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COVID-19 management in heart transplanted recipients: registry of Almazov national medical research centre

Aim	This study presents the experience of managing patients with COVID-19 after cardiac transplantation (CT).
Material and methods	Infectious complications (IC) following CT are a leading cause for morbidity and mortality. A prolonged incubation period, atypical IC symptoms, and originally altered results of laboratory and instrumental diagnosis are characteristic of recipients due to immunosuppression. In 2020, the coronavirus infection (COVID-19) rapidly spread worldwide, and timely diagnosis and searching for effective treatments for this disease became a major challenge. From January 2010 through July 2020, 148 patients received orthotopic heart transplants at the V.A. Almazov National Medical Research Center; 34 of these patients died by the present time and were excluded from this analysis. 114 patients were included into the retrospective evaluation of results. These patients had been a part of the group followed up at the Center for more than a month.
Results	From March through July 2020, 12 (10.5%) of 114 CT recipients were infected with the virus SARS-CoV-2. In 75% (n=9) of the sick patients, the COVID-19 infection developed after more than one year after CT. From the first day of clinical symptoms, mycophenolic acid/everolimus were temporarily suspended. The outpatient treatment was started on the first day and included an antiviral therapy (oseltamivir), mucolytics (bromhexine), vitamin C, and anticoagulants. If the disease onset was associated with pyretic fever the empiric antibacterial levofloxacin treatment was administered due to a high risk of mixed infection. Hospitalized patients with moderately severe COVID-19 (n=3) were treated with oxygen inhalation through nasal cannula and prone position with a positive effect.
Conclusion	Remote counseling of patients after CT and consistency of the outpatient treatment with recommendations of managing transplant physicians provided timely diagnosis of IC, early administration of treatment, and the absence of COVID-19 complications. Reducing the regimen of immunosuppressive therapy (antiproliferative agents) for up to 14 days facilitated infection control and was not associated with acute rejection crisis and/or impairment of the transplant function.

Keywords	Cardiac transplantation; coronavirus infection; COVID-19; infectious complications
For citation	Simonenko M.A., Fedotov P.A., Sazonova Y.V., Monosova K.I., Sitnikova M.Y., Nikolaev G.V. et al. COVID-19 management in heart transplanted recipients: registry of Almazov National Medical Research Centre. Kardiologiia. 2020;60(12):4–12. [Russian: Симоненко М.А., Федотов П.А., Сазонова Ю.В., Моносова К.И., Ситникова М.Ю., Николаев Г.В. и др. Ведение реципиентов после трансплантации сердца с COVID-19: регистр ФГБУ «НМИЦ им. В.А. Алмазова». Кардиология. 2020;60(12):4–12]

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Introduction

Infection complication (IC) is a major cause of morbidity and mortality in patients who have undergone heart transplantation (HT) [1]. Bacterial (43.6%) and viral (41.7%) ICs prevail in the long-term post-transplantation period, while fungal ICs develop in 10.2% of cases [2]. Immunosuppression translates into an extended incubation period and atypical IC symptoms in recipients, including no or low-grade fever, whether the infection process is severe or not. Patients who have undergone HT may have initial abnormal findings of laboratory tests and investigations: decreased leukocyte count (due to immunosuppression, cytomegalovirus infection, Epstein-Barr infection, invasive pulmonary aspergillosis, etc.), elevated leukocyte count (due to glucocorticoid (GC) therapy), and residual post-IC ground-glass opacities in pulmonary parenchyma on chest computed tomography (CT) scans. In 2020, novel coronavirus disease (COVID-19) spread rapidly around the world. The key goal in treating this disease is the timely diagnosis and development of effective approaches to managing such patients [3]. Since the beginning of 2020, single clinical cases have been published that describe the course of COVID-19 in patients who had undergone solid organ transplantation [3–5]. In this work, we will share our experience of managing patients infected with SARS-CoV-2 who have undergone HT.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1342

Aim

To evaluate the aspects of COVID-19 in patients who have undergone HT, treatment possibilities, and the effects of the infection on the heart transplant function.

