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CASE REPORT

Autologous skeletal myoblast sheet implantation for pediatric dilated cardiomyopathy: A case report

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Abstract

Background In children with dilated cardiomyopathy, heart transplantation is the last treatment option. However, new regenerative treatments, such as cell therapy, have attracted scientific attention. We have previously demonstrated the efficacy of autologous skeletal myoblast sheet implantation for treatment of ischemic and dilated cardiomyopathy in adults. Because of the mechanism underlying this cell therapy, a similar effectiveness is expected for patients with pediatric dilated cardiomyopathy.

Case Herein, we describe the case of a child with dilated cardiomyopathy who underwent an autologous skeletal myoblast sheet implantation, which proved to be safe, and led to sustained maintenance and improvements in cardiac function and clinical status.

Keywords Autologous skeletal myoblast sheet · Cell therapy · Pediatric dilated cardiomyopathy · Myocardial regeneration

Introduction

Pediatric dilated cardiomyopathy (DCM) is a life-threatening disease [1], but ventricular assist device (VAD) therapy is now becoming a well-established treatment, and the outcomes of children with DCM have been improved by VAD support [2]. Unfortunately, the waiting period of pediatric heart transplantation is much longer for children than adults, and long-term VAD therapy results in a risk of developing various complications. Currently, regenerative medicine by cell therapy is an expected novel treatment option for heart failure to avoid VAD therapy or to postpone the timing of a VAD implantation [1]. We have previously demonstrated the efficacy of autologous skeletal myoblast sheet (ASMS) implantation as a treatment of ischemic cardiomyopathy (ICM) and DCM in preclinical and clinical studies in adults [3–6]. Because of the mechanism underlying ASMS implantation, such as angiogenesis due to a cytokine paracrine effect, sufficient effectiveness is expected in pediatric DCM.

Herein, we describe the case of a child with pediatric DCM who underwent ASMS implantation. We provide detailed information regarding the safety and efficacy of ASMS therapy in a pediatric patient.

Case

Our case involves a 3-year-old boy (body weight, 14.8 kg; height, 97.4 cm) who was diagnosed with DCM based on the detection of cardiomegaly at 9 months of age. His heart failure progressed even under maximum oral medication with an angiotensin-converting-enzyme inhibitor (ACEI) and β-blocker, and his Ross heart failure classification progressed to the third degree. He was transferred to our institute for regeneration therapy and was enrolled in our clinical trial, which was conducted according to the Guidelines on Clinical Research Using Human Stem Cells from the Japanese Ministry of Health, Labor, and Welfare (UMIN ID; UMIN000015893).

First, 3 g of skeletal muscles were harvested from the vastus medialis of the lower leg, and myoblast cells derived from autologous skeletal muscles were isolated and cultured. Two cell sheets were produced with 4.4×10^8 myoblast cells using temperature-responsive cell-culture dishes (UpCell,

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CellSeed; Tokyo, Japan). At 2 months after harvesting the skeletal muscle, cell sheets were placed and fixed onto the anterior and lateral walls of the left ventricle as widely as possible with stitches and fibrin glue via left intercostal thoracotomy. Six months have elapsed since the cell sheet implantation, and the patient has been followed-up in an outpatient setting with the same dose of ACEI and β-blocker.

Arrhythmias and adverse events were assessed to determine the treatment safety. No deterioration of arrhythmia was detected by Holter electrocardiography after sheet implantation (Table 1). The postoperative course after the skeletal muscle was harvested, implantation of the cell sheets was uneventful, and no critical adverse events were observed.

