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METASTATIC CARDIAC TUMORS: LITERATURE REVIEW AND OWN OBSERVATION OF TESTICULAR TUMOR METASTASIS IN THE RIGHT VENTRICLE OF THE HEART

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Background: **Tumors of the heart are uncommon and usually benign (in 93% cases myxomas are observed). More often secondary, metastatic tumors are detected in the heart, as a rule, at pronounced progression of the malignant neoplasm with multiple lesions of other internal organs (lung, pleura, liver, etc.). Literature review on cardiac metastases of different tumors is given.** ***Case Report:*** **Own observation of a young man with rare single metastasis of malignant testicular germ cell tumor with predominance of embryonic carcinoma in the right ventricle of the heart is presented; the primary tumor was detected after metastasis revealing. The diagnostic algorithm using routine histological study supplemented with immunohistochemistry, including detection of cytokeratin pan, cytokeratin 5/6, cytokeratin 7, CD30, OCT4, TTF-1, hCG, and AFP markers expression, is described.**
Key Words: **embryonic carcinoma, cardiac metastasis, morphological diagnostics.**

Cardiac tumors are rare and histologically heterogeneous neoplasms (0.002–0.3% in the population), primary originating from the heart tissue or metastasizing through the blood and lymphatic vessels, or sprouting into the heart from other organs [1–4]. The first mention of cardiac tumor belongs to 1559, when M.R. Columbus at the autopsy found neoplasm of the left ventricle.

More than 90% cardiac tumors are not diagnosed during the patient's life due to nonspecific or very mild clinical symptoms. Most often clinical signs are dyspnea, cough, tachycardia, arrhythmia, chest pain, heart failure, cardiac tamponade, and systemic thromboembolism [2]. Cardiac tumors are detected accidentally, usually at surgery or autopsy (in 2.3–7.1% cases) [5, 6].

Cardiac tumors are diagnosed taking into account data of echocardiography, electrocardiography, radiography, ventriculography, MRI and MSCT of the heart and biopsy results.

About 75% cardiac tumors are benign, and 25–33% are malignant (Table).

Primary cardiac tumors account for 0.02–5% of all neoplasms of the heart, secondary (metastatic) tumors are revealed almost in 95% cases, i.e. 13–40 times more often [7]. Benign cardiac tumors are myxomas (in 50–75% cases), teratomas, rhabdomyomas, fibromas, hemangiomas, lipomas, papillary fibroelastomas, pericardial cysts, paragangliomas, etc. Malignant cardiac tumors are sarcomas (angiosarcoma is found almost in 30% cases, rhabdomyosarcoma — in 20%), pericardial mesothelioma and lymphoma [8].

Extracardiac mediastinal and pericardial tumors that lead to the heart compression constitute a separate group.

Table. The most common primary cardiac tumors

Benign	Cases, %	Malignant	Cases, %
Myxoma	24–50 (according to other data – up to 75)	Angiosarcoma	7
		Rhabdomyosarcoma	5
		Mesothelioma	4
Lipoma	8	Fibrosarcoma	3
Papillary fibroelastoma	8	Lymphoma	1
Rhabdomyoma	7		
Fibroma	3		
Hemangioma	3		
Teratoma	3		
Mesothelioma of the atrioventricular node	2		

Metastatic tumors account for 1.5–8% of all cardiac neoplasms; most often they affect pericardium, less often — endocardium and valves, and heart muscle.

Secondary cardiac and pericardial lesions due to infiltrative tumor growth are commonly detected at mediastinal lymphomas (25.7%).

Cancer metastases are most common in the pericardium; usually metastases of lung (30.7%; with squamous cell variant in 35.9%), gastrointestinal tract (25.7%), kidney (10.3%), and mammary cancer (7.6%) are revealed [9].

Metastases at melanoma, lung carcinoma and mammary cancer are characterized by the most pronounced cardiotropic effect. Thus, heart lesions are detected in 64% patients with melanoma metastases, but intravital diagnosis of intracardiac melanoma metastases does not exceed 2%. Cardiac metastases more often are detected in non-Hodgkin lymphoma than in Hodgkin disease [10–12].

Also in literature cardiac metastases are described at kidney, esophageal, and cholangiocellular cancer, squamous cell carcinoma of the neck, testicular malignant neoplasms, etc. [13, 14].

