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Treatment of Pediatric Patients With COVID Infection After Heart Transplantation

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ABSTRACT

The COVID-19 pandemic that has been ongoing since the beginning of 2020 has forced health care into a difficult struggle for wellness and the lives of patients. International data and our observations show that the course of the disease in these patients is different than in the general population. Symptoms depend on the immunosuppression and severity of viremia. The period of viral replication is much longer. Our observations include 4 pediatric patients post heart transplant who became infected with the coronavirus. One patient was infected in the hospital during perioperative period. Two others required hospitalization because of the severity of symptoms, and 1 was treated on an outpatient basis. The applied treatment included the reduction of immunosuppression, low-molecular-weight heparin, amantadine or remdesivir, steroids, and supplementation with zinc and vitamins C and D. Based on the antigenic tests performed, we determined the period of active replication to be 3 to 8 weeks from the onset of the first symptoms.

THE severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that has been ongoing since the beginning of 2020 has forced health care into a difficult struggle for the wellness and lives of patients. For the time being, the number of cases in Poland has reached 2.9 million, with 75,000 of those being lethal. Although the pediatric population appears to be less exposed to SARS-CoV-2 virus infection, the number of infections continues to grow. The course of the disease in children may differ from that of adults, although it can still be just as dangerous. According to international data, the course of SARS-CoV-2 in patients from transplant departments differs from that of rest of the population. Following heart transplantation, pediatric patients are at risk for a more severe course of SARS-CoV-2 infection. Additionally, these patients, because of their young age and the use of immunosuppressive drugs, non-specific symptoms of the disease may occur. These symptoms might include skin changes (rashes) or gastrointestinal disorders [1]. There are no guidelines regarding the treatment of SARS-CoV-2, especially in pediatric transplant patients. Extrapolation to this specific population from published data should be done with caution. The guidelines of the International Society for Heart and Lung Transplantation on the SARS-CoV-2 pandemic

underline 3 aspects of infection protection: limiting social interactions, balancing the need for patient visits to a medical center, and treatment with immunosuppressive drugs. A pandemic and the risk for infection are not in themselves an indication to change standard immunosuppression. Decisions to discontinue or reduce the dose of immunosuppressants should be made on an individual patient basis in conjunction with clinical data.

The Paediatric Group of the Canadian Transplant Society has published an algorithm for the management of SARS-Cov-2 virus infection in kidney transplant patients [2]. According to the similarity of the immunosuppressive strategy for heart transplant patients, we consider this algorithm with reducing only antiproliferative drugs. In severe courses and in cases of progressive deterioration of the patient's condition, it is recommended that calcineurin inhibitors be reduced as well.

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Table 1. Patient Data

Patient	Age	Sex	Cause of original disease	Time post-transplant	Immunosuppressive drugs/doses during onset	Immunosuppressive drugs/doses after adjustment	COVID symptoms time to resolution	Present status	Hospitalization (yes/no)	Length of hospitalization	Anti-viral drugs	Antigen test result
LM	11	Boy	RCM	16 mo	CS 100/75 mg MMF 500/250 mg	CS 100/75 mg MMF 500/250 mg	3 mo	Alive	No	0	No	Negative
RA	11	Boy	DCM	1 mo	TAC 2 × 6 mg MMF 500/250 mg	TAC 1 × 11 mg MMF 0	3 w	Alive	Yes	6 wk	Amantadine	Negative
JM	16	Girl	HCM	6 mo	TAC 6/5 mg MMF 500/250 mg Encorton 20 mg	TAC 2 × 5 mg	2 mo	Alive	Yes	2 mo	Remdesivir	Negative
KŁ	17	Boy	DCM	2 y	TAC 1 × 3.5 mg MMF 250/ 250 mg Encorton 5 mg	TAC 1 × 2 mg MMF 250/250 mg Encorton 5 mg	2 mo	Alive	Yes	3 mo	Amantadine	Negative

CS, cyclosporin; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; MMF, mycophenolate mofetil; RCM, restrictive cardiomyopathy; TAC, tacrolimus.

Here we describe 4 pediatric patients who developed an infection after heart transplantation. None of the 4 were vaccinated against SARS-Cov-2 because, at the time, no recommendations existed.

