Intraluminal formations of the heart are a heterogeneous group: from blood clots to malignant neoplasms. The nosology of these formations can only be determined by morphological research. Myxofibrosarcoma of the heart is a rare malignant tumor. According to modern concepts, myxofibrosarcoma belongs to the group of intimal sarcomas, subgroup of undifferentiated pleomorphic sarcomas. We describe two cases of myxofibrosarcoma of the heart: in one subject against the background of inflammatory myofibroblastic heart tumor; in another subject - with a history of breast cancer and diffuse large B-cell lymphoma. An attempt was made to identify similar mutations in patients with these tumors according to the literature.

Key words: myxofibrosarcoma of the heart; inflammatory myofibroblastic tumor of the heart; immunohistochemical study; tumor of the heart

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Primary cardiac tumors are rare and present a major difficulty in diagnosis. According to a systematic review, the incidence of primary cardiac tumors is 0.002-0.3%. Myxomas account for 90% of cardiac tumors, and the most common malignant cardiac tumor is sarcoma. The prevalence of myxofibrosarcoma (MFS) is less than 1% of cardiac malignancies [1].

Inflammatory myofibroblastic tumor (IMT, plasma granuloma, inflammatory pseudotumor, xanthomatous granuloma, inflammatory fibromyxoid tumor, pseudosarcomatous inflammatory proliferation) was first described by H. Brunn et al. in 1939. The tumor has been described in all organs and in all age groups but occurs most frequently in childhood. The most frequent localization of the tumor is in the lung [2]. The literature contains data on the possibility of metastases and angioinvasion of extracardiac IMT [3]. According to some authors, tumor recurrence occurs in 8% of patients and is attributed to inadequate tumor resection or adjuvant treatment [4]. The World Health Organization classifies IMT as a tumor of uncertain biological potential.

The World Health Organization defines MFS as a malignant tumor composed of fibroblasts with varying amounts of intercellular collagen and abundant myxoid stroma. According to modern concepts, MFS belongs to the intimal sarcoma group, a subgroup of undifferentiated pleomorphic sarcomas [5]. The molecular pathogenesis of MFS remains incompletely elucidated.

The aim of our paper is to present and discuss 2 rare cases of myxofibrosarcoma of the heart.

Clinical Case No.1.

A 40-year-old male patient complained of increasing dyspnea on exertion with an increase in NYHA functional class from II to IV within 1-month, lower extremity edema, dry cough, chest pain at night in the supine and left lateral positions, and the ability to sleep only in the sitting position. Differential diagnostic search included tuberculosis, hypothyroidism, lower respiratory tract infection, and chronic heart failure. Echocardiography (Echo) revealed a mass in the left atrial cavity (LA) obstructing outflow from the LA; myxomatous changes in the mitral and tricuspid valve leaflets, LA dilatation. The mass floated, rushed into the left ventricle, and obstructed the mitral valve orifice with the formation of critical mitral stenosis. Blood flow at the valve was accelerated, and the mean gradient increased. There was early systolic mitral regurgitation with two eccentric narrow jets along 2/3 of the LA lateral wall and interatrial septum, signs of high pulmonary hypertension.

Based on the vital signs, the decision was made to perform surgery to remove the LA mass. The mass was a round-oval lobular tissue of white-yellow color, soft-elastic consistency, and a size of 4.0 x 4.5 x 3.5 cm. At one of the poles was a 2.0 x 1.5 cm “pedicle” attached to the posterior wall of the LA. In section, the tissue was heterogeneous: the periphery was white-yellow, whereas the central part was red-pink (Fig. 1). The mass was removed with adjacent atrial sections; it was not possible to reliably assess the resection margin.

Histologically, the mass was a low cellular tumor lined with endothelium with a distribution of cells predom-
inantly at the periphery of the tumor and few in the central parts, which were during an abundant eosinophilic, dense, loose, and myxoid stroma. Spindle-shaped cells without clear boundaries, round, and elongated nuclei, with finely distributed chromatin, with single small nuclei in individual cells, visible under 200× magnification. Nuclear atypia was not pronounced. Cells with mitotic figures are scattered. The stroma is vascularized due to some thin-walled vessels. Faint diffuse and small focal infiltration by small lymphocytes with mature nuclear morphology was noted (Fig. 2).