Almost any malignant tumor can metastasize in the heart: pleural mesothelioma — in 48.4% cases, melanoma — in 27.8%, lung adenocarcinoma — in 21.0%, undifferentiated carcinoma — in 19.5%,

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Abbreviations used: AFP – alpha-fetoprotein; GCT – germ cell tumor; hCG – human chorionic gonadotropin; IHC – immunohistochemistry; TTF-1 – thyroid transcription factor-1.

mammary carcinomas — in 15.5%, esophageal squamous cell carcinoma — in 18.0%, lymphomas and hemoblastoses — in 9.0%, thyroid and kidney tumors — in 7.0%, liver neoplasms — in 1.2%, colorectal cancer — in 1.4–2.0%. On autopsy metastases in patients with malignant neoplasms are found in 4–18% cases (16.8% — in persons younger than 64 years and 8.5% — in the age after 85) [12, 15–17].

Cardiac metastases usually look like small dense knots; however, in sarcomas and lymphomas diffuse tumor infiltration of the organ is found [18, 19].

As a rule, cardiac metastases are revealed after primary tumor detection, and only 10% of the time of their existence manifest clinically.

Malignant cardiac tumors are associated with poor prognosis; even if completely resected, they are often detected at the late stage, when only palliative treatment is possible [20–22].

According to the literature, 5-years survival in benign cardiac tumors is 83%, in malignant neoplasms — 30%, in metastatic lesion — 26%, in multiple cardiac tumors — does not exceed 15% [8].

Cardiac tumors manifestations are caused by the type of neoplasm, its localization, size, and ability to decay. Tumors of the heart, both primary and secondary, can cause shortness of breath, acute pericarditis, cardiac tamponade, rhythm disturbances, atrioventricular blockage, congestive heart failure, and embolic syndrome.

Late diagnosis is not uncommon in malignant cardiac tumors, as the symptoms of the disease are usually nonspecific, they are detected only with massive damage to the heart, also they are prone to rapid progression, as evidenced by our clinical observation.

THE CLINICAL CASE

Patient T., male, 24 years old, hospitalized to the Amosov National Institute of Cardiovascular Surgery January 16, 2013 with a preliminary diagnosis “tumor of the right ventricle of the heart”. According to the patient, occasionally after physical exertion, blood pressure increases were noted. During the last month there was a progressive shortness of breath, which was the reason for appeal to the cardiologist at the place of patient’s residence. On echocardiography in the cavity of the right ventricle a rigid formation, tightly connected to its wall was revealed. In order to clarify the diagnosis and make a decision about possible surgical treatment, the patient was referred to Amosov National Institute of Cardiovascular Surgery.

At hospitalization: the patient is well-fed, the skin is pale, marked swelling of the lower extremities. Complaints on constant shortness of breath and fatigue with little physical exertion. Severe congestive heart failure was not detected.

Moreover, while anamnesis collecting and further examination, it was found that in childhood the cryptorchidism was diagnosed, but no treatment was performed.

According to the laboratory data, no other pathological changes were detected. Auscultation revealed systolic murmur of low intensity in the projection of the tricuspid valve. On the X-ray a slight increase of the heart was noted; on the electrocardiography — complete blockade of right brunch of the bundle. The heart rate was 80 in 1 min. Blood pressure 120/80 mm Hg. Moderate hypertrophy of the right ventricle of the heart. Coronary insufficiency was not found.

On two-dimensional echocardiography in the right ventricular cavity, a massive rigid formation 9 × 6 cm was detected with transition to outflow tract and its obturation (Fig. 1); light insufficiency of the mitral and tricuspid valves was revealed. Contractility and size of the left ventricle were satisfactory (ending diastolic index — 42 ml, ejection fraction — 58%).

Computed tomography revealed a neoplasm that filled the right ventricle cavity and tightly accreted to its anteroposterior wall (Fig. 2). It was not possible to identify the degree of subvalvular apparatus defeat.