Material and methods

The study was performed in accordance with the Declaration of Helsinki. From January 2010 to July 2020, a total of 148 (107 male and 41 female recipients, mean age 46.7±14.0 years) orthotopic bicaval HT procedures were performed in the Almazov National Medical Research Center (Moscow, Russia). Left ventricular ejection fraction (LVEF) before HT was 22.5±10.2%. After surgery, 16 recipients died within 1 month. Another 18 patients who died in the long-term period after HT were not included in this analysis. The retrospective analysis included 114 patients from the dispensary group of the Center's register, who were followed up for more than 1 month.

Post-transplantation care protocol

Patients (n=110) were immunosuppressed by basiliximab (83%, n=95) or antithymocyte globulin (13%, n=15) and received triple agent immunosuppressive therapy following HT (calcineurin inhibitors, mycophenolic acid/everolimus and GCs). Calcium supplements (calcium carbonate+colecalciferol), hypolipidemic drugs (statins, if necessary, combined with fibrates or ezetimibe), proton pump inhibitors were administered in all patients as concomitant treatment. Antiarrhythmic, antihypertensive, antiplatelet/anticoagulant drugs were administered as indicated. In the first 12 months after HT, the IC prevention regimen included nistatin (prevention of oral candidosis) for 1–1.5 months, sulfamethoxazole+trimethoprim (prevention of pneu mocystis pneumonia) in combination with folic acid for 6 months, and valganciclovir (prevention of cytomegalovirus infection (CMVI)) for 12 months.

Outpatient visits and/or remote consultations were carried out by telephone or the Internet at least once a month. If necessary, patients were examined and admitted to the hospital.

Aspects of COVID-19 in post-HT patients were evaluated between March and July 2020. The study assessed the findings of the laboratory tests and clinical investigations. These included complete blood count and leukocyte profile, C-reactive protein (CRP), oropharyngeal swab for COVID-19, chest X-ray/multislice CT (MSCT), and concentrations of immunosuppressive drugs. The functions of the heart transplant were analyzed more than 1 month after the disease, including electrocardiogram (ECG), echocardiography, blood troponin, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Patients with moderate COVID-19 were subjected to endomyocardial biopsy (EMB) and coronary angiography (CA) after disease management, in order to evaluate the functions of the heart transplant after forced reduction of immunosuppressive therapy.

Statistical processing of the data obtained was performed using SPSS 22.0. The data was expressed as the means and standard deviations (M±SD) and the absolute and relative values (n (%)).

Results

Between March 2020 and July 2020, 12 (10.5%) recipients of the 114 patients who had undergone HT were infected with SARS-CoV-2. The disease was complicated by pneumonia in 11 patients, and an asymptomatic course was observed in 1 patient with no data confirming lung damage (Table 1). COVID-19 was diagnosed by laboratory test (polymerase chain reaction (PCR) for SARS-CoV-2 RNA) and/or diagnostic investigations (chest X-ray/MSCT). The majority of patients (n=9; 75%) had COVID-19 developed in more than 12 months after HT. None of the recipients traveled outside the Russian Federation from January 2020 to the present day or outside their regions of residence since March 2020. Four patients had contact with COVID-19 (see Table 1), including in one case, both the patient and his wife tested positive for SARS-CoV-2 antibodies (IgG) 1.5 months after the onset of symptoms.

Seven (59%) recipients with COVID-19 had concomitant chronic obstructive pulmonary disease (COPD), due to which inhaled bronchodilators were administered in the pre- and post-transplant periods, and one recipient had a history of invasive pulmonary aspergillosis.

Monitoring management

On day 1 of the onset of the IC clinical symptoms, each recipient contacted the transplant surgeon in charge over the phone (Table 1). Later, the remote monitoring of the recipients was extended by physical examination carried out by a primary care physician from a local outpatient clinic and/or ambulance physicians. Patients monitored by primary care physicians regularly reported their general condition (daily, every 3 hours) and reported blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen blood saturation (SaO_2) to the transplant surgeon in charge. Laboratory tests were made at home until recovery from the infectious disease. If patients were admitted to the hospital, they were managed by infectiologists at the Almazov National Medical Research Center and received daily remote consultations from the transplant surgeon in charge.

