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COMPLICATED CLINICAL CASE: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION IN PATIENT WITH RECIDIVOUS CARDIAC MYXOMA

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ABSTRACT

The clinical case demonstrates the difficulties of differential diagnosis and the determination of treatment tactics in a patient with chronic thromboembolic pulmonary hypertension, recidivous cardiac myxoma and radiographic pattern of dissemination in lung tissue.

Key words: *chronic tromboembolic pulmonary hypertension, cardiac myxoma, syndrome of dissemination in the lungs, guanylatcyclase stimulators, riociguat*

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Chronic thromboembolic pulmonary hypertension (CTEPH) – precapillary form of pulmonary hypertension, in which chronic obstruction of large and medium branches of pulmonary arteries, as well as secondary changes in the microcirculatory bed of the lungs lead to a progressive increase in pulmonary vascular resistance and pulmonary artery pressure with the development of severe dysfunction of the right heart and heart failure [1].

For the diagnosis of CTEPH in clinical practice, the following criteria are used: an increase of average pressure in pulmonary artery more than 25 mm Hg and pulmonary vascular resistance more than 2 Wood units at a normal pulmonary artery wedge pressure <15 mm Hg according to the right heart catheterization (RHC) data; presence of chronic, organized blood clots or emboli in pulmonary arteries of the elastic type (pulmonary trunk, lobar,

segmental, subsegmental pulmonary arteries) despite the ongoing effective anticoagulant therapy for at least 3 months. [1].

There is information about the presence of risk factors associated with the development of CTEPH, such as demographic features, the presence of markers of genetic thrombophilia, splenectomy, ventriculo-venous shunts for treatment of hydrocephalus, installation of central intravenous catheters or electrodes of the pacemaker, replacement therapy with thyroid hormones, oncological and chronic inflammatory diseases. [2].

Most often CTEPH is formed as a complication of acute thromboembolism into pulmonary artery system in patients with deep vein thrombosis of the lower extremities, and also on the background of hypercoagulation in the pathology of the blood coagulation system. However, in the modern literature, information is given on the rare sources of pulmonary thromboembolism, including the myxoma of the right atrium.

Cardiac myxoma – Is the primary intracavitary histologically benign heart tumor, which in many cases has a clinically malignant and even fatal course. Myxoma can be detected in any heart cavity, but its most frequent localization is in the left atrium (LA) (75% of cases), in 20% of cases the tumor is found in the right atrium (RA), and least often (5% of cases) in the heart ventricles, sometimes involving the valve apparatus. [3].

The tumor can be fixed to the atrium wall or the atrial septum with a long leg, which determines the possibility of prolapse into the atrioventricular orifice. High mobility of myxomes lead to obstruction of blood flow, manifested by symptoms that are typical for stenosis of the left or right atrioventricular orifice and the formation of a heart failure clinic for small or large blood circulation, respectively.

In the tumor, there may be such dystrophic changes as necrosis, hemorrhage, also there may be pockets of calcification, which are often covered with blood clots, which is typical for myxoma of the RA [4].

In 65% of cases, the surface of the cardiac myxoma is smooth, however, a villous and papillary histological structure is often found, the consistency of such tumors is mild, jelly-like in the absence of the fibrous center, villi are loose. It is these types of structure that make possible the fragmentation of the tumor with subsequent embolization of the arteries of the brain, spleen, pulmonary artery.

As an example, illustrating the formation of CTEPH as a complication of embolism in the pulmonary artery by tumor masses of myxoma of the right atrium, the following clinical case is presented.

Patient H., born in 1968, was first hospitalized in the department of pulmonary hypertension and heart diseases in connection with dyspnea arising during physical activity (lifting to the second or third floor), periodic tingling pain in the chest without connection to physical activity, swelling of the lower limbs to the level of the mid-calf.