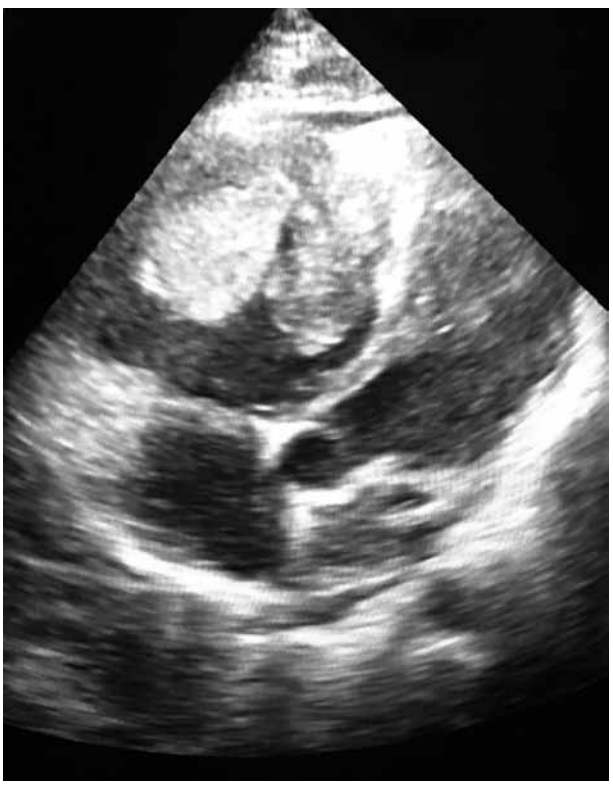

Fig. 1. Echocardiography. The neoplasm 9 × 6 cm in the right ventricular cavity with outflow tract obturation

Fig. 2. Computed tomography. Tumor filling the right ventricle cavity and tightly fused to its anterior wall in the region of the apex

Because of the high risk of complete obstruction of the right atrioventricular orifice, tumor fragmentation and embolic complications, surgery was performed at artificial blood circulation. Right ventricular wall mobility was significantly limited. In a right ventricle cavity a neoplasm with a tuberous, thrombus-coated surface, adjacent to the tricuspid valve, was revealed (Fig. 3).

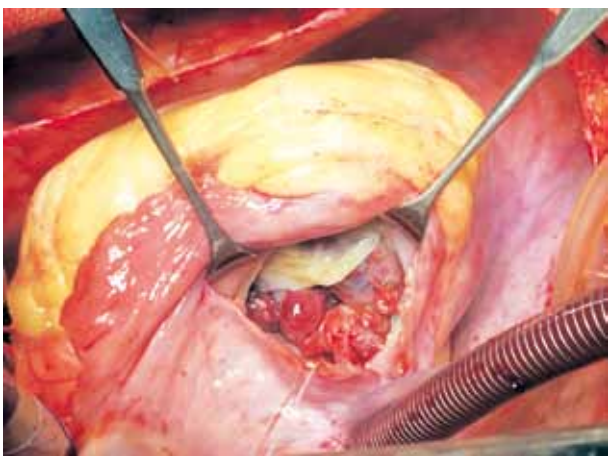

Fig. 3. Intraoperative photo. Clots-coated neoplasm on the surface of tricuspid valve

After clots removing a whitish dense-elastic formation, 8 × 6 × 6 cm was revealed, with irregular shape, fused to the anterior wall of the right ventricle and papillary muscles, spreading to the apex of the right ventricle with deep invasion into the myocardium. The tumor was removed by fragments, while trying to maintain the integrity of papillary muscles and tricuspid valve chords (Fig. 4). Valve apparatus was not affected.

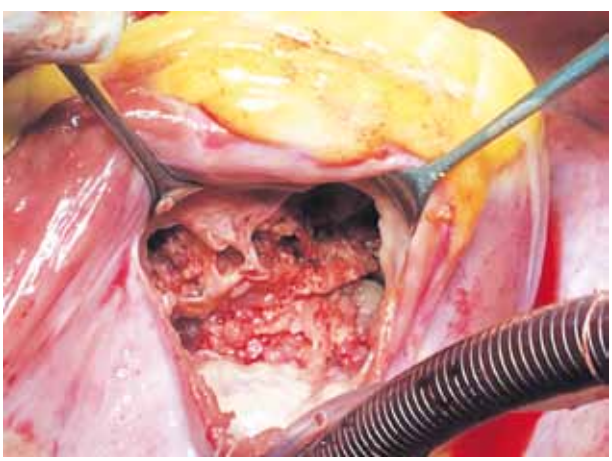

Fig. 4. Intraoperative photo. Stage of the tumor removing. Isolation of the chordal-papillary apparatus of the tricuspid valve

Preliminary clinical diagnosis was established: myxoma or sarcoma of the right ventricle of the heart.