Table 1. Characteristics of post-HT patients with confirmed COVID-19

#	Patient	Time after HT	Age, years	Continuous therapy		Onset of the disease	Clinical symptoms	Oropharyngeal swab for COVID-19	Chest X-ray/CT	Concomitant pulmonary disease
				Immunosuppression and prevention of infection complications at the onset of COVID-19	Correction and duration of immunosuppressive therapy during the treatment of COVID-19					
1	M.	2 years	58	Tacrolimus + MMF	MMF withdrawn for 14 days	April 2020	Fever for up to 20 days, dry cough, back pain, asthenia, decreased BP, lack of appetite, dry cough. Mild	Negative	Bilateral polysegmental lung damage, pleuropneumonia, bilateral interstitial changes, ground-glass opacities	COPD, pulmonary emphysema
2	M.	5 months	52	Tacrolimus + MMF + GCs. Valganciclovir, sulfamethoxazole + trimethoprim	No correction was performed due to lack of symptoms and evidence of pneumonia	April 2020	Absent	Positive Contact with COVID-19	No findings	COPD
3	B.	8 months	30	Tacrolimus + MMF + GCs. Valganciclovir	MMF withdrawn for 14 days, tacrolimus dose reduction under laboratory control of the drug concentration	May 2020	Fever for up to 18 days, asthenia, sore throat when swallowing, lack of appetite, throat irritation, elevated BP. Mild pneumonia	Negative	Ground-glass opacity, 25%	No
4	E.	2 years	49	Tacrolimus + MMF + GCs	MMF withdrawn for 21 days, tacrolimus dose reduction due to increased blood concentration of the drug Restarting the drug was limited by COVID-19-associated agranulocytosis and EBV replication	May 2020	Fever with chills for up to 12 days, asthenia, anosmia, lack of appetite, dyspnea, decreased BP. Moderate pneumonia	Positive	Ground-glass opacities, 32–50%	COPD, history of invasive lung aspergillosis
5	B.	9 years	62	Tacrolimus + everolimus	Everolimus withdrawn for 48 hours	May 2020	Low-grade fever for up to 21 days, back pain, elevated BP. Mild pneumonia	Negative	Ground-glass opacity, 5%	COPD, pulmonary emphysema
6	G.	4.5 years	62	Tacrolimus + everolimus	Everolimus withdrawn for 48 hours	May 2020	Fever for up to 2 days, back pain, throat irritation. Mild pneumonia	Negative	Ground-glass opacities	COPD
7	G.	7 years	47	Tacrolimus + MMF	MMF withdrawn for 48 hours	May 2020	Episodes of low-grade fever for up to 14 days, throat discomfort when swallowing, back pain. Mild pneumonia	Negative Contact with COVID-19	Ground-glass opacities	COPD, pulmonary emphysema

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1342

Table 1 (continuation). Characteristics of post-HT patients with confirmed COVID-19

#	Patient	Time after HT	Age, years	Continuous therapy		Onset of the disease	Clinical symptoms	Oropharyngeal swab for COVID-19	Chest X-ray/CT	Concomitant pulmonary disease
				Immunosuppression and prevention of infection complications at the onset of COVID-19	Correction and duration of immunosuppressive therapy during the treatment of COVID-19					
8	M.	6.5 years	69	Tacrolimus + MMF	MMF withdrawn for 19 days (restarting the drug was limited to COVID-19-associated decreased neutrophil count and replication of EBV). Cyclosporine dose reduction based on the assessment of blood concentration of the drug	May 2020	Fever, anosmia, lack of appetite, throat irritation, upper and lower extremity muscle pain, and back pain. Moderate pneumonia	Negative Contact with COVID-19	Ground-glass opacities, 35–40%	COPD
9	D.	7.5 years	37	Tacrolimus + MMF	MMF withdrawn for 14 days	June 2020	Fever for up to 10 days, anosmia, asthenia, decreased BP, lack of appetite, back and chest pain. Moderate	Positive	Ground-glass opacity, 20%	No
10	V.	5 years	68	Tacrolimus + everolimus	Everolimus withdrawn for 48 hours	June 2020	Fever for up to 5 days, asthenia, back pain, lack of appetite, throat irritation. Mild	Negative	Ground-glass opacities	No
11	P.	5 months	58	Tacrolimus + MMF + GCs	MMF withdrawn for 14 days	July 2020	Fever for up to 10 days, back and chest pain, asthenia, dyspnea, lack of appetite, elevated BP. Mild	Negative	Ground-glass opacity, 8%	No
12	F.	6.5 years	64	Tacrolimus + MMF	MMF withdrawn for 14 days	July 2020	Fever for up to 10 days, asthenia, back and chest pain, lack of appetite, nausea.	Positive Contact with COVID-19	Ground-glass opacity, 25%	No

HT, heart transplantation; CT, computed tomography; MMF, mycophenolic acid/mycophenolate mofetil; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GC, glucocorticoid; EBV, Epstein–Barr virus.

