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HEART TRANSPLANTATION FOR PRIMARY CARDIAC SARCOMA

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Primary cardiac sarcoma is a rapidly progressive, aggressive cardiac tumor that is very rare in the general population. Conservative treatment for this tumor is not very effective. The only effective treatment is radical surgical removal of the malignancy. However, if sarcoma removal cannot be performed, heart transplantation (HT) becomes the only treatment option. The median survival of heart recipients with preoperative cardiac sarcoma is 8.5 months. Globally, such operations are performed in a small number. This paper presents the first experience of HT for a patient with primary cardiac sarcoma in the Russian Federation.

Keywords: heart transplantation, primary cardiac sarcoma, immunosuppressive therapy.

INTRODUCTION

Primary cardiac tumors are a rare entity with an overall incidence of 0.001–0.02% of all cardiac tumors [1, 2]. According to reports, the disease has an unfavorable prognosis, and the only effective method of treatment remains radical surgical removal of the tumor, if it is possible [3]. If it is an unresectable cardiac sarcoma (CS), HT becomes the only radical method of treatment [4]. Currently, there are data on a small number of cases of patients with CS with no regional and distant metastases, who have undergone HT. The role of HT in patients with CS is controversial. For example, Coelho P. et al. cite data from the clinical case of a patient with CS who underwent HT. The authors draw attention to the fact that the survival rate of patients with CS without surgical treatment is 9–11 months. The follow-up time of the heart recipient in this study was 7 years. The authors showed that HT can be a successful method of treatment for unresectable and non-metastatic CS [6]. On the contrary, Jimenez Mazuecos J.M. et al. in their study including 8 CS patients could not find any advantages of HT in this category of patients. The authors found no significant differences in survival between the groups of CS patients who did not undergo HT and those who underwent HT (11 and 12 months, respectively) [7]. In the Russian Federation, no cases of HT for CS have been registered so far, so this clinical case is important.

CLINICAL CASE STUDY

Recipient baseline data

Patient U., a 17-year-old male, grew and developed according to his age. In September 2019, a mass was detected in the cardiac apex region by a chest X-ray for the first time. The child was consulted by a tuberculosis specialist and no evidence of tuberculosis was obtained. During a medical examination in September 2020, ECG revealed repolarization changes in the form of negative T waves in leads III, aVF, and V3–V6; no further follow-up examination was performed, no medications were prescribed. He was infected by COVID-19 in October 2020, and was examined by a cardiologist in December 2020, taking into account the above-described changes on ECG; he was diagnosed with acute myocarditis. The patient was admitted to a hospital located at his place of residence. Echo findings: cardiac chambers were not enlarged, contractility was preserved, left ventricular (LV) hypertrophy was not detected, a volume echo-positive mass measuring 76 × 48 × 39 mm was detected in the apex region. Heart MRI was performed as a follow-up examination, which revealed a heterogeneous neoplasm, emanating from the LV myocardium at the diaphragm dome level, with clear and even contours, without perifocal infiltration, measuring 89 × 65 × 65 mm, caudally displacing 1.7 cm and compressing the diaphragm; regional lymph nodes not enlarged (Fig. 1).

In January 2021, he underwent a scheduled in-patient examination. Echo findings: a crescent-shaped mass surrounded the inferolateral and posterolateral surface of the LV and the posterior wall of the right ventricle (RV), heterogeneous, with areas of dissection. Compared to the study in December 2020, the size of the tumor slightly increased and was 95 × 65 × 67 mm with no apparent vascularization.

In March 2021, the patient was admitted to the Center for the Treatment of Women, Children and Youth with a perinatal center and the Charité center for Genetics (Berlin, Germany). On March 18, 2021, percutaneous

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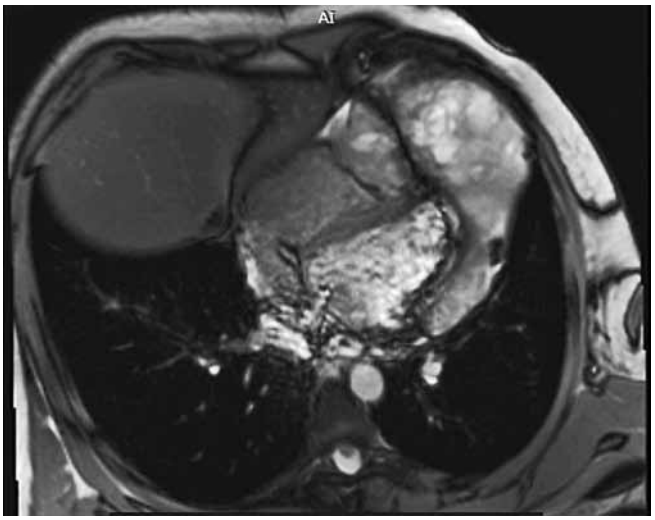