METHODS OF THE STUDY

Tumor tissue after fixing for 12 hours in neutral formalin was subjected to standard paraffin wiring and pouring into paraffin. Paraffin sections were stained with hematoxylin and eosin, and then immunohistochemistry (IHC) was performed according to a conventional procedure with antibodies cytokeratin pan (clone AE1/AE3), CD30 (clone Ber-H2), OCT-4 (clone NRG1.1), thyroid transcription factor-1 (TTF-1) (clone 8G7G3/1), cytokeratin 5/6 (clone D5/16/B4), cytokeratin 7 (clone OV-TL 12/30), human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP). We used UltraVision Quanto Detection System HRP (Thermo SIENTIFIC®), with anti-mouse IgG (H+L), anti-rabbit IgG (Y+L), labeled with peroxidase.

RESULTS

Histological study of tumor tissue sections, stained with hematoxylin and eosin, revealed acinar and solid structures built of epithelioid cells with a moderate eosinophilic cytoplasm, vesicular nuclei, containing 1 to 4 basophilic nucleoli, with multiple mitoses (Fig. 5). Thus, embryonal carcinoma with seminoma sites was suspected (Fig. 6, 7). The tumor tissue showed extensive necrosis (Fig. 8).

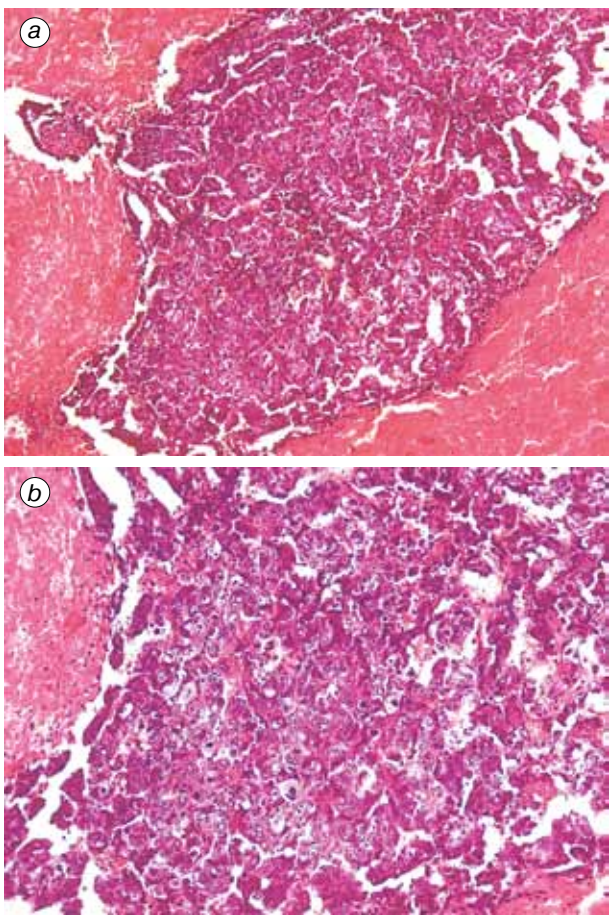

Fig. 5. Cardiac tumor tissue, stained with hematoxylin and eosin, × 100 (*a*) and × 200 (*b*)

In order to confirm the diagnosis we performed IHC test with cytokeratin pan, cytokeratin 5/6, cytokeratin 7, CD30, TTF-1, OCT4, hCG, AFP.

Positive reaction in most tumor cells similar to embryonic carcinoma was marked with cytokeratin pan, and CD30. In some tumor cells similar to seminoma, expression of OCT4 was observed, and in a small area — hCG expression was found (Fig. 9–11). The IHC reactions with other antibodies were negative. Thus, a germ cell tumor (GCT) — an embryonic carcinoma (80% predominance) with sites of seminoma and chorion carcinoma was diagnosed.