From the history of the disease it is known that the patient from his youth was engaged in sports, underwent several medical examinations, in which pathology was not revealed. In 1993, he noted an episode of hemoptysis, about which he was examined by a phthisiatrician, but pulmonary tuberculosis was excluded.

When questioned, it also became clear that the older sister in the autopsy was diagnosed with a cardiac myxoma, which caused a lethal outcome.

In 1995, the patient suddenly lost consciousness and because of that he was urgently hospitalized in a hospital. At the examination, a right-ventricular myxoma of large dimensions (5.0*8.0 cm) was diagnosed, which prolapsed into the cavity of the right ventricle. At the same time, chest X-ray revealed a bilateral lower lobe pneumonia and signs of pulmonary hypertension. According to vital indications, the patient underwent operative treatment – removal of myxoma of the RA with a leg, resection of the RA wall with suturing of the right atrial defect.

Since May 2007, the patient has had dyspnea, in connection with which an outpatient examination was conducted, according to which a relapse of myxoma of the RA was revealed. In January 2008, an in-patient examination was conducted to determine the further treatment tactics in connection with the revealed formation in the RA cavity (according to echocardiography in the RA cavity, we see an echo formation of 50x38 mm, movable, not obstructing blood flow through the TV, pressure in the right ventricle 30-35 mm Hg). It was decided that surgical treatment is necessary. Myxoma of the RA has been removed together with the plastic of the interatrial septum and the right atrium with using a xenopericardial patch. Histological study of the intraoperative material determined the villous structure of myxoma with focus of hemorrhage and loss of fibrin mass.

A few months after surgery, the patient noticed an episode of hemoptysis, but did not seek medical help. In 2011, on the background of satisfactory state of health, repeated echocardiography was performed, which revealed a myxoma of the LA. The patient was again hospitalized. An operation was performed to remove the myxoma of the LA together with atrioplastic of the right and left atrium by a xenopericardial patch. In connection with the previously identified signs of pulmonary hypertension according to the chest X-ray the patient underwent computed tomography of the chest, the results of which revealed local wall contrast defects (blood clots) in subsegmental branches of the right and left pulmonary arteries. Treatment with warfarin was prescribed with recommendations to maintain the target level of the international normalized ratio (INR) 2.0-3.0, however, sufficient control of this indicator was not carried out. Since 2016, the patient began to worry about severe dyspnea during physical activity and the appearance of swelling of the lower extremities. At the examination at the place of residence, according to echocardiography, an increase in systolic pressure in the pulmonary artery up to 55 mm Hg, an increase in the size of the LA up to 4.3 cm, an increase of the RA area (29 mm^2) and tricuspid regurgitation of the third degree were revealed.

The patient was hospitalized into the Federal State Budget Institution "National Medical Research Center of Cardiology" of the Ministry of Health of the Russian Federation for examination in connection with the aggravation of well-being and to determine the further tactics of treatment.

Upon admission, the patient complained of dyspnea arising during physical activity (lifting to the second or third floor), periodic tingling pain in the chest without connection to physical activity, swelling of the lower limbs to the level of the mid-calf.

According to the physical examination, the condition of the patient at the time of admission was of moderate severity, the skin was clean, physiological coloring, the lymph nodes were not palpable, the apparent pathology of the osteoarticular and muscular system was not registered. The shape of the chest is normosthenic, both halves of the chest participated in the act of breathing evenly, palpation of the chest painless, a clear pulmonary sound was determined. At auscultation vesicular breathing with a hard tinge and pneumosclerotic rales in the lower parts on both sides were heard. When examining the circulatory system, the expansion of the borders of the relative cardiac dullness was not detected. During auscultation, the clear tones of the heart,