Clinical and laboratory findings

The onset of the disease was most often accompanied by low-grade fever, general weakness, and back pain. Three recipients were admitted to the Center on days 3–10 of the disease due to decreased BP 74–100/55–62 mm Hg, increased RR more than 25 brpm, and reduced SaO_2 91–93%.

At the beginning of the infection, 50% of patients had a decreased neutrophil count $(0.63–1.1)\times10^9$/L and elevated CRP levels 15–117 mg/L, which recovered to normal over time. Troponin and ferritin levels were not determined during the acute period of ICs. Oropharyngeal swabs for SARS-CoV-2 were tested in all patients within days 3–21 from the onset of ICs. MCST, used to verify pneumonia of highly probable COVID-19 origin, was performed on days 1–14 after the onset of clinical symptoms. Molecular genetic (qualitative) blood testing showed the replication of the Epstein-Barr virus in 2 of

the 3 hospitalized patients, but blood tests for the herpes viruses were not performed in ambulatory patients.

Immunosuppressive management

At the time of the onset of clinical symptoms of the infection, every third patient (n=4 of 12) received triple component immunosuppressive therapy (tacrolimus/cyclosporine+mycophenolic acid+methylprednisolone). From day 1 of fever onset, mycophenolic acid was temporarily withdrawn (for up to 14 days). The decision to restart the drug was made individually depending on the clinical picture and the findings from the laboratory tests and clinical investigations. Two-component immunosuppressive therapy with tacrolimus and everolimus was administered in 2 patients. Given the mild course of the disease and levels of the inflammation markers (normal neutrophil count, elevated CRP <20 mg/L), evaluation everolimus was withdrawn for 48 hours. The dose of calcineurin inhibitors was adjusted according to tacrolimus/cyclosporine concentrations, while GCs were continued at the same dose. The target level of tacrolimus was the blood concentration within 9–11 ng/mL, cyclosporine 80–110 ng/mL.

Treatment of viral infection and pneumonia

Treatment was initiated in all patients on day 1 after the onset of symptoms and was carried out following the recommendations of the Ministry of Health of Russia [6]. Outpatient treatment included the antiviral therapy (oseltamivir 75 mg bid), mucolytics (bromhexine 8 mg tid), ascorbic acid (500 mg bid), if new oral anticoagulants were not used in the scheduled regimen, subcutaneous injections of enoxaparin sodium (1 mg per 1 kg of body weight) were added. Paracetamol was recommended as an antipyretic drug. If the disease debuts with low-grade fever (>38.0° C for 48 hours or more), empirical antibacterial therapy levofloxacin was used due to high risk of mixed infection (6 of 12 patients). Amoxicillin+clavulonic acid was used in one patient with the history of recurrent pneumonia 2 to 3 times a year due to previously established levofloxacin intolerance (Table 2). Three patients with moderate COVID-19 admitted to the Center were subjected to nasal-cannula oxygen therapy and positioned prone with a positive effect.

One recipient at high risk of airway ICs (history of COPD, invasive lung aspergillosis, CMV disease, recurrent Klebsiella pneumoniae pneumonia) receiving three-component immunosuppressive therapy (tacrolimus+mycophenolic acid+methylprednisolone for recurrent transplant rejection events). SARS-CoV-2 infection developed in the 2 years after heart transplantation. The virus was discovered by the oropharyngeal swab. Bilateral pneumonia (lung damage area 32% on day 4 of the disease, 50% on day 10, see Figure 1) was moderate (RR 30 brpm, SaO_2 92%), and the patient was admitted to the Center's intensive care unit. The course of COVID-19 was complicated by severe leucopenia and neutropenia with the progression to agranulocytosis, severe thrombocytopenia (up to 45×10^9/L), and Epstein-Barr virus replication in the blood (positive blood PCR). Troponin levels were normal during the acute stage of the ICs (0.03 ng/mL). Hydroxychloroquine was added given the severity of the patient's condition and according to the current guidelines of the International Society of Heart and Lung Transplantation (ISHLT) as of April 2020 [7]. The decision was taken to abandon azithromycin due to the high risk of developing heart transplant dysfunction and neurological complications, associated with drug interactions with immunosuppressive therapy, and the risk of progression of arrhythmological complications. After stopping the latest allograft cell rejection event, the