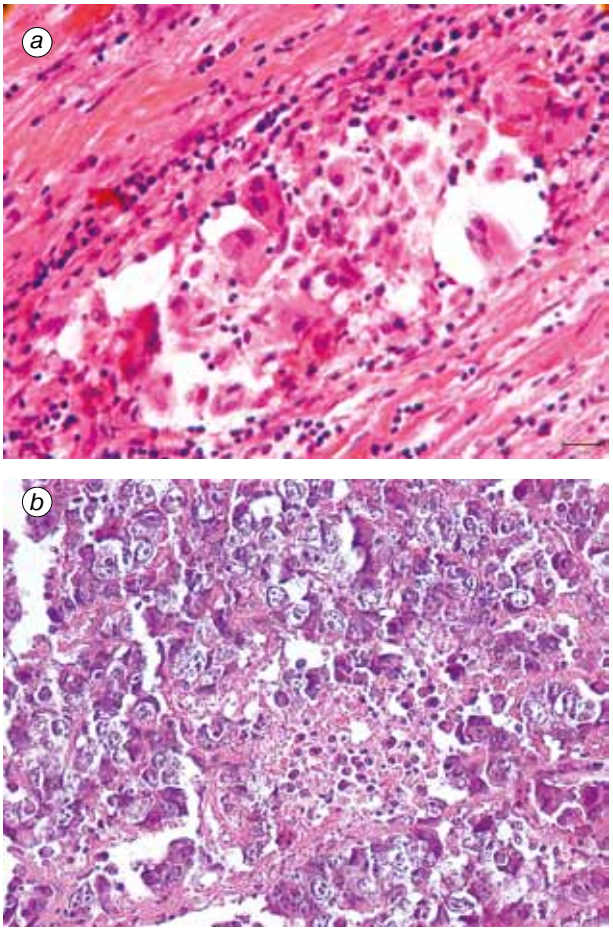

Fig. 6. Cardiac tumor tissue with sites of seminoma: large cells with light cytoplasm and big light nuclei, nucleoli are well contoured, in some nuclei 2 to 4 nucleoli are seen. Lymphoid infiltration of the stroma. Staining with hematoxylin and eosin, × 100 (*a*), × 400 (*b*)

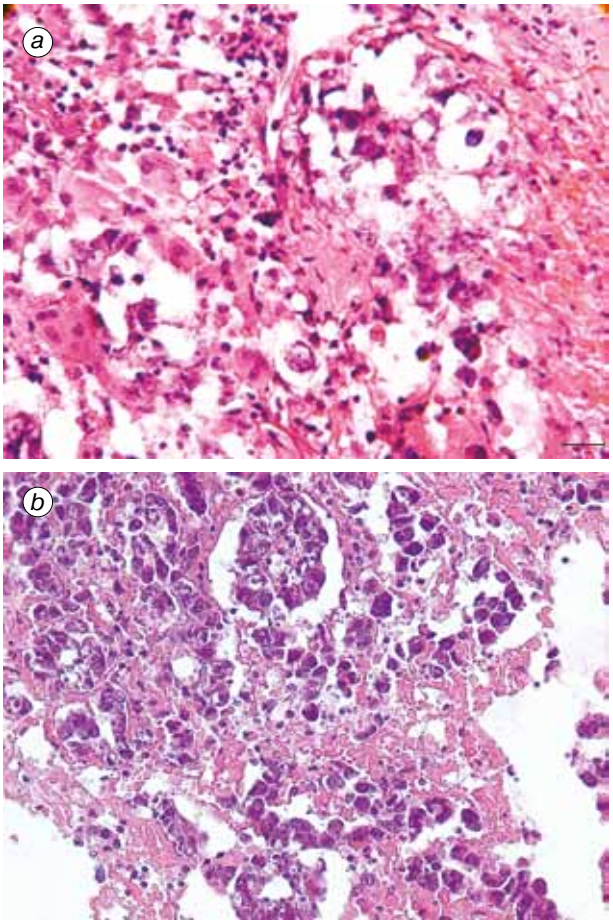

Fig. 7. Cardiac tumor tissue with sites of embryonic carcinoma: cells are large and more atypical compared to seminoma, with atypical hyperchromic nuclei. Large multinuclear ugly cells are seen in the tumor tissue. Staining with hematoxylin and eosin, × 100 (*a*), × 400 (*b*)

Conclusion of the morphological study: a GCT (metastatic) of the right ventricle of the heart with predominance of embryonic carcinoma (80%), sites of seminoma and chorion carcinoma. Most likely (taking into account the anamnesis), the primary tumor originated from an undescended testicle. An additional examination was recommended to identify the primary neoplasm.