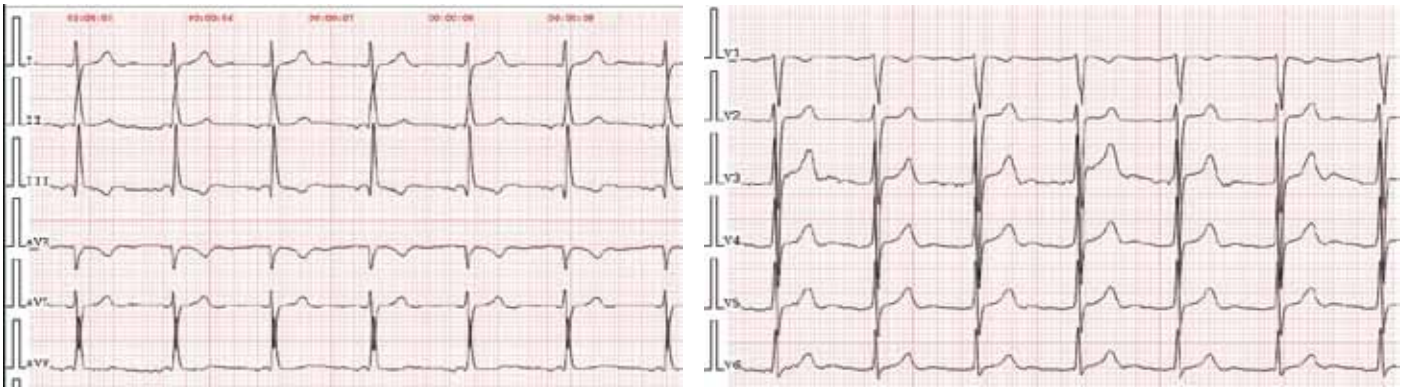

Figure 1. ECG of patient H. upon admission

accent of the second tone above the point of auscultation of the pulmonary artery, systolic murmur in the region of the xiphoid appendage with carrying along the breastbone, the right rhythm with a heart rate of 76 beats per minute, arterial pressure 110/70 mm Hg were determined. When studying the digestive system, the urinary system, no pathological changes were identified. Mental status is not changed, the function of sense organs saved.

According to electrocardiography, an ectopic atrial rhythm with a heart rate of 73 beats per minute, a deviation of the electric axis of the heart to the right, a violation of intraventricular conduction were identified (Fig. 1).

The results of echocardiography (EchoCG) showed a negative dynamics in comparison with the data from December 2016 (Table 1). An increase in the right heart was detected (right atrial area = 27 cm2, right ventricle enlarged: anteroposterior size = 3.6 cm, apical = 4.8 cm). Expansion of the pulmonary artery trunk (2.9 cm). Pulmonary hypertension of 2nd degrees (systolic pressure in the pulmonary artery 65 mm Hg). Insufficiency of the tricuspid valve of the 2nd degree. There are no signs of a central venous pressure increase.

Based on the results of chest X-ray examination, signs of high pulmonary hypertension identified. Moore's index is 34 % (norm ≤30%), the Lupi index is 31% (norm ≤33%), the descending branch of the right PA 31mm (norm ≤15 mm), the left PA – 33 mm (norm ≤24 mm). In addition, in the projection of the upper and lower lobes on the left, middle and lower lobes on the right, multiple

Table 1. Echocardiography indicators of patient H. from December 2016 and during hospitalization

Index	October 2016	January 2017	NORM
Aorta, cm	2,9	3,6	2,0-3,7
LA, cm	4,3	4,1	2,0-4,0
EDD,cm	5,9	5,5	4,2-5,8
EF, %	More than 60	More than 60	More than 60
IVST, cm	0,9	1,1	0,7-1,1
LVPWT, cm	0,9	1,0	0,7-1,1
AP RVD, cm	3,0	3,6	Less than 3,2
S RA, cm^2	29	27	Less than 17
RVAWT, cm	0,4	0,4	Less than 0,5
PASP, mm Hg.	55	65	Less than 25
PAT, cm	2,8	2,9	Less than 2,5
Tricuspid regurgitation	3rd degree	2nd degree	0-1
TAPSE	-	1,8	More than 1,7

focal seals with smooth, well defined contours from 5 to 15 mm in diameter were found, which corresponded to the dissemination syndrome in lung tissue (Fig. 2).

