sciendo

Journal of Cardiovascular Emergencies 2020;6(2):43-47
DOI: 10.2478/jce-2020-0007

CASE REPORT

Early Acute Graft Rejection in a Heart Transplanted Child with Dilated Cardiomyopathy

Iolanda Muntean[1], Asmaa Carla Barmou[2], Anca Ileana Sin[3], Horatiu Suciu[4], Rodica Togănel[1]

[1] Clinic of Pediatric Cardiology, Emergency Institute of Cardiovascular Diseases and Transplantation, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Clinic of Pediatric Cardiology, Emergency Institute of Cardiovascular Diseases and Transplantation, Târgu Mureș, Romania
[3] Department of Cell and Molecular Biology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[4] Clinic of Cardiovascular Surgery, Emergency Institute of Cardiovascular Diseases and Transplantation, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

ABSTRACT

Dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy in children. Heart transplantation is considered standard therapy in dilated cardiomyopathy with end-stage heart failure. We present a case of a 15-year-old patient diagnosed with DCM in the neonatal period, who underwent heart transplantation for end-stage heart failure. Despite the use of induction therapy, the endomyocardial biopsy performed at two weeks post-transplant revealed mixed moderate cellular (2R) and humoral (pAMR2) allograft rejection. Aggressive rejection treatment was initiated with good outcome. Besides endomyocardial biopsy, advanced echocardiography can also be a valuable noninvasive tool for rejection assessment.

Keywords: heart transplantation, acute rejection, dilated cardiomyopathy, advanced echocardiography, children

ARTICLE HISTORY

Received: April 8, 2020
Accepted: May 4, 2020

CORRESPONDENCE

Asmaa Carla Barmou
Str. Gheorghe Marinescu nr. 50
540136 Târgu Mureș, Romania
Tel: +40 265 216 368
E-mail: asmaa.carla@yahoo.com

INTRODUCTION

Pediatric cardiomyopathies are a rare heterogeneous group of heart muscle diseases with small incidence worldwide, but with a major impact on mortality and morbidity in the pediatric population.[1] In children, dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy, accounting for almost 60% of cases, and the most frequent cause of heart transplantation.[2] According to the International Society for Heart and Lung Transplantation (ISHLT), DCM was the cause of pediatric heart transplants in almost 38% of infants and 54% of children between the ages of 11 and 17 years.[3] Post-transplant, there are still numerous challenges.

Despite significant progress in immunosupression therapy, ISHLT data reports that almost 40% of recipients experience acute rejection in the first months after transplant, with a smaller survival rate.[4] In most cases, acute graft rejection is caused by cellular rejection with a T lymphocyte-mediated response. Humoral rejection occurs

Iolanda Muntean: Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: iolanda.muntean@gmail.com
Anca Ileana Sin: Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: anka_sinn@yahoo.com
Horatiu Suciu: Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40265215551, E-mail: horisuciu@gmail.com
Rodica Togănel: Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: rodicatoganel@gmail.com

when the immune system of the recipient starts to produce antibodies directly against the allograft tissue. Even though antibody-mediated rejection occurs months or even years post-transplant, in some cases, acute humoral rejection can occur within hours or days.

CASE PRESENTATION

We present a case of a 15-year-old patient diagnosed with DCM in the neonatal period, who underwent heart transplantation for end-stage heart failure.

On review of his medical history, at two months of life, the patient underwent cardiac surgery for atrial septal defect closure. At 1.5 years of age, he was diagnosed with DCM, and anticongestive treatment was started. Over the years, despite maximal medical treatment, his clinical condition continued to deteriorate, with severe limitation of physical activity, weight loss (BMI: 14.1; percentile: 0.1; z-score: −3.8), and the appearance of non-sustained ventricular tachycardia documented on 24-hour Holter monitoring. At this point, the patient was listed for heart transplant. Prior to the transplant, cardiac catheterization revealed a normal pulmonary vascular resistance index of about 0.97 Woods units/m^2.

A matching donor (same blood group and comparable weight) was found, and orthotopic heart transplantation was performed using the bicaval technique. Post-transplant, initial management included induction therapy with thymoglobulin (R-ATG) and high-dose corticosteroids, and maintenance immunosupression therapy was based on a triple association with calcineurin inhibitor (tacrolimus), antiproliferative agent (Mycophenolat Mofetil, MMF), and corticosteroids. The immediate postoperative course was favorable, and the patient was extubated on day 2 after the transplant.