The first patient was a 14-year-old girl. Six months after heart transplantation, she was treated with standard immunosuppression, tacrolimus (TAC), mycophenolate mofetil (MMF), and glucocorticosteroids. She was transplanted at 13 years of age after being diagnosed with familial obstructive hypertrophic (OHT) cardiomyopathy. Because of the high immunization after OHT, she was treated with rituximab, admitted to postoperative follow-up after typical treatment of SARS CoV-2 infection. On admission, a polymerase chain reaction (PCR) test was positive. She developed symptoms of infection with fever $\leq 40^{\circ}$ C. We also observed high levels of glucose ≤ 600 mg. Her treatment included remdesivir, low-weight-molecular heparin (LWMH), ceftriaxone, caspofungin, and dexamethasone. The patient was regularly monitored for interleukin (IL)-6, C-reactive protein (CRP), procalcitonin (PCT), leukocytosis, and viremia on an antigen test. IL-6 levels fluctuated and reached their highest concentration on day 40 of treatment (483 pg/mL) and the first negative antigen test result was 8 weeks after diagnosis.

The second case was an 11-year-old boy who was 17 days post-heart transplantation owing to heart failure during the course of dilated cardiomyopathy. After exposure to SARS-CoV-2, the PCR test was positive. The patient was treated with standard immunosuppression (TAC, MMF, and glucocorticosteroids). He did not present clinical features of infection. We discontinued MMF and low-molecular-weight heparin (LMWH) antithrombotic prophylaxis, steroids, and amantadine were introduced. The patient was supplemented with zinc and vitamins C and D. IL-6 as well as inflammatory indicator levels (CRP, PCT, and leukocytosis) were continuously monitored. Three weeks after diagnosis, the treatment was terminated and confirmed by a negative test result.

The third patient was a 17-year-old boy who previously underwent a heart transplant at the age of 15, owing to dilated cardiomyopathy. Two years after the heart transplantation, he was admitted to the hospital with respiratory failure on oxygen therapy and oliguria requiring dialysis. The PCR test was positive. He also had diarrhea, weakness, and a raised temperature. Before the infection, the patient was treated according to the classic immunosuppression. Because of SARS-CoV-2 infection, MMF was discontinued. LMWH, amantadine, and steroids as well as supplementation of zinc and vitamins C and D were also introduced. The treatment was terminated after 8 weeks with renal and respiratory system recovery and the patient's test was confirmed to be negative.

The fourth patient was a 12-year-old boy who was diagnosed with heart failure in the course of restrictive cardiomyopathy. The heart transplantation was performed when he was 9 years of age and since then he was treated with cyclosporine and MMF. Three years after transplantation, he was infected as demonstrated by a positive PCR test. This patient was treated only symptomatically (anti-inflammatory) with no changes in his immunosuppressive scheme. Three months after diagnosis of the infection, the antigenic test was negative.

All but one patient received certain treatment: Discontinuation of MMF and introduction of thromboprophylaxis using LMWH. The steroid therapy was continued according to the schedule or was started if the patient was not receiving steroid before infection. Zinc preparations were administered to the patients, as were vitamin C and D as well as amantadine or remdesivir (Table 1).

CONCLUSIONS

Because of the short duration of the clinical trials, we do not have unified treatment standards. At the beginning of the pandemic, the pediatric patient population seemed to be less exposed to SARS-CoV-2 infection. However, over time it has been demonstrated that even this group of patients may experience a severe course of SARS-CoV-2 infection, especially when organ transplant patients are considered. It seems to be problematic that in these patients, because of their young age and use of immunosuppressive medications, nonspecific symptoms of the disease may occur. Therefore, we should be extremely cautious when diagnosing such patients. We noticed that there is no single image assigned to patients after heart transplantation, who were infected

with SARS-CoV-2. Each of our patients showed different symptoms, but we used a similar treatment for each of them, which brought the expected therapeutic effect. The time period of viremia, that we controlled with antigen test, lasted from 3 to 8 weeks, which is much longer in comparison to the standard population.

DATA AVAILABILITY

The data that has been used is confidential.

REFERENCES

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