After surgery the patient's condition improved: dyspnea and edema of the lower extremities disappeared, tolerance to moderate physical activity increased. The patient was discharged from the hospital on the 10th day after surgery, further examination and treatment in the oncological hospital was recommend, where the primary tumor of the undescended testicle was revealed and removed. Tumor's morphological structure and cells immunophenotypes were similar to the cardiac metastatic neoplasm. The final morphological diagnosis: testicular GCT with prevalence of embryonic carcinoma (80%) and sites of seminoma, and chorion carcinoma. GCT metastasis in the right ventricle of the heart. Chemotherapy was prescribed with positive dynamics.

DISCUSSION

The rare clinical case of the secondary tumor of the right ventricle of the heart is given. The patient suffered from untreated cryptorchidism, and the primary tumor originated from the undescended testicle. This case is unique, since there were no typical metastases in retroperitoneal lymph nodes and lungs; the patient had a single cardiac metastasis.

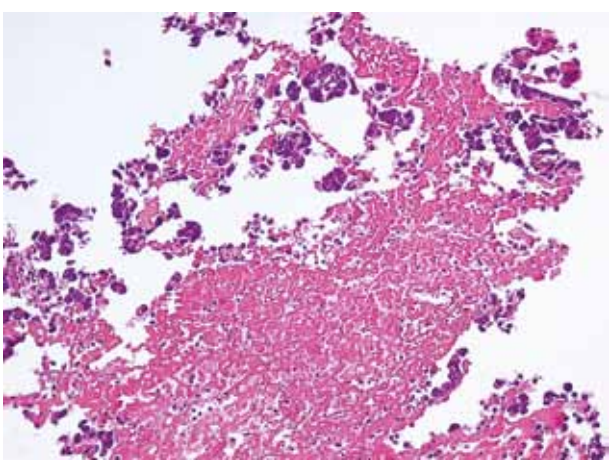

Fig. 8. Cardiac tumor tissue with foci of necrosis. Staining with hematoxylin and eosin, × 200

In the available literature we found single, extremely rare observations of metastatic heart lesions in testicular malignant neoplasm (less than 5%) [16–18]. It was rather difficult to assume the single metastasis of seminoma in the right ventricle of the heart, even taking into account the anamnesis of the disease.

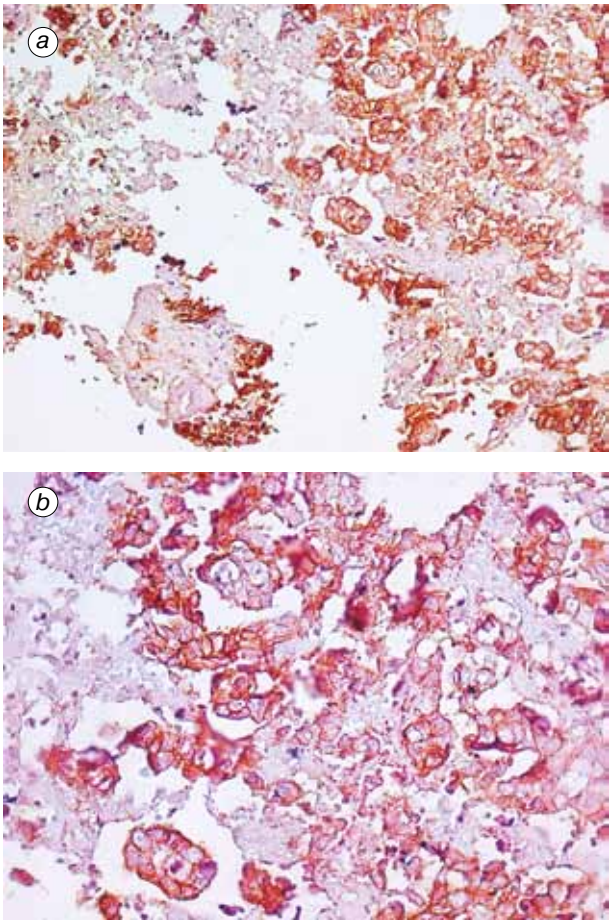

Fig. 9. The IHC study. Tumor tissue of the right ventricle of the heart. CD30 expression confirmed embryonic carcinoma sites in the tumor samples, × 200 (*a*), and × 400 (*b*)