Subsequently, a progressive deterioration of the patient's clinical condition was noted, with fatigability, progressive enlargement of the abdomen with positive fluid wave test, hepatomegaly, mild pedal edema, and absent breath sounds over the lower right chest. SaO_2 (100%) and blood pressure (111/64 mmHg) were normal. The laboratory analysis revealed elevated BNP levels (2,419 pg/mL) and marked anemia (8 g%). Chest radiography showed a right-sided pleural effusion and right diaphragmatic paralysis, and the abdominal ultrasound demonstrated a large amount of ascites (Figure 1). Echocardiography was also performed and revealed pericardial effusion, left ventricular diastolic dysfunction (restrictive type) with normal ejection fraction, but impaired longitudinal strain indices (AP4-LS: −16%, AP3-LS: −10%, AP2-LS: −12%, global LS: −13%) (Figure 2). The echocardiography also revealed thickened myocardium, hyperechogenic, granular aspect of the interventricular septum, and elevated LV mass (154.45 g/m^2). The electrocardiogram showed low QRS voltage with signs of myocardial injury.

In this context, we suspected early graft rejection, and cardiac catheterization with endomyocardial biopsy was performed 17 days after the heart transplant. The hemodynamic assessment of the right heart showed elevated right arterial pressure (27/31/22 mmHg), with elevated pulmonary arterial pressure (43/20/29 mmHg) and pulmonary wedge pressure (16 mmHg). The histopathological examination described focal lymphocyte infiltration in perivascular areas, with myocardial necrosis and active

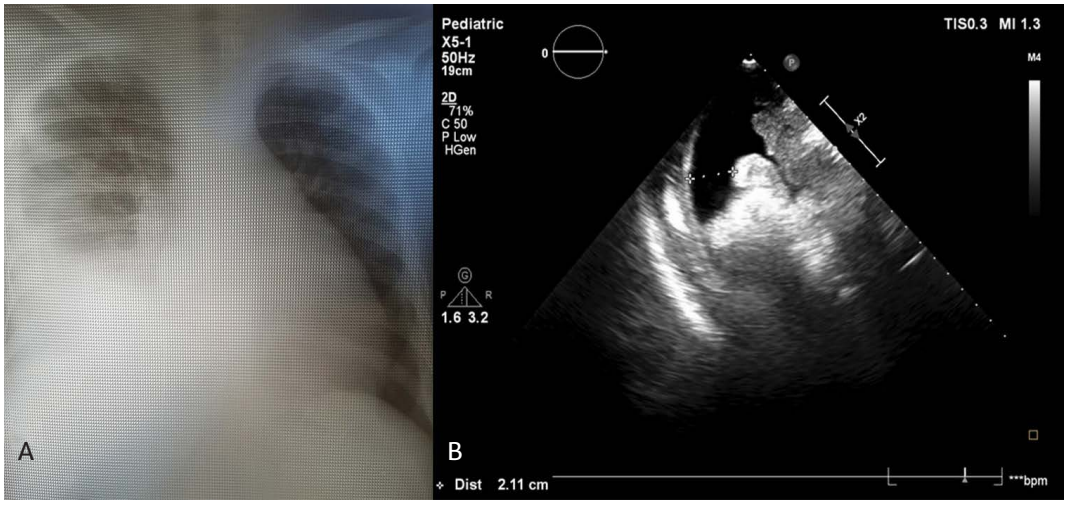

FIGURE 1. Chest radiography revealing right-sided pleural effusion and right diaphragmatic paralysis (**A**); abdominal ultrasound demonstrating a large amount of ascites (**B**)