Table 2. Treatment of COVID-19 complicated by pneumonia in patients with the heart transplant

#	Patient	Oseltamivir	Hydroxychloroquine	Levofloxacin	Amoxicillin + clavulanic acid	Bromhexine	Anticoagulant/antiplatelet drugs	Vitamin C	Vitamin D
1	M.	+	–	+	–	+	Antiplatelet drugs	–	+
2	B.	+	–	+	–	+	Anticoagulant drugs	+	+
3	E.	+	+	+	–	+	Anticoagulant drugs	+	+
4	B.	+	–	–	–	+	Antiplatelet drugs (2)	+	+
5	G.	+	–	–	–	+	Anticoagulant drugs	+	+
6	G.	+	–	–	–	+	Antiplatelet drugs	+	+
7	M.	+	–	+	+	+	Anticoagulant drugs	+	+
8	D.	+	–	+	–	+	Anticoagulant drugs	+	+
9	V.	+	–	+	–	+	Anticoagulant drugs	+	+
10	P.	+	–	+	–	+	Anticoagulant drugs	+	+
11	F.	+	–	+	–	+	Anticoagulant drugs	+	+

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1342

patient developed supraventricular extrasystoles and supraventricular tachycardia with HR of 110–170 bpm, due to which verapamil was administered. The functions of heart transplant were examined one month after the infection was stopped. Global contractility of the left and right ventricles was preserved (LVEF 69%, TAPSE 17 mm, pulmonary artery systolic pressure 35 mm Hg), there was neither rejection events (endomyocardial biopsy R0/AMR1) nor allograft vasculopathy (CA).

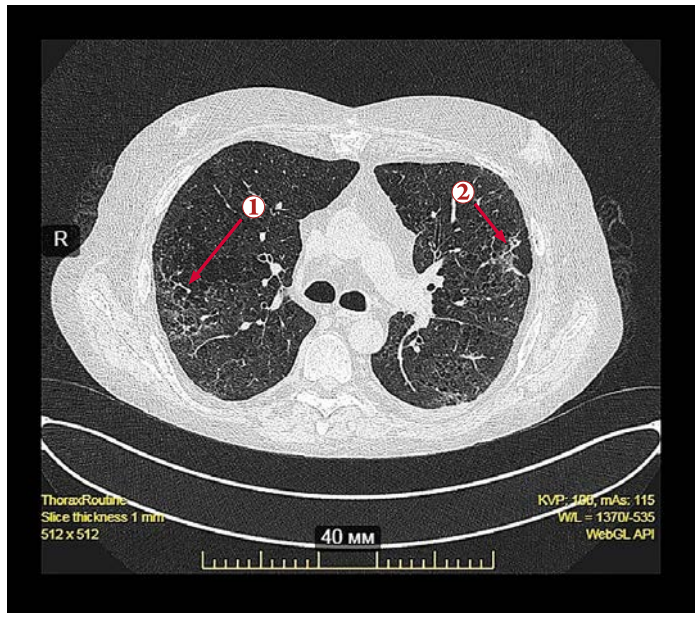
There was a trend to decreased BP in 3 patients, due to which doses of antihypertensive drugs were adjusted during outpatient management with positive effect. After stopping the infection, the initial doses were restarted. However, the onset of infection was accompanied by elevated BP up to 150–190/90–102 mm Hg in 3 recipients, which required increasing doses of antihypertensive drugs. After recovery, the drug doses remained elevated.

Despite treatment and subjective improvement, all patients had fever and thoracic and/or lumbar back pain for 14–21 days. Troponin and NT-proBNP levels were normal in patients with lung damage according to the control MSCT scanning in 1–1.5 months after the infection. The allograft function was investigated (ECG, echocardiography) in the hospitalized recipients at least once a week (hospital stay for up to 14 days). The other recipients underwent the investigation of cardiac function in 1 month. At the same time there was no data confirming damage of the heart transplant within that time frame: sinus rhythm was preserved, LVEF did not decrease.