Due to identified changes in pulmonary tissue, two goals of further examination were identified, such as differential diagnostics of dissemination in the lungs and confirmation of the presence of CTEPH.

When performing chest fluoroscopy, multiple focal shadows (5x15x25 mm) are represented by vascular formations with characteristic pulsation, some vessels are expanded, many are located at the intersection of the vascular branches, that suggests the presence of multiple aneurysms of segmental and subsegmental orders. To clarify the nature of multiple formations in pulmonary tissue, multispiral computed tomography of the chest was performed (MSCT of the chest), where local aneurysmal dilatations of the pulmonary artery branches, thrombosis of the pulmonary artery branches of segmental and subsegmental orders and multiple intrathoracic anastomoses were detected (Figure 3 A, B).

According to the results of invasive pulmonary angiography, changes in pulmonary arteries were found, which is typical for CTEPH.

According to medical examination, the following diagnosis was formulated: chronic tromboembolic pulmonary hypertension. Functional class II-III (WHO). Operations to remove the myxoma of the right atrium were performed in 1995, 2008 and operation to remove myxoma of the left atrium with atrioplasty of the right and left atriums by a xenopericardial patch were performed in 2011. Chronic heart failure – stage 2A. Given the history of the disease, a possible source of embolism in the pulmonary artery was a recurrent villous myxoma of the RA.

Taking into account the presence of a combination of proximal and distal thrombotic lesions, aneurysmal enlargement of the branches of the pulmonary artery, triple sternotomy in anamnesis, and characteristics of the hemodynamic profile, it was decided to refrain from surgical treatment (thromboendarterectomy and balloon angioplasty of the branches of the pulmonary artery). In this regard, recommended PAH-specific therapy with riotsiguat drug, an initial dose of 3 mg per day under the control of blood pressure with a further increase in the dose up to 7.5 mg per day. And also the patient was prescribed a warfarin drug 3.75 mg/day under the control of target international normalized ratio (INR) values of 2.5-3.5, veroshpiron 50 mg per day and torasemide 5 mg per day 1-2 times a week if necessary.

DISCUSSION

The complications of early detection of chronic tromboembolic pulmonary hypertension in this patient consisted of a long period of asymptomatic course of the disease against the background

