitis. The history was supported by the negative results of serological testing. There were no physical signs or echocardiographic confirmation of congenital heart disease. History, physical examination and laboratory data revealed no signs of chronic hemolysis and shistosomiasis. Thyroid function test showed normal levels of thyroid hormones.

History of the patient's exposure to drugs and toxins known to induce PAH was carefully collected. The patient had never take anorexigens, selective serotonin reuptake inhibitors, phenylpropanolamine, cocaine, pergolide or amphetamines.

As the result of our investigation, the differential diagnosis had narrowed to two possible causes for PAH: idiopathic or heritable PAH. The patient reported no family history of PAH. Therefore, the only remaining diagnosis in this case was idiopathic PAH.

IPAH remains a chronic disease without a cure. However, modern drug therapy leads to a significant improvement in patients' symptoms and a slower rate of clinical deterioration [8, 9]. The management of IPAH in patients with comorbid coronary artery disease (CAD) is even more difficult. We followed the guidelines of the European Society of Cardiology and American Heart Association concerning the treatment of PH in our case patient [10, 11, 12].

As we know, only approximately 10% of patients with IPAH can be defined as positive acute responders by the results of RHC. Such patients are most likely to show a sustained response to long-term treatment with high doses of CCBs and they are the only patients that can safely be treated with this type of therapy [13]. Our patient was lucky to be one of them. The presence of relative tachycardia (100-110 beats per minute) favored the prescription of diltiazem (480 mg daily) for our patient. The heartbeat rate reduced to 90 beats per minute after 1 week of treatment and didn't show further dynamics. Adding 7.5 mg of ivabradine twice daily decreased the heart rate to 68-74 beats per minute. Also, a modern targeted IPAH treatment was started: 2.5 mcg of iloprost inhaled 6 times daily. In few days jaw pain developed as a side effect, but it didn't require the termination of therapy. Other components of therapy were: 2,5 mg of warfarin once daily under the control of the international normalized ratio to prevent thrombotic events, and 12,5 mg of captopril three times daily to enhance blood pressure control. The follow-up done in 3 months showed an increase in exercise capacity according to a 6-minute walking test (300m in comparison to 120m at the beginning of therapy) and improvement in clinical symptoms. The B-type natriuretic peptide level was still moderately elevated, but lower than at the beginning of therapy. As the result of treatment the severity of pulmonary hypertension in our patient changed from the III to the II functional class according to WHO (1998) [14].

**Conclusion.** The present case underscores the need to consider a broad differential diagnosis for marked dyspnea in mature patients, especially when the intensity of dyspnea is out of proportion to the severity of underlying heart or lung diseases, or when symptoms fail to subside as expected in response to conventional therapy. Early diagnosis of IPAH is vitally important for initiating modern therapy in order to improve the quality and duration of life in such patients. As a result of the treatment, the significant clinical improvement was achieved in the patient, including reduced severity of symptoms, enhanced tolerance to physical exercise according to the 6-minute walk test, reduced functional class of heart failure and improved prognosis.

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Figure 1. High-resolution computed tomography showing pronounced dilatation of the pulmonary artery trunk as well as main, lobar and segmental arteries, and tortuosity of the arteries