Cardiac function and clinical status were assessed to determine the efficacy of the treatment. The left ventricular (LV) volume remained unchanged after the treatment compared to the baseline values; LV contraction, derived from the biplane modified Simpson's method, was sustainably ameliorated compared to the preoperative value as assessed by echocardiography (Fig. 1). LV asynergy was not present before implantation and did not develop afterwards. Trivial mitral regurgitation was detected before implantation, but was not observed on the post-implantation examinations. The degree of Ross heart failure classification improved

Table 1 Measurements

	Holter ECG		Heart failure classification	Cardiopulmonary exercise test	Blood test	Chest X-ray	Cardiac catheterization			
	PVC (%)	Lown	Ross	6MWT (m)	BNP (pg/dL)	CTR (%)	RAP (mmHg)	PAP (mmHg)	PCWP (mmHg)	CI (mL/min/m^2)
PRE	< 0.1	4a	3	328	3.8	55.5	5	17	8	3780
POST1m	< 0.1	1	–	–	11.8	53.7	–	–	–	–
POST3m	< 0.1	1	1	–	8.3	51.5	–	–	–	–
POST6m	< 0.1	1	1	364	18.1	49.2	3	16	8	4350

ECG electrocardiogram, *PVC* premature ventricular contraction, *6MWT* 6−min walk test, *BNP* brain natriuretic peptide, *CTR* cardiothoracic ratio, *RAP* right atrial pressure, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *PRE* before sheet implantation, *POST1m* 1 month after sheet implantation, *POST3m* 3 months after sheet implantation, *POST6m* 6 months after sheet implantation

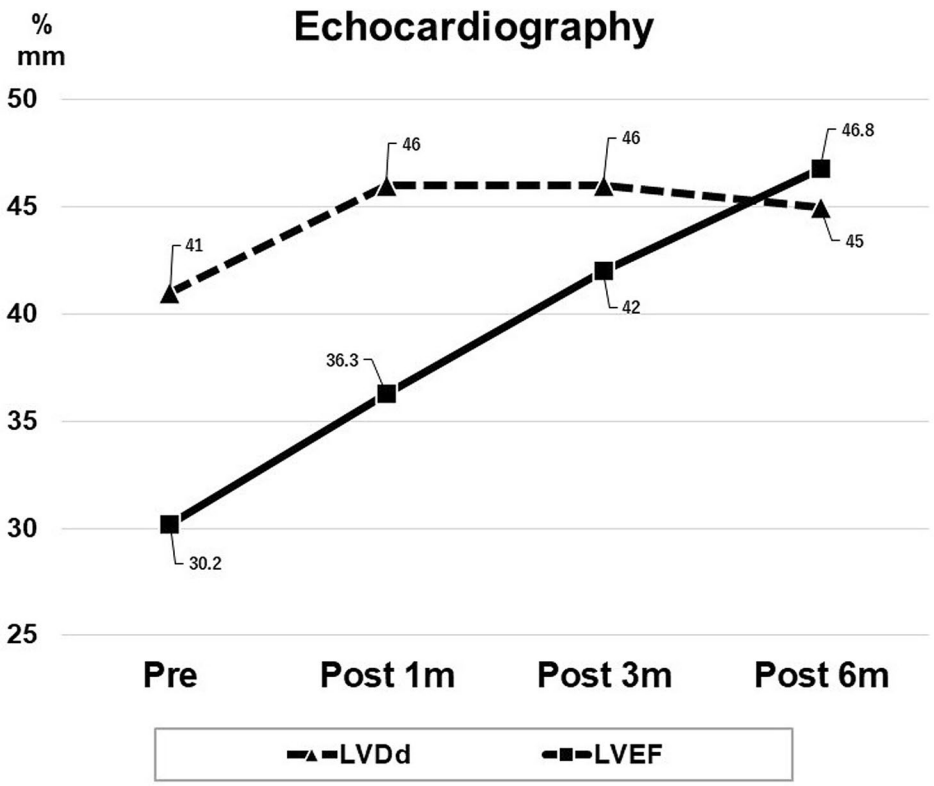

Fig. 1 Preoperative and postoperative measurements of left ventricular function by echocardiography. The preoperative and postoperative left ventricular end-diastolic dimensions (LVDds) (dashed line with black, upward-pointing triangles) were equal. However, the changes in left ventricular ejection fraction (LVEF) derived from biplane modified Simpson's method (solid line with black squares) gradually improved after sheet implantation. Pre before sheet implantation, Post1m 1 month after sheet implantation, Post3m 3 months after sheet implantation, Post6m 6 months after sheet implantation

from the third to the first degree at 3 months after sheet implantation; no deterioration has been observed to date (Table 1). The patient was assessed via the 6-min walk test as a cardiopulmonary exercise test, and a trend of improvement was observed (Table 1). When comparing his symptoms of heart failure before and after sheet implantation using a questionnaire answered by his parents, cold extremities, respiratory distress, and excessive sweating improved after sheet implantation.