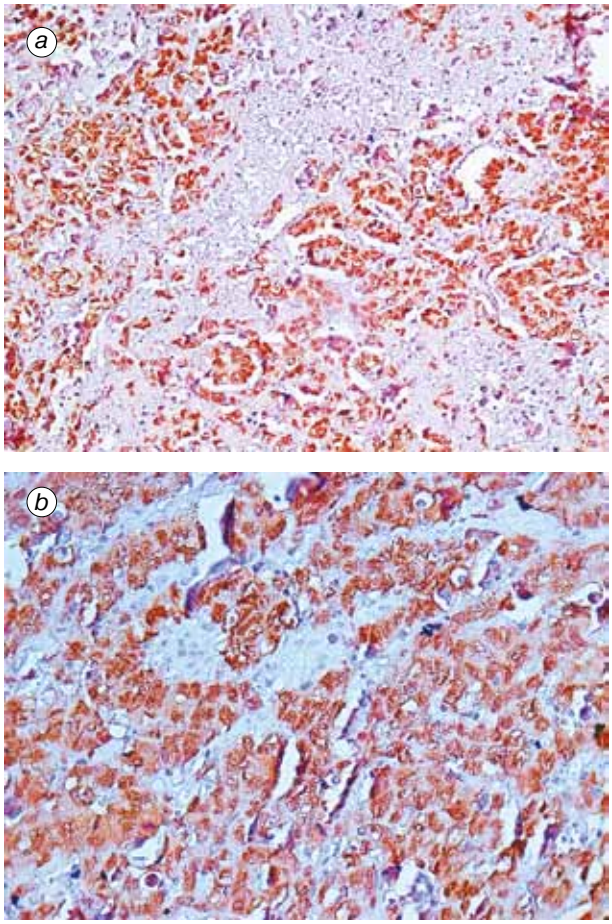

Fig. 10. The IHC study. Tumor tissue of the right ventricle of the heart. OCT4 focal expression confirmed seminoma sites in the tumor samples, × 200 (*a*), and 400 (*b*)

Testicular tumors account for 1 to 3% of all neoplasms in men and occur at a frequency of 1–5 per 100,000, the peak incidence falls on the age of 15–34 years; in 95–99% cases testicular tumors are malignant.

Most testicular neoplasms (95%) are GCT [23]. Caucasian race patients are affected at least 4–5 times more often than Negroid one, the highest incidence is noted in the Scandinavian countries and in New Zealand.

In general, testicular GCT are rare, but most common solid malignancies in men aged 15 to 40 years and the most common cause of cancer patients death in this age group. Testicular GCT divided into seminomas and nonseminomas, which include teratomas, chorion carcinoma, and yolk sac tumors [24–27]. Testicular tumors, built of a single histological type cells, are observed in 60%, mixed neoplasms — in 40%.

In a case of cryptorchidism (especially if the testicle is located in the abdominal cavity, not in the inguinal canal), the risk of malignant testicular tumor occurrence increases 4–6 times. No testis in the scrotum is observed in 2–4% of full-term and in 15–30% of premature newborns, as well as in 1% of males over 1 year [28, 29].

Testicular tumors are characterized by early metastases: most often the regional (retroperitoneal) lymph nodes and lungs are affected, liver, mediastinal lymph nodes, brain, kidneys, bones, bone marrow and skin.

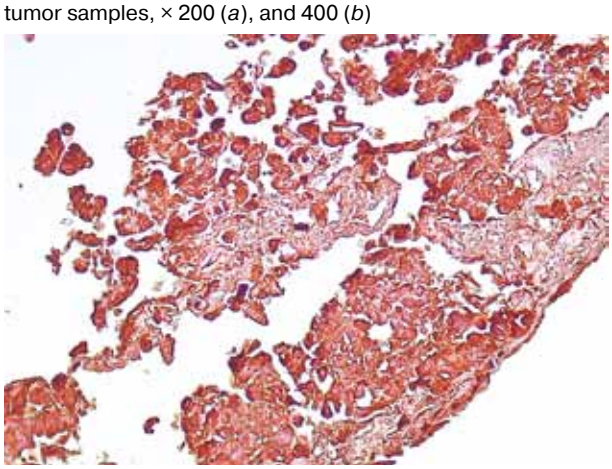

Fig. 11. The IHC study. Tumor tissue of the right ventricle of the heart. hCG focal expression confirmed chorion carcinoma sites in the tumor samples, × 400

Metastases in the heart are observed in 0.9–5% patients with malignant testicular tumors [30, 31].