The main differential diagnoses were myxoma, fibroelastoma, IMT, myxofibrosarcoma, and myxoid leiomyosarcoma. Immunohistochemical examination revealed cytoplasmic expression of vimentin, smooth muscle actin, desmin, and pancytokeratin on tumor cells. Expression of S100 protein (a family of multigenic group of non-biquitous cytoplasmic intracellular Ca²⁺-binding proteins), anaplastic lymphoma kinase, and myogenin was not detected on the tumor cells. The Ki67 index of proliferative activity of tumor cells was 5-15% (Fig. 3). The patient was diagnosed with an inflammatory myofibroblastic cardiac tumor, which was surgically removed.

In the early postoperative period, complications occurred due to postpericardiotomy syndrome, which was successfully treated. No intracavitary LA masses were detected on the control Echo. The patient received extensive therapy with nonsteroidal anti-inflammatory drugs in the postoperative period and was discharged to a sanatorium.

Two years later, the patient again developed dyspnea on light exertion and on the left side. She was examined as an outpatient and a LA mass was discovered. ECG findings: atrial flutter with irregular conduction of excitation to the ventricles and a heart rate of 130 bpm, incomplete right bundle branch block, repolarization disturbance in the form of negative and biphasic T waves in most leads. Echo: marked mitral valve obstruction with high pulmonary hypertension, mass of LA.

Given the possibility of embolic complications, emergency surgery was performed to remove a mass in the left atrium through the right atrium and interatrial septum. It was impossible to radically remove the mass because it had visibly invaded the orifice of the pulmonary veins and the area of the mitral

Fig. 1. Macroscopic view of inflammatory myofibroblastic cardiac tumor.

Fig. 2. Inflammatory myofibroblastic tumor of the heart: a - low cellular tumor lined with endothelium, with cell distribution mainly along the tumor periphery; b, c - round, oval and spindle-shaped tumor cells in dense stroma (magnification 20, 200 and 400, respectively, staining with hematoxylin and eosin, further HE).

Fig. 3. Immunohistochemical examination of an inflammatory myofibroblastic cardiac tumor with different antibodies (brown stain), magnification 100.
valve fibrous ring. The mass was resected as much as possible, preserving the unmodified atrial tissue.

The removed mass was lobular, 5.0 x 4.0 x 2.5 cm in size, partially covered by smooth endocardium, yellowish-white in section, with necrosis and hemorrhage (Fig. 4). On histologic examination, the tumor was a lobular tumor composed of polymorphic atypical spindle-shaped and round cells in a myxomatous and fibrous stroma. Necrosis and hemorrhages were present (Fig. 5).

On immunohistochemical examination, tumor cells expressed p53 protein, vimentin, smooth muscle actin, membrane-binding mucin type 4, mouse microchromosome subtype 2 protein, and focal expression of CD56 (CD, differentiation cluster) was observed (Fig. 6). There was no expression of desmin, myogenin, anaplastic lymphoma kinase, pancytokeratin, epithelial membrane antigen, CD99, CD34. The patient was diagnosed with myxofibrosarcoma. The proliferative Ki67 activity was 20%. Thus, this patient developed myxofibrosarcoma on a background of inflammatory myofibroblastic tumor.

In the postoperative period, atrial flutter was recorded on the ECG (Fig. 7). No complications occurred in the postoperative period and the patient was discharged for outpatient treatment. The condition and dynamics of the patient’s disease in the next phases of treatment are unknown.

Clinical case No.2

A 50-year-old patient with infiltrating ductal carcinoma of the left breast, intermediate malignancy grade T4N1M1, diffuse B-cell lymphoma, with radiotherapy and chemotherapy in 2010, complained of marked weakness, shortness of breath that occurred with minimal physical activity, in the prone position, insomnia, and dry cough 11 years later.

The ECG showed incomplete left bundle block, incomplete right bundle block, repolarization changes in the form of decreased T amplitude of diffuse nature.

According to the Echo data, the right ventricle (RV) shows a volumetric mass of in-
homogeneous, heterogeneous structure with a size of 3.5 x 3.8 cm, originating from the basal portions of the anterolateral wall of the RV and obstructing blood flow. The RV exit tract pressure gradient was 48 mm Hg, and the effusion in the pericardial cavity was approximately 250 ml (Fig. 8).

After multispiral computed tomography of the heart, the RV mass with infiltration into the pericardium, pericardial effusion, drainage into the left pleural cavity, formation of the left mammary gland, and left S4 atelectasis were observed.

Whole-body positron emission tomography showed a focus with pathologic accumulation of radiopharmaceuticals in the RV with irregular contours; heterogeneous, with scintigraphy dimensions of 78 x 73 x 56.5 mm. Primary multiple neoplasia was suspected: primary cardiac and left breast tumors with secondary involvement of axillary lymph nodes (Fig. 9).