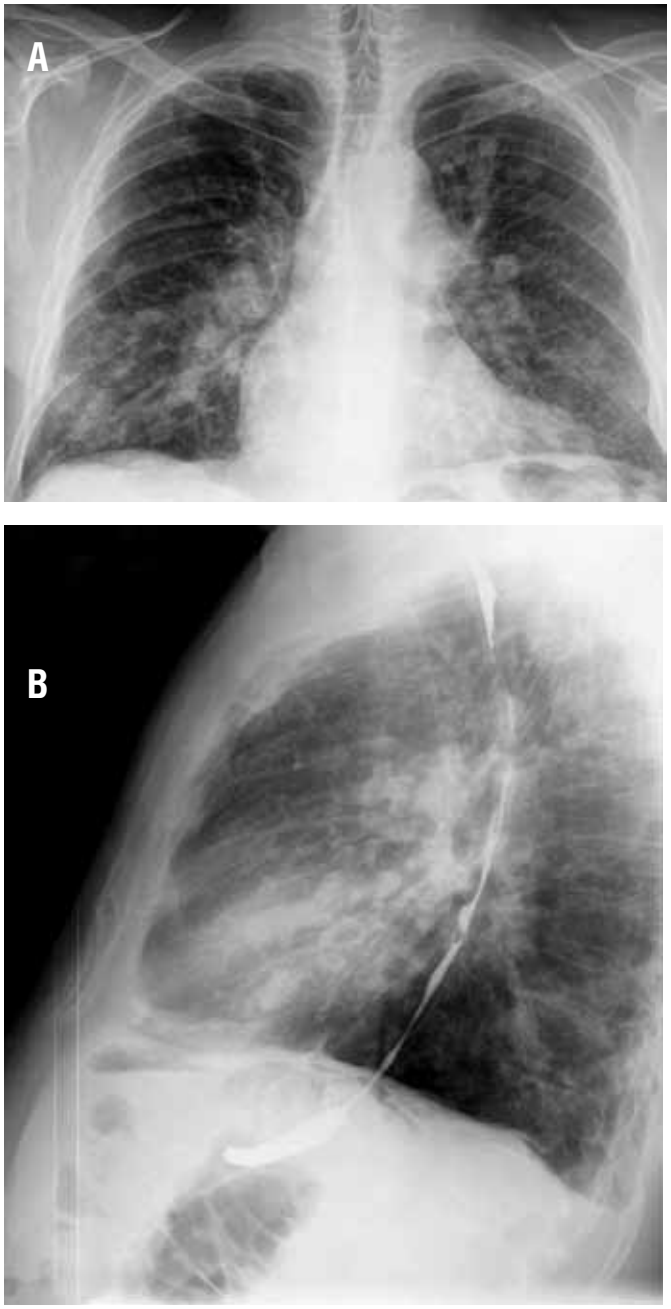

Figure 2. Chest radiography of patient H. in the straight (A) and left lateral projection (B)

of embolism in the pulmonary artery system by tumor masses, recurrent villous myxoma of the RA.

It should be noted that with cardiac myxoma embolic complications, according to various sources, are registered in 40-50% of cases. In myxomes of the LA, embolisms are observed in the arteries of a large circle of circulation. The myxoma of right heart can serve as a source of embolism of the branches of the pulmonary artery, leading to the formation of CTEPH and dysfunction of the right heart. In the literature, there is evidence that by histological structure of the embolus, extracted from the pulmonary artery, cardiac myxoma can be diagnosed, which was later confirmed during surgical interventions [5].

Despite a lot of immunohistochemical studies, the question of the cellular origin of cardiac mixoma is being discussed. Most researchers agree that the tumor originates from reserved subendocardial multipotent mesenchymal cells. However, there is also a point of view that cardiac myxoma develops from endocardial sensory nerve tissue. [6].

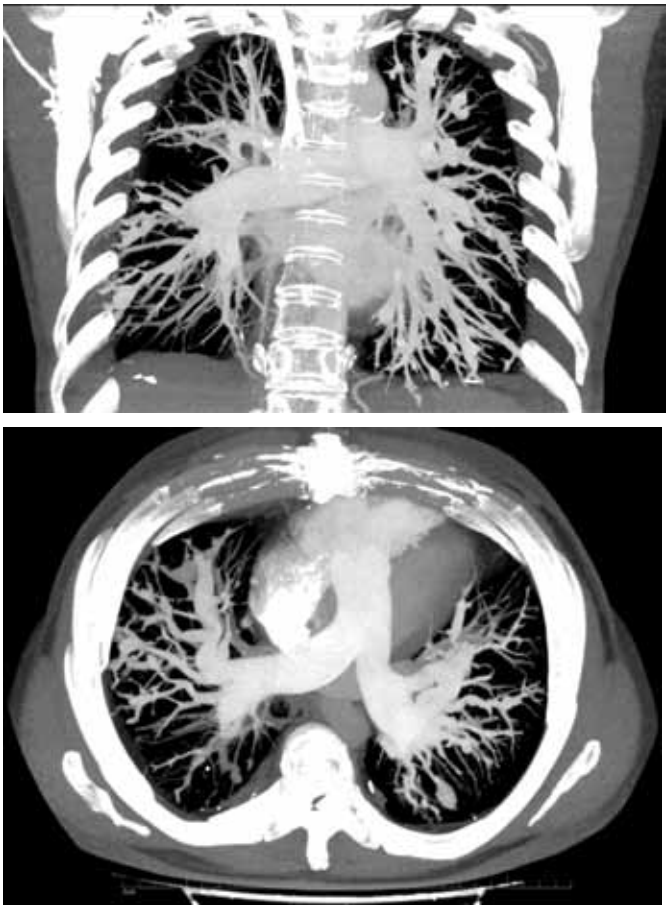

Figure 3. Chest multispiral computer tomography (CT) of the patient H.