Discussion

Patients with heart transplants are a risk group for SARS-CoV-2 infection. They may have a more extended incubation period (more than 14 days), and clinical manifestations. In addition, the findings of laboratory tests and instrumental investigations may differ from the typical picture in patients who do not receive immunosuppressive therapy [8, 9]. According to local protocols adopted at the corresponding transplantation centers, all recipients of solid organs are followed up after transplantation by the transplant surgeons in charge. Due to the adverse epidemiological situation around COVID-19, various scientific heart transplantation communities (ISHLT, European Society of Organ Transplantation (ESOT), American Society of Transplantation (AST)) recommended reducing scheduled hospital admissions and face-to-face outpatient visits and continuing regular follow-up through telemedicine counseling. Since March 2020, patients with heart transplants who received follow- up in the Center were also transferred to remote counseling. Regardless of the time after HT, patients were advised to stay at home, follow personal hygiene rules and wear face masks outdoors, monitor daily their body temperature and body temperature of their cohabitants and stay at the place of residence or place of temporary residence until the epidemiological situation stabilizes. If the patient has new complaints, their condition changes, or COVID-19 is suspected, then their attending physician, if the patient is hospitalized at the local hospital, should report these events to the transplant surgeon in charge for remote counseling and corrective immunosuppressive therapy [8, 10].

Figure 1. Computed tomography findings in patient E. (49 years old) on day 10 from the onset of the disease: ground-glass reticular opacities (1), increasing volume of pulmonary tissue damage from 32 to 48%, pleural fluid. Irregular, cord-like pulmonary consolidation areas (2) (mainly in the left lung) against previously detected ground-glass opacities



There is currently no data on the incidence of COVID-19 in patients with heart transplants. According to our findings, despite their unfavorable immunological status, only 10.5% of heart recipients followed up at the Center had COVID-19 with the first 5 months of the pandemic in the Russian Federation. No deaths were reported in followed-up post-HT patients during this period. The clinical picture was typical and similar in all patients: asthenia, low and high-grade fever, throat irritation and back pain, typical in the case of COVID-19 in patients after organ transplantation [3, 11]. Clinical manifestations of the disease in such patients may have atypical nature (absence of fever or serious complaints regardless of the infection's severity) [3]. Variable BP trends were observed: 3 patients had arterial hyper-

tension, requiring enhancing antihypertensive therapy, while the other 3 patients, on the contrary, had a significant decrease in BP, which led to its withdrawal.

There is no specific COVID-19 prevention for patients with heart transplants [4, 6, 10–12]. Despite this and the current immunosuppressive therapy, there were no severe cases and fatal disease outcomes. This may be due to the fact that the post-transplantation management protocol adopted in the Almazov National Medical Research Center includes drugs that can contribute to the reduction of the coronavirus infection risk.These include statins (post-transplantation dyslipidemia, immunosuppressive and anti-inflammatory effects of the drug) and vitamin D in the calcium supplements (prevention of development or treatment of osteoporosis) or as a single agent (in vitamin D deficiency or hyperparathyroidism) [13].

The findings of laboratory tests and clinical investigations of patients with heart transplants should be evaluated considering historical data, including the amount of immunosuppressive therapy, sequelae of invasive pulmonary aspergillosis, exclusion of fungal and/or viral (including Epstein-Barr virus, CMV) or mixed infections. Diagnosis and treatment of the infection in heart recipients should be accompanied by evaluating the allograft function and controlling immunosuppressive drug concentrations over time. Laboratory abnormalities can be challenging. For example, increased troponin levels can indicate heart transplant dysfunction, acute crisis or chronic rejection, allograft vasculopathy, and damage due to viral infection (infection and stress-induced cardiomyopathy, coronary thrombosis, etc.). When interpreting ferritin levels, the time of the last cardiac surgery with cardiopulmonary bypass and the current use of iron supplements should be taken into account.