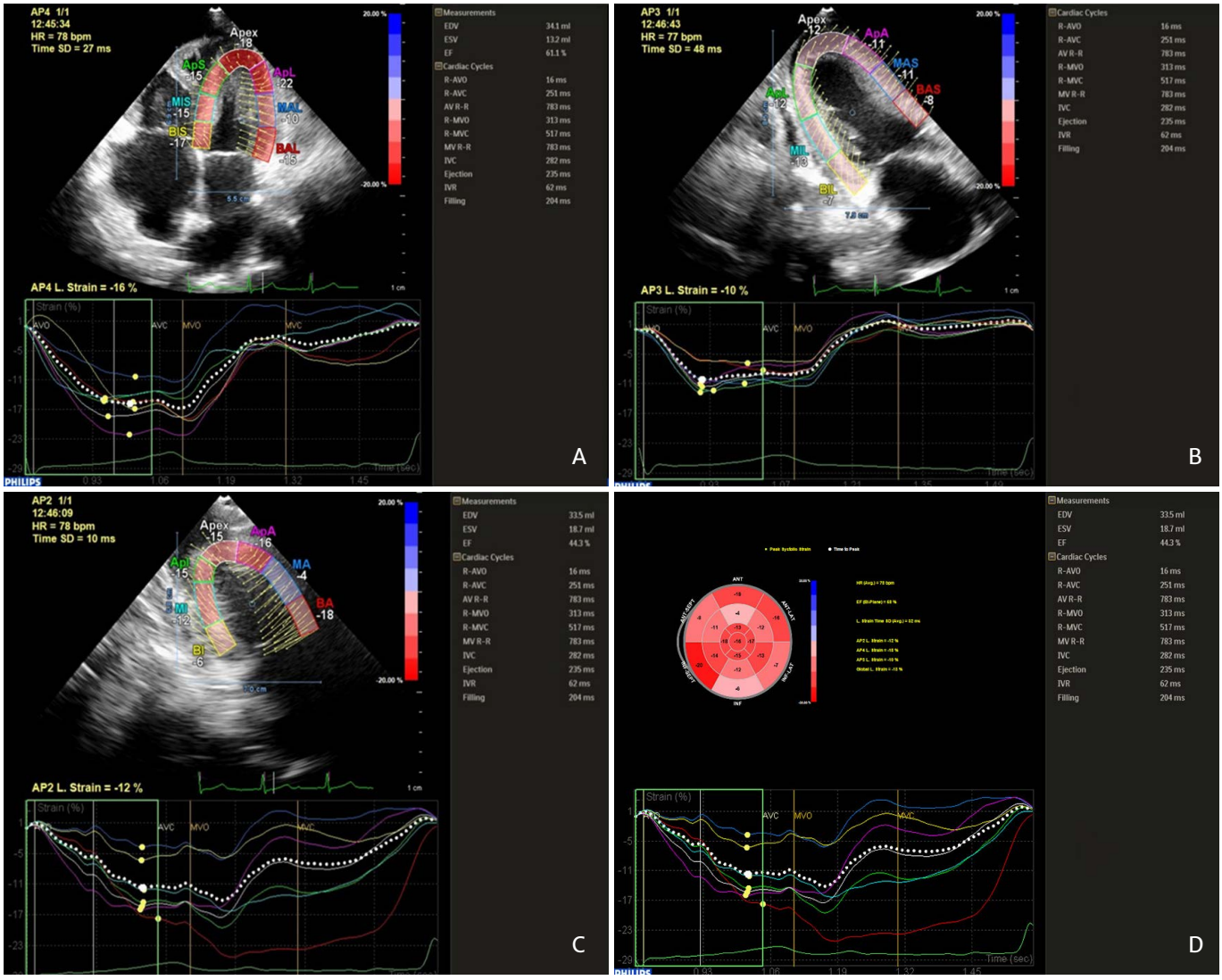

FIGURE 2. Speckle-tracking analysis showing impaired LV longitudinal strain indices at the time of endomyocardial biopsy, suggestive for rejection: AP4-LS: −16% (**A**), AP3-LS: −10% (**B**), AP2-LS: −12% (**C**), global LS: −13% (**D**)

inflammatory changes. The immunohistochemistry was positive for CD34 and CD31. Therefore, according to ISHLT criteria, the patient was diagnosed with mixed moderate cellular (2R) and humoral (pAMR2) allograft rejection. Aggressive rejection treatment was initiated with thymoglobulin (R-ATG), pulse corticosteroid therapy, and intravenous immunoglobulin. Also intravenous milrinone and deleukocyted blood transfusion have been added. Following the rejection treatment, tacrolimus, MMF, and oral prednisone were continued. After several days, the patient presented acute abdominal pain with subocclusive syndrome. Consequently, MMF was replaced with mycophenolic acid, and the patient's general condition improved, his BNP level decreasing to 52.1 pg/mL. The ST segment and T wave were present on the ECG, and echocardiography showed decreased LV mass (104.46 g/m^2), normal LV diastolic function, and slightly increased longitudinal strain parameters (AP4-LS: −18%, AP3-LS: −14%, AP2-LS: −12%, global LS: −15%). Endomyocardial biopsy was repeated and showed regression of the lesions (ISHLT 0). The patient's legal guardian agreed to the publication of his data, and the institution where the patient had been admitted, approved the publication of the case.