Most testicular GCT, except of chorion carcinoma metastasize through lymphatic vessels. In patients with aggressive disseminated testicular tumors (usually nonseminoma with trophoblast elements), metastases of any location may occur [32].

Seminoma (38–50% of testicular neoplasms) occurs at a later age than other GCT, usually after 30; it is detected in 60% cases of testicular tumors in cryptorchidism. The neoplasm is built of nests of tu-

mor cells with light cytoplasm and vacuolized nuclei; marked lymphoid infiltration of the stroma is seen, often — foci of necrosis.

At diagnosis establishing metastases in regional lymph nodes are detected in 25% patients, distant metastases — in 1–5%. According to the literature, even at the I clinical stage seminomas are able to metastasize (in 20% cases) [33, 34].

Embryonic carcinoma (32%) is the second most common testicular tumor after seminoma, and more aggressive [29]. According to the literature, 84% of embryonic testicular carcinomas are found in mixed GCT. Tumor cells are more primitive than in seminoma, in 24% cases foci of necrosis and calcification are identified in the neoplasm tissue. Solid variant of embryonic carcinoma is revealed in 55% cases, glandular — in 17%, papillary — in 11%; rarer variants mean "nests" (3%), micro- (2%), and pseudopapillary (1%) structure. In addition, such tumors often contain structures resembling neoplasms of the yolk sac (34%), and chorion carcinoma (46%) [35].

The pure form of chorionic carcinoma is less than 0.5% of testicular tumors. However, the frequency of chorionic carcinoma detection in mixed testicular GCT has not been established reliably [36].

In the chorionic carcinoma sites of cyto- and syncytiotrophoblast, fanciful cells, foci of necrosis and hemorrhages are identified [29].

Chorion carcinoma early metastasizes into lungs, liver, brain and other organs [37]. Testicular GCT with sites of chorion carcinoma in 11% give regional, in 7% — distant metastases [36].

Testicular yolk sac tumors are often detected in children, they are not very aggressive, but in adults prognosis is poor. The tumor consists of primitive epithelial-like germ cells forming glomerular-like structures, surrounding the capillaries (Schiller — Duval bodies) [29].

Most testicular GCT can be diagnosed by routine histological study, but IHC is the key to determine neoplasm subtypes and an individualized treatment regimen, to estimate prognosis of the disease.

Immunophenotypes of various testicular GCT differ. OCT4 expression is characteristic for seminoma, AFP — for yolk sac neoplasms, hCG — for chorion carcinoma [38]. Cytokeratins negative expression allowed to exclude metastases of adeno- and squamous cell carcinoma, including lung tumors (no TTF-1 expression). CD30 expression helped to identify sites of embryonic carcinoma in the tumor tissue, OCT4 and hCG focal expression — to find foci of seminoma and chorion carcinoma. AFP negative expression allowed to exclude yolk sac tumor.

According to data of Amosov National Institute of Cardiovascular Surgery, in 1979–2018 years 912 patients with cardiac tumors have been under observation, among them 63 (6.9%) — with malignant neoplasms different in histology and localization. Most often cardiac malignancies were found in the left atrium (24 (38.1%) cases), least often — in the right ventricle (in 6 (9.5%) patients).

In practice, certain difficulties arise when it is necessary to determine variants of cardiac tumor spread, and to differentiate primary and metastatic neoplasms [39].

CONCLUSION

Cardiac tumors are uncommon, it causes the difficulty of their clinical and morphological diagnosis. A detailed clinical examination is very important for excluding metastatic nature of the neoplasm. Metastases of testicular GCT is very uncommon variant of a secondary malignant cardiac neoplasm. To verify the tumor clinical data, and results of histological study should be considered, also IHC with a wide panel of antibodies is necessary, including markers to exclude lung cancer, thymoma, GCT. The recommended panel of antibodies: cytokeratin pan, cytokeratin 7, cytokeratin 5/6, TTF-1, CD30, AFP, hCG, OCT-4.

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