Immunosuppressive and cardiovascular therapy in patients after organ transplantation should be corrected only by the transplant surgeon, taking into account the patient's history. The correction of immunosuppressive therapy described above (i.e., a temporary withdrawal of mycophenolic acid/everolimus) followed the recommendations of heart transplant societies on the management of recipients in case of COVID-19 [11, 12]. Regardless of the severity of the infection, complete withdrawal of immunosuppressive therapy is not recommended because of the risk of acute rejection and transplant dysfunction. Given that antimetabolites were withdrawn to maintain a fine balance of immunosuppressive therapy and drugs used to treat ICs, tacrolimus was maintained, and the target tacrolimus level remained within 9–11 ng/mL. The infection was manageable during this therapy and regressed without signs of allograft dysfunction. This is consistent with the findings of several trials showing in vitro and in vivo effects of tacrolimus in non-toxic concentrations on the inhibition of coronavirus replication [14]. This tacrolimus effect is still under study and should be confirmed in larger trials.

EMB and CA were performed in patients with moderate COVID-19 after stopping ICs, and it is planned to admit patients with mild disease at an earlier stage, in order to perform an invasive evaluation of the heart transplant function. Given the duration of immunosuppressive therapy reduction, the particularities of the denervated heart function, the effect of viral infection on the heart transplant function (e.g., CVMI associated heart transplant rejection and/or allograft vasculopathy caused by CMVI) [15], possible extra myocardial damage by SARS-CoV-2 virus [16], EMB and CA after COVID-19 will allow timely measures to be taken.

Commencement of treatment of the viral disease from day 1 in the case of suspected COVID-19 allows its course to be controlled, thus reducing the rate of emergency hospitalizations, and increasing patient survival. Mucolytics (bromhexine), anticoagulant drugs, and ascorbic acid should include in the regimen for heart recipients with COVID-19. The COVID-19 treatment protocols are being developed, and the experience of some transplant surgeons shows positive results of using oseltamivir in patients after transplantation of solid organs [17]. The following regimen was effective in followed-up heart recipients: antiviral drugs (oseltamivir, oseltamivir+valganciclovir, oseltamivir, hydroxychloroquine; for up to 14 days), antibacterial agents (increased body temperature >38.0°C, Kl. pneumoniae carrier and/or history of frequent bacterial ICs: levofloxacin or amoxicillin+clavulanic acid, for up to 14 days), antithrombotic drugs (anticoagulant and/or antiplatelet drugs, for up to 21 days), mucolytics (for up to 21 days) and vitamins C and D (ащк up to 21 days) [6], and temporary reduction of immunosuppressive therapy. The decision was taken on an individual basis for each recipient whether to add antibacterial depending on the history and the findings of laboratory tests and clinical investigations. Interleukin-6 (IL-6) inhibitors tocilizumab or sarilumab can be used in severe COVID-19 [12]. According to the British Transplantation Society (BTS), GCs (dexamethasone intravenously 6 mg/day) for 10 days are indicated to treat moderate to severe COVID-19 in patients after transplantation of solid organs [11].

When administering various drugs, it is necessary to consider drug interactions, control concentrations of immunosuppressive drugs, and monitor the heart

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1342

transplant function [18]. According to the recommendations of the International Society of Heart and Lung Transplantation (ISHLT) dated August 19, 2020, the following drugs are not recommended for patients after cardiothoracic transplantation: remdesivir, lopinavir/ritonavir, chloroquine/hydroxychloroquine, and COVID-19 convalescent blood plasma [12].

The recent analysis of magnetic resonance imaging (MRI) data of the heart in patients with the history of COVID-19 has shown that almost 80% have myocardial damage [17], which can subsequently result in its progressive dysfunction. This course of events is highly likely in therapeutically immunosuppressed patients with heart transplants and raises the question of correcting the management algorithms for heart recipients who had COVID-19, using myocardial MRI to screen viral damages 1–3 months after the disease.

Conclusion

Remote consultations and consistent management of patients after heart transplantation by local healthcare providers following the recommendations of the transplant surgeons in charge allowed for the timely diagnosis of the complications, early treatment and contributed to the uncomplicated course of COVID-19. Reducing the use of immunosuppressive drugs (antiproliferative agents/antimetabolites) for 14 days contributed to controlling the disease and was not accompanied by an acute rejection episode and/or a reduced function the heart transplant.

Limitations

The retrospective evaluation of the cases of the novel coronavirus disease was carried out in a sample of patients limited only to the Center. The levels of troponin, ferritin, and N-terminal pro-brain natriuretic peptide were not determined in the acute period of the disease.

No conflict of interest is reported.

The article was received on 09/09/2020

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