Fig. 1. Cardiac tumor detected on a heart MRI in patient U., 17 years old

CT-guided needle biopsy of the heart tumor was performed. Biopsy findings: malignant cardiac spindle cell tumor, with no clear linear differentiation, about 340 mL in volume, myocardial infiltration through spindle cell neoplasia. A study for the presence of tumor metastases in organs and systems was performed, no evidence of metastases was found.

Antineoplastic polychemotherapy (PCT) was chosen as the conservative therapy. The PCT regimens and duration are shown in Table 1.

Given that radical surgical treatment was not possible, the patient was consulted in absentia at the Shumakov National Medical Research Center of Transplantology and Artificial Organs (Shumakov Research Center). In August 2021, he was examined at Shumakov Research Center. Based on the results of clinical and laboratory examination, the patient was placed on the heart transplant waiting list and was discharged in a stable condition.

After discharge at his place of residence, second-line chemotherapy (VIT blocks) was continued. Due to development of leukopenia (2.14 × 10^9/L), granulocytopoiesis stimulation with filgrastim was performed.

Table 1

Antineoplastic polychemotherapy regimens and duration

S/N	PCT block regimen	PCT block composition	Duration
1	I2VA (5 courses)	Vincristine Actinomycin Ifosfamide	31/03/2021–16/06/2021 13/07/2021–14/07/2021
2	VIT	Vincristine Irinotecan Temodal	24/08/2021–16/09/2021 07/10/2021–11/10/2021 29/10/2021–02/11/2021

Heart transplantation and early postoperative period

On November 27, 2021, the patient (initial weight and height – 66 kg and 182 cm) underwent bicaval orthotopic heart transplantation (OHT). The donor was a 48-year-old woman (height 170 cm, weight 80 kg). The cause of cerebral death was acute hemorrhagic stroke with ventricular rupture. Graft ischemic time was 317 minutes, cardiopulmonary bypass lasted for 171 minutes. HT proceeded typically. A peculiarity of the operation was that due to a pronounced adhesion process between the neoplasm and the left pericardial area, the tumor-like neoplasm was removed in a single block with the left pericardium and the recipient's heart (Fig. 2). Tracheal extubation was performed on postoperative day 1. After HT, temporary pacing and inotropic support with