Cytologic analysis of pericardial fluid revealed no evidence of the presence of lymphoproliferative disease. The main differential diagnostic search included: cardiac lymphoma, metastasis of breast carcinoma, and primary cardiac mass. It was decided to perform an endomyocardial biopsy to decide on further treatment tactics.

Histologic examination revealed the tumor as spindle-shaped cells in a myxoid matrix (Fig. 10). On immunohistochemical examination, the tumor cells did not express CD20, prolactin-induced protein (PIP), mammoglobin, or pancytokeratin; proliferative activity Ki-67 was 22%. Immunophenotyping of the sarcomas expressed murine microchromosome subtype 2 protein, vimentin and smooth muscle actin, and membrane-binding mucin type 4; there was no expression of myogenin, desmin, S100 protein, myoblast determination protein 1, or CD34 (Figure 11). The immunophenotype of the tumor was consistent with that of cardiac myxofibrosarcoma.

The patient had tumor infiltration of the anterior and lateral walls of the RV. As a result, complete surgical excision of the tumor was not possible. The patient was treated with palliative chemotherapy. The patient’s condition and dynamics as well as further treatment in the next stages are not known.

**DISCUSSION**

The pathogenesis of IMT is not fully understood. Despite numerous studies, only hypotheses about the origin of this tumor have been presented. More than 21 partner genes involved in the pathogenesis of IMT have been discovered, and the spectrum of these genes is updated every year [6]. It is known that 50 to 70% of tumors have a rearrangement of the ALK gene resulting in a chimeric protein with tyrosine kinase activity, which can be detected by immunohistochemical examination or FISH. Genetically, more than half of IMTs belong to the so-called “ALKom” family (ALK - anaplastic lymphoma kinase; ALK is activated in some types of solid tumors). Thus, oncogenic activation of ALK plays an important role in the pathogenesis of the following tumors: anaplastic large cell lymphoma, non-small cell lung carcinoma, medullary renal carcinoma, neuroblastoma, and anaplastic thyroid carcinoma [7]. In 2011, the Food and Drug Administration (FDA) approved the first targeted drug, crizotinib, for the treatment of patients with ALK-positive tumors [8].

In the heart, IMT usually grows as a cavitory mass on a pedicle connected to the endocardium, but there are also data about the growth of this tumor around the coronary arteries, which can lead to acute coronary syndrome and sudden cardiac death of the patient [10].

The clinical manifestations of IMT vary widely, ranging from an asymptomatic course to manifestations of heart failure, angina, and...
transient ischemic attacks [11]. The leading diagnostic method is Echo examination, which can detect an intracavitary mass in the ventricle and establish the primary differential diagnosis with thrombotic masses. If a ventricular cavity mass is found, the primary differential diagnosis includes thrombi, myxomas, and non-myxomatous masses.

IMT exhibit high morphologic variability, ranging from predominantly hyalinized stroma with a small number of spindle-shaped cells with a background inflammatory infiltrate to highly cellular myofibroblastic proliferates.

The gold standard of treatment is complete surgical excision of the tumor. Radiation therapy is successfully used for inoperable neoplasms and recurrences. If the lesion has invaded the heart, complete surgical removal may not be possible because the tumor spreads directly to vital structures such as coronary arteries or pulmonary veins, so additional treatments should be considered. There are numerous data on successful regression of the tumor with oral corticosteroid therapy, in which most patients experienced a significant reduction in the size of the residual lesion and did not require additional surgery [12].

In our case, it remains unclear whether this was a recurrence of IMT with conversion to MFS or whether MFS developed de novo after removal of IMT or whether MFS developed from residual IMT tissue. There are no reports in the literature of conversion of IMT to MFS, but rapid recurrence of IMT in a five-month-old child [13] and rapid growth of MFS in a 57-year-old woman [14] have been described.

MFS have a very heterogeneous karyotype with different clones observed not only in each individual patient but also in different sections of the same tumor. There is evidence in the literature that activation of the AKT/mTORC2 pathway correlates with the histological grade of malignancy and progression of MFS [15]. It is also described that two-thirds of MFS exhibit overexpression of MET (tyrosine kinase receptor; upon binding to its ligand, hepatocyte growth...