Discussion

Here, we demonstrate the feasibility and safety of ASMS therapy for children with DCM. Despite pediatric DCM presenting a very poor prognosis because of progressive heart failure, cardiac function analysis by echocardiography and cardiac catheterization revealed the maintenance and recovery of cardiac function after sheet implantation. Furthermore, the BNP value was still within the normal range, although there were some changes after implantation. Therefore, the patient's status improved, as assessed using the Ross heart failure classification and quality of life, and his exercise capacity also increased.

We have previously reported an anti-heart failure effect of autologous skeletal myoblast sheet implantation therapy in preclinical and clinical ICM and DCM studies in adults [3–7]. After a detailed ASMS therapy analysis in an animal model of ICM and DCM, the paracrine effect of the cytokines released from a myoblast cell sheet exhibited anti-hypertrophic, anti-fibrotic, and angiogenic effects on the heat failure myocardium [4–6]. DCM is a cardiomyopathy with multiple etiologies; pathologically, it results in a loss of capillaries, hypertrophic cardiomyocytes, and fibrotic changes in children with DCM. Therefore, the mechanism of ASMS therapy seems to also work in children with DCM.

Previous reports have shown the greater potential cardiac regenerative capacity of myocardial tissue [1] and greater cytokine release potential of ASMS implantation in younger patients [7]. Therefore, ASMS therapy might be more effective in children with DCM than in adults.

As regenerative therapy does not have the potential to change the genetic background of the underlying disease, previous pediatric cardiac regenerative studies have only shown the short-term effects [1]. Moreover, our case report presents the short-term efficacy of autologous skeletal myoblast sheet implantation therapy for 6 months after implantation, but it has the potential to be a bridging therapy to heart transplantation in pediatric patients with DCM.

Conclusion

ASMS implantation is a feasible and safe therapy for pediatric DCM and can potentially help to maintain and improve the patient's cardiac function and clinical status. However, more cases of patients with long-term follow-ups are needed in future studies to clarify the efficacy of ASMS therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Pavo IJ, Michel-Behnke I. Clinical cardiac regenerative studies in children. World J Cardiol. 2017;9:147–53.
2. Morales DLS, Rossano JW, VanderPluym C, Lorts A, Cantor R, St Louis JD, et al. Third annual pediatric interagency registry for mechanical circulatory support (Pedimacs) report: Preimplant characteristics and outcomes. Ann Thorac Surg. 2019;107:993–1004.
3. Sawa Y, Yoshikawa Y, Toda K, Fukushima S, Yamazaki K, Ono M, et al. Safety and efficacy of autologous skeletal myoblast sheets (TCD-51073) for the treatment of severe chronic heart failure due to ischemic heart disease. Circ J. 2015;79:991–9.
4. Miyagawa S, Domae K, Yoshikawa Y, Fukushima S, Nakamura T, Saito A, et al. Phase I clinical trial of autologous stem cell-sheet transplantation therapy for treating cardiomyopathy. J Am Heart Assoc. 2017;6:e003918.
5. Kondoh H, Sawa Y, Miyagawa S, Sakakida-Kitagawa S, Memon IA, Kawaguchi N, et al. Longer preservation of cardiac performance by sheet-shaped myoblast implantation in dilated cardiomyopathic hamsters. Cardiovasc Res. 2006;69:466–75.
6. Miyagawa S, Saito A, Sakaguchi T, Yoshikawa Y, Yamauchi T, Imanishi Y, et al. Impaired myocardium regeneration with skeletal cell sheets: A preclinical trial for tissue-engineered regeneration therapy. Transplantation. 2010;90:364–72.
7. Ozawa H, Miyagawa S, Fukushima S, Itoh E, Harada A, Saito A, et al. Sirtuin1 regulates the stem cell therapeutic effects on regenerative capability for treating severe heart failure in a juvenile animal model. Ann Thorac Surg. 2016;102:803–12.