There is a lot of conflicting data about the possibility of relative malignancy of cardiac myxoms. According to the literature, during the histological examination of the operating material, malignancy of recurrent cardiac myxoms often can be observed. In favor of the possibility of the development of malignant potential can be mentioned a fact that myxoma cells can infiltrate the walls of the vessels, destroying the muscle layer and leading to the development of aneurysms, including the branches of the pulmonary artery. In addition, the formation of pre-stenotic aneurysms may be because of violation of hemodynamics due to obturation of branches of the pulmonary artery by embolic masses. [7]. Roentgenologically, local vascular enlargements are similar to disseminated process in lung tissue. In this regard, the correct interpretation of the X-ray picture in patients with cardiac myxoma and CTEPH is necessary. The most accurate methods of differential diagnosis in such cases considered multispiral computed tomography – pulmonary angiography and invasive pulmonary angiography with intra arterial contrast.

CTEPH is an unique form of pulmonary hypertension, because it is potentially curable by surgical methods of treatment. [8]. However, in some cases, it is impossible to carry out surgery, which makes us search for alternative methods of therapy. At the present time, a theoretical basis has been accumulated in favor of the use of PAH-specific therapy in case of CTEPH, based on the physiological, pathomorphological and functional characteristics of these forms of pulmonary hypertension. With this form of pulmonary hypertension, there is a violation of the synthesis of nitric oxide, and the functioning of the signal pathway "soluble guanylate cyclase – cyclic guanosine monophosphate (cGMP)", which plays an important role in the development and progression of the disease.

Riociguat is a type of drug, that stimulates soluble guanylate cyclase. By raising the level of cGMP, riociguat leads to

vasorelaxation, reduction of proliferation and has an antifibrotic effect. In the CHEST-1 study, the possibility of achieving therapeutic goals in patients with inoperable CTEPH and in patients with persistent or recurrent pulmonary hypertension after thrombendarterectomy was demonstrated [9]. The possibility of riociguat drug to positively influence on an increase in the distance in the 6-minute walk test at 39 m by the 16th week of treatment ($p<0.001$) has been shown, a decrease in the level of NT-proBNP by 444 pg/ml ($p<0.001$) and a decrease in pulmonary vascular resistance by 226 dyne*s*cm-5 ($p<0.001$), improvement of the functional class by WHO ($p=0.003$). [10]. It is important to note that the positive effects of the drug persisted in the long-term treatment of patients with inoperable CTEPH.

According to the recommendations of the ESC/ERS Guidelines 2015 on the diagnosis and treatment of patients with pulmonary hypertension, riociguat is currently the only drug with an evidence base for treatment of persistent / residual PH after surgical treatment and for patients with inoperable form of CTEPH. Patients are also recommended lifelong anticoagulant therapy, while there is currently no evidence base on the effectiveness of new anticoagulant drugs [11].

CONCLUSIONS

This clinical case demonstrates the formation of CTEPH as a rare complication of recurrent villous myxoma of the RA. Difficulties in diagnosis were the presence of an atypical radiographic pattern, which is similar to a disseminated process in the lungs. The use of such diagnostic methods as MSCT-pulmonary angiography and invasive pulmonary angiography, allowed to make an accurate diagnosis.

Inoperable patients are recommended to use PAH-specific therapy, where riociguat should be the first choice drug.

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