Fig. 9. Positron emission tomography - whole body imaging (a). Foci of pathologic accumulation of 18F-fluorodeoxyglucose radiopharmaceutical (RPC) in the left mammary gland, left axillary region, giant focus of pathologic RPC accumulation in the right ventricle. RPC accumulates in the urinary bladder as it is physiologically excreted through the urinary tract. In the right ventricle (b), a volumetric mass occupying ¾ of the cavity can be seen and is characterized by pathologic accumulation of RPC (indicated by a white arrow). Fluid is detectable in the pericardial cavity and left pleural cavity (indicated by gray arrows).

Fig. 10. Endomyocardial biopsy, cardiac myxofibrosarcoma in 2 biopsy fragments: a - magnification 20 (HE stain), b - magnification 40 (HE stain), c - magnification 40, van Gieson stain, d, e, f - magnification 100, 200 and 400, respectively (HE stain).

Fig. 11. Immunohistochemical examination of myxofibrosarcoma of the heart with different antibodies (brown stain), magnification 100.
factor, it activates a variety of cellular signaling pathways, including involvement in proliferation, motility, migration, and invasion), which correlates with unfavorable clinicopathologic factors and independently predicts shorter survival [16].

The most common complaints in patients with MFS are dyspnea and syncope. Syndromically, patients most commonly show signs of cardiac and valvular failure. On physical examination, heart murmurs, paradoxical pulse, hypotension, and tachycardia are most noted in these patients [17]. ECG changes have been described, some of which were also observed in our cases: bundle branch block and decreased amplitude of the T wave. Bundle branch block may be associated with invasive growth. Decreased amplitude of T wave may be caused by myocardial and endocardial damage. MFS cardiac metastases may present as epileptic seizures, acute impairment of cerebral blood flow, and intracerebral hematoma [18].

Surgical treatment is the main treatment for sarcomas of the heart. Depending on tumor stage and degree of differentiation, the results of surgical treatment vary widely. However, there is evidence in the literature that patients who have tumor resection have a significantly higher survival rate than patients without surgery [19].

In the second patient, we have a history of primary multiple cancers and the occurrence of primary cardiac MFS, which can be explained by common mutations in the genome. As described above, progression of MFS correlates with activation of the AKT pathway. We found evidence in the literature that this pathway may also be involved in the oncogenesis of breast ductal carcinoma. HER2 activates the cytoplasmic domain of HER3, which in turn triggers the AKT pathway and thus the prooncogenic cascade [20]. There is evidence of MET overexpression in breast tumors, which is associated with higher mortality. However, in Asian patients as well as in HER -2-positive breast carcinomas, overexpression of MET does not affect prognosis [21]. There are reports of PIK3CA-mutated B-cell lymphomas such as that of our patient. Mutations in PIK3CA lead to activation of the same AKT pathway, which triggers another prooncogenic cascade [22]. Thus, in our patient, activation of the ACT pathway may have triggered the oncogenesis of multiple tumors. Unfortunately, we can neither confirm nor deny this assumption at this stage. Therefore, genome sequencing will be performed in this patient to identify mutated genes and to find a possible targeted therapy.

Currently, several targeted drugs are known to block the ACT pathway: Ipatasertib (GDC-0068), Capivasertib (AZD5363), Afuresertib (GSK2110183) Uprosertib (GSK2141795), Triciribine (PTX-200), Cenisertib (R763/ AS703569). However, only the drug alpelizib is approved for clinical use, whose indication is a combination of the following conditions: HR+, HER2- advanced or metastatic breast cancer; PIK3CA gene mutation (PIK3CA+); disease progression during or after hormone therapies. Theoretically, if mutations in the AKT pathway are detected, it could be reasonable to treat this patient with alpelizib off-label if no other drugs are available for treatment in clinical trials.

The trend toward personalized medicine has been actively discussed in the world recently. For patients with primary multiple cancers as well as rare tumors, this principle should be applied first. Since surgical resection of MFS is not a radical treatment of the tumor, patients require additional chemotherapy. It is reasonable to consider the biological characteristics of the tumor when choosing this therapy. Unfortunately, we currently do not know enough about all genetic rearrangements of MFS. For this reason, NGS genome screening is recommended for these patients. Further treatment of patients should ideally be done with targeted therapy or CAR -T-cell therapy to achieve the best possible long-term results.

CONCLUSION

Myxofibrosarcoma may develop on a background of inflammatory myofibroblastic tumor. Immunohistochemical examination and FISH for ALK mutations in an inflammatory myofibroblastic tumor is recommended. If ALK mutations are detected, clinical follow-up is required to rule out other tumors in the ALK family. Myxofibrosarcoma may share genetic disorders with other tumors involving the AKT pathway and characterized by overexpression of MET, which should be further investigated for targeted therapy.

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