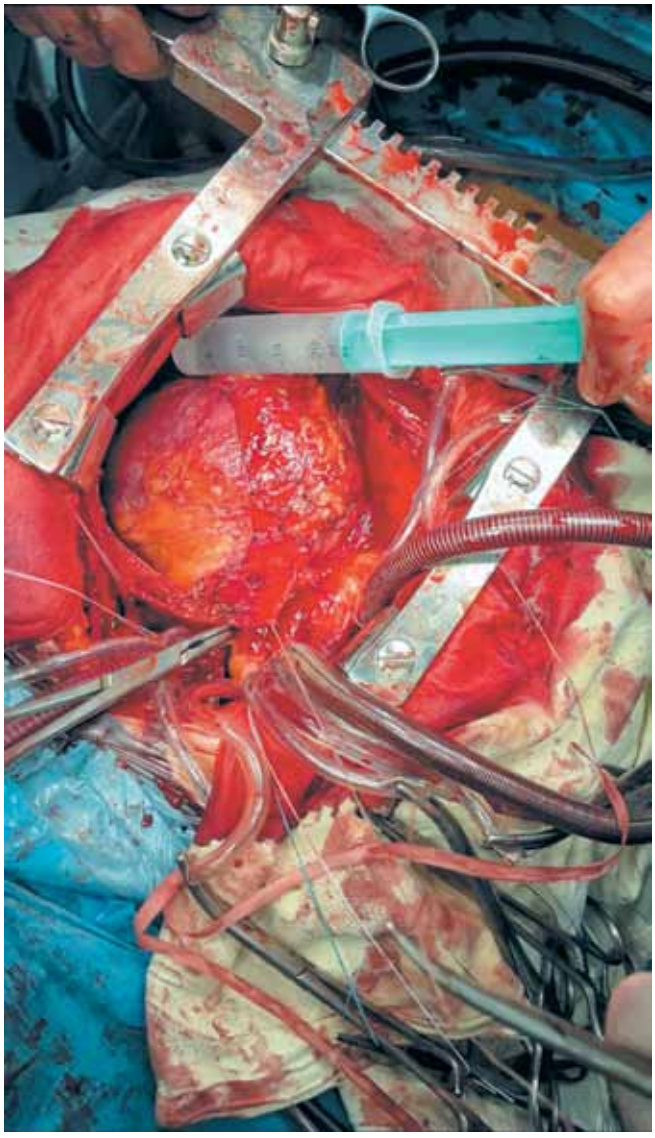

Fig. 2. Heart transplantation in patient U., 17 years old

dopamine at a 3 μg/kg/min dose with a gradual dose reduction against the background of resolving myocardial insufficiency were required.

Basiliximab was administered as induction according to the accepted guidelines for the management of heart transplant recipients.

Table 2

Postoperative period and survival in patients with malignant heart tumors after heart transplantation. Gowdamarajan et al.

Study	Age, Sex	PCT	Death	Follow-up (months)
Jamieson et al.	17 y.o., F	No	Yes	75
Horn et al.	13 y.o., M	Yes (before and after OHT)	Yes (metastases)	15
Aravot et al.	43 y.o., F	No	No	66
Aufiero et al.	31 y.o., F	No	No	12
Yuh et al.	57 y.o., F	Yes (after OHT)	Yes (metastases)	14
Baay et al.	34 y.o., M	Yes (before and after OHT)	No	33
Bachet et al.	35 y.o., M	No	Yes (relapse)	18
Demkow et al.	4 months, M	No	No	8
Mark et al.	2 y.o., F	No	Yes (rejection)	8
Crespo et al.	31 y.o., M	Yes (before OHT)	Yes (metastases)	8
	32 y.o., M	Yes (before and after OHT)	Yes (metastases)	9
Valente et al.	38 y.o., F	No	No	36
	40 y.o., F	No	No	28
Siebermann et al.	31 y.o., F	No	Yes (metastases)	2
Michler	42 y.o., F	Yes (before and after OHT)	No	6
	49 y.o., F	Yes (before OHT)	No	34
	26 y.o., F	No	No	60
	49 y.o., F	No	No	38
	39 y.o., F	Yes	Yes	3.5
	3.5 months, F	No	No	105
Almenar	29 y.o., F	Yes (before OHT)	Yes	2
Noirclerk	unknown	Yes (before OHT)	No	20
Gowdamarajan et al.	64 y.o., M	No	Yes	3
	7.5 y.o., M	Yes	Yes	11.5
	28 y.o., F	No	Yes	11.5
	9 y.o., M	No	Yes	11.5
	61 y.o., F	No	Yes	36
	8 y.o., M	Yes (after OHT)	Yes	21

Note: M, male; F, female; OHT, orthotopic heart transplantation; y.o., years old; PCT, palliative chemotherapy.

Table 3

Postoperative and survival in patients with malignant heart tumors after heart transplantation. Li H. et al.

Age / Sex	Histology (Grade)	Tumor location	Pre-OHT surgeries / Interval (months)	PCT (before and after OHT)	Tumor relapse (months)	Survival (months)
63 / M	Synovial sarcoma (G3)	LV, RV	Partial resection / 7	Yes (before and after OHT)	Lungs (1)	Death (5)
48 / M	Angiosarcoma (G3)	RA, RV	Biopsy / 3	Yes (after OHT)	Liver, Chest (4)	Death (5)
27 / F	Angiosarcoma (G3)	RA, RV	Biopsy / 2	Yes	Lungs (12)	Death (15)
49 / F	Undifferentiated pleomorphic sarcoma (G3)	RA, LA, LV	Partial resection / 5	Yes	PV (33); Liver, PV (40)	Death (43)
49 / F	Undifferentiated pleomorphic sarcoma (G2)	LA, LV	Partial resection / 9	No	No	Death from acute rejection / 18
61 / M	Myxoid liposarcoma (G2)	RV	Partial resection / 3	No	No	Alive / 93

Note: M, male; F, female; OHT, orthotopic heart transplantation; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; PV, pulmonary vein; PCT, palliative chemotherapy.