DISCUSSIONS

In this article, we presented a clinical case of early graft rejection in a patient with DCM and progressive, severe heart failure with life-threatening arrhythmia, who received a heart transplant at the age of 15 years.

DCM is one of the most common types of cardiomyopathy in the pediatric population, with an annual inci-

dence of almost 0.6 cases per 100,000. Despite maximal medical treatment, heart transplant is considered standard therapy. Based on multicenter observational studies, recent guidelines were developed in order to use cardiac transplant in patients with DCM. Waitlist mortality is still high, and studies report that almost 40% of patients with end-stage heart failure due to DCM have significant complications with an increased risk of morbidity and mortality while on waitlist.[5] Efforts are still ongoing in order to assess the proper time for heart transplant listing and to identify risk factors that can be involved in waitlist mortality.[6] According to the Pediatric Cardiomyopathy Registry Study Group, patients with decompensated heart failure with severe dilatation of the LV and low ejection fraction have a higher risk of mortality.[7] Singh *et al*. found that the degree of LV dilatation is associated with a poor prognosis and an increased risk of death while on the waiting list and 6 months after heart transplant.[8] Furthermore, the risk of death is greater in patients diagnosed with severe DCM in the first months of life. Another factor associated with a worse outcome is the severity of heart failure signs and symptoms at cardiac evaluation.[8] In the case we presented, the patient was considered high-risk due to the fact that prior to transplant he showed signs and symptoms of end-stage heart failure, with life-threatening arrhythmias and severe dilatation of the LV. In this context, due to irreparable cardiac disease, a transplant was considered the only remaining therapeutic choice, with a better survival rate post-transplant.

After heart transplant, the patient received immunosuppression therapy divided into two parts: induction therapy and maintenance therapy. In our transplant center, induction therapy is given in order to prevent early graft rejection. The role of induction therapy is still debatable between transplant centers because of higher risk of post-transplant infectious complications and lymphoproliferative disorders, and every transplant center uses its own induction protocol.[9] Despite the fact that there is no direct association between higher graft survival and induction therapy, ISHLT data suggests that induction therapy is widely used, with almost 70% of cardiac recipients receiving induction therapy in the last years. Regarding maintenance therapy, the ISHLT reports that most pediatric heart transplant centers use the association of tacrolimus as the centerpiece and adjuvant therapy (MMF/mycophenolic acid and corticosteroids) due to a series of studies in adults that showed an improved long-term prognosis and fewer adverse effects compared with other drugs regimens.[10] In our case, despite the use of induction therapy and studies showing that tacrolimus-treated patients have a lower rate of rejection in the first year post-transplant (compared with other immunosuppressive drugs),[10] after two weeks post-transplant, the endomyocardial biopsy revealed mixed cellular and humoral rejection.

Endomyocardial biopsy is considered the gold standard for the diagnosis of graft rejection. Nevertheless, due to the potential risks of cardiac catheterization, the role of noninvasive imaging in assessing pediatric patients after orthotopic heart transplantation has increased lately. Echocardiography is a noninvasive, fast, and widely available imaging method, with remarkable developments lately in terms of myocardial deformation, 3D echocardiography, and also intrauterine diagnosis.[11,12] Regarding orthotopic heart transplantation, some authors suggested that LV mass increases and tissue Doppler indices decrease during rejection episodes.[13–15] Serial myocardial perfusion imaging (MPI) measurements can be used for the detection of rejection.[13,16] Also, multiple scoring methods have been proposed using M-mode parameters or tissue Doppler measurements. Furthermore, several studies have emphasized the utility of strain in diagnosing rejection, describing a worsening of longitudinal and circumferential strain in patients with rejection.[13,18–20] In our heart transplanted child, the echocardiographic assessment revealed increased LV mass, restrictive-type LV diastolic dysfunction, and decreased LV longitudinal strain at the time of endomyocardial biopsy, suggesting rejection. These echocardiographic parameters improved after rejection treatment.

CONCLUSIONS

Heart transplantation is considered standard therapy in DCM with end-stage heart failure. Early graft rejection is a severe, life-threatening complication in heart transplanted children. Prompt diagnosis and treatment is mandatory. Besides endomyocardial biopsy, advanced echocardiography can also be a valuable noninvasive tool for rejection assessment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Wilkinson JD, Landy DC, Steven DC, et al. The Pediatric Cardiomyopathy Registry and heart failure: Key Results from the first 15 years. Heart Fail Clin. 2010;6:401-413. doi: 10.1016/j.hfc.2010.05.002.

2. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003;348:1647. doi: 10.1056/NEJMoa021715.
3. Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant. 2016; 35:1185-1195. doi: 10.1016/j.healun.2016.08.018.
4. Boucek MM, Aurora P, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: tenth official pediatric heart transplantation report – 2007. J Heart Lung Transplant 2007;26:796. doi: 10.1016/j.healun.2007.07.035.
5. Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation. 2012;126:1079-1086. doi: 10.1161/CIRCULATIONAHA.110.011999.
6. Dipchand AI. Current state of pediatric cardiac transplantation. Ann Cardiothorac Surg. 2018;7:31-55. doi: 10.21037/acs.2018.01.07.
7. Alvarez J, Wilkinson JD, Lipshultz SE. Outcome predictors for pediatric dilated cardiomyopathy: a systematic review. Prog Pediatr Cardiol. 2007;23:25-32. doi: 10.1016/j.ppedcard.2007.05.009.
8. Singh TP, Sleeper LA, Lipshultz S, et al. Association of left ventricular dilatation at listing for heart transplant with postlisting and early posttransplant mortality in children with dilated cardiomyopathy. Circ Heart Fail. 2009;2:591-598. doi: 10.1161/CIRCHEARTFAILURE.108.839001.
9. Darragh R. Should Induction therapy be the standard protocol in pediatric heart transplant recipients? J Heart Lung Transplant. 2018;38:435-436. doi: 10.1016/j.healun.2017.09.006.
10. Goldfarb SB, Levvey BJ, Cherikh WS, et al. Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Lung and Heart-Lung Transplantation Report – 2017; Focus Theme: Allograft ischemic time. J. Heart Lung Transplant. 2017;36:1070-1079. doi: 10.1016/j.healun.2017.07.017.
11. Gozar L, Marginean C, Toganel R, et al. The role of echocardiography in fetal tachyarrhythmia diagnosis. A burden for the pediatric cardiologist and a review of the literature. Med Ultrason. 2017;19:232-235. doi: 10.11152/mu-892.
12. Marginean C, Gozar L, Marginean CO, et al. Prenatal diagnosis of the fetal common arterial trunk. A case series. Med Ultrason. 2018;20:100-104. doi: 10.11152/mu-1084.
13. Soslow JH, Samyn MM. Multi-modal imaging of the pediatric heart transplant recipient. Translational Pediatrics. 2019;8(4):322-338. doi: 10.21037/tp.2019.08.04.
14. Pauliks LB, Pietra BA, DeGroff CG, et al. Non-invasive detection of acute allograft rejection in children by tissue Doppler imaging: myocardial velocities and myocardial acceleration during isovolumic contraction. J Heart Lung Transplant. 2005;24:S239-S248. doi: 10.1016/j.healun.2004.07.008.
15. Behera SK, Trang J, Feeley BT, Levi DS, Alejos JC, Drant S. The use of Doppler tissue imaging to predict cellular and antibody-mediated rejection in pediatric heart transplant recipients. Pediatr Transplant. 2008;12:207-214. doi: 10.1111/j.1399-3046.2007.00812.x.
16. Flanagan R, Cain N, Tatum GH, Debrunner MG, Drant S, Feingold B. Left ventricular myocardial performance index change for detection of acute cellular rejection in pediatric heart transplantation. Pediatr Transplant. 2013;17:782-786. doi:10.1111/petr.12153.
17. Hernandez LE, Shepard CW, Menk J, et al. Global left ventricular relaxation: A novel tissue Doppler index of acute rejection in pediatric heart transplantation. J Heart Lung Transplant. 2015;34:1190-1197. doi: 10.1016/j.healun.2015.03.027.
18. Sehgal S, Blake JM, Sommerfield J, Aggarwal S. Strain and strain rate imaging using speckle tracking in acute allograft rejection in children with heart transplantation. Pediatr Transplant. 2015;19:188-195. doi: 10.1111/petr.12415.
19. Godown J, McEachern WA, Dodd DA, et al. Temporal changes in left ventricular strain with the development of rejection in paediatric heart transplant recipients. Cardiol Young. 2019;29:954-959. doi: 10.1017/S1047951119001185.
20. Colquitt JL, Jeewa A, Morris SA, et al. Diminished Global Longitudinal Strain Predicts Late Allograft Failure in Pediatric Heart Transplant Recipients. JACC Cardiovasc Imaging. 2017;10:1529-1531. doi: 10.1016/j.jcmg.2017.01.016.