The patient was transferred to the ward on postoperative day 3 for follow-up and treatment. According to echocardiography at the time of transfer to the ward, global systolic function of the left ventricle was satisfactory (LV ejection fraction 62%). Against the background of resolving right ventricular insufficiency, the dose of inotropic support with dopamine was gradually decreased. In this case, a triple immunosuppressive therapy was used, which included a combination of calcineurin inhibitors (tacrolimus), antimetabolites (mycophenolate mofetil), and corticosteroids (methylprednisolone).

Coronary angiography and endomyocardial biopsy were performed to exclude graft rejection and transmissible atherosclerosis. Endomyocardial biopsy detected no acute cellular and antibody-mediated graft rejection; no stenotic lesion of the graft coronary arteries was diagnosed by coronary angiography.

After discharge from the Shumakov Research Center, ribociclib therapy was initiated at a dose of 600 mg once a day in a cycle of 21–28 days, with six cycles planned in total.

Given the patient's history of CS, immunosuppressive therapy was converted to the "tacrolimus-everolimus-methylprednisolone" regimen, followed by conversion to "tacrolimus-everolimus" immunosuppressive therapy.

Three months after transplantation, the immunosuppressive therapy protocol was changed to the "tacrolimus-everolimus-methylprednisolone" regimen under control of tacrolimus and everolimus blood concentrations, the target values were achieved (tacrolimus concentration 5.31 ng/mL, everolimus concentration 3.24 ng/mL). According to a control endomyocardial biopsy dated March 23, 2022, no acute graft rejection was detected. Echo showed no evidence of graft dysfunction.

DISCUSSION

CS is one of the most rarely detected malignant heart tumors with the most aggressive course and unfavorable prognosis in patients. HT is the only radical method of treatment in patients with unresectable and non-metastatic CS. HT on one hand allows to increase the length and quality of life of a patient, but the use of immunosuppressive therapy is a risk factor for early tumor recurrence [8]. Also, the need for chemotherapy in the postoperative period [9] has a negative impact on the heart graft. Life expectancy of heart transplant recipients in this category of patients averages from 9 to 36 months [10]. It should also be taken into account that there are no special therapy regimens and clinical guidelines for the treatment of patients after HT for CS; managing such patients is on an individual basis, taking into account all the features of the postoperative period [11].

In world practice, there are a small number of cases of patients with non-metastatic CS, who underwent HT. For example, Gowdamarajan A. et al. in 2000 published a literature review, which included 28 patients aged from 4 months to 64 years [4]. Results of the studies are shown in Table 2.

In 2016, Li H. et al. published their study, which included 46 CS patients (40 patients were included in the study based on literature sources, 6 patients were the clinic's own observation) who underwent HT, as well as 7 CS patients who received palliative therapy [5]. Table 3 presents data from clinical cases (6 heart recipients) by Li H. et al.

The one-year, two-year, and five-year survival rates of the heart recipients (n = 46) were 61% ± 7%, 44% ± 8%, and 26% ± 8%, respectively. There was no significant difference (p = 0.768) between the median survival of the 6 recipients in Table 3, which was 15 months (5 to 93 months) and that of the remaining 40 recipients, which was 16 months (2 to 112 months). This study showed that neoadjuvant or adjuvant chemotherapy did not confer a survival advantage after HT.

The immunosuppressive therapy regimen in the patients in the reports published so far was a triple therapy, including calcineurin inhibitors (cyclosporine, tacrolimus), azathioprine/mycophenolate mofetil and methylprednisolone.

The survival of CS patients who underwent HT in all of these studies is significantly lower than the survival of recipients after HT without a history of CS; this makes it necessary to perform HT in CS patients [12]. Foreign reports show that marginal donors could be used as a more acceptable strategy for managing such patients [5].

However, in most foreign studies, authors point to the need for HT in patients with CS depending on the patient's clinical status. In the absence of large, randomized trials, it is important to determine the necessity and effectiveness of HT in each individual case. There is also no consensus on the need for chemotherapy courses after HT. This has forced researchers to decide empirically on the treatment and management of patients after HT.

By the time of writing this paper, the follow-up period in our case was 10.5 months. Further observation and publication of this clinical case will allow us to draw conclusions about the effectiveness of the therapy, graft function, and long-term outcomes in this patient.

The authors declare no conflict of interest.

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