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Brief Report

Intramyocardial administration of autologous bone marrow mononuclear cells in a critically ill child with dilated cardiomyopathy

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Abstract Almost half of the children with symptomatic dilated cardiomyopathy receive a transplant or die within 2 years; however, cardiac stem cell transplantation has become a promising therapeutic option. The present case demonstrates for the first time, to our knowledge, the intramyocardial administration of autologous bone marrow mononuclear cells in a critically ill 4-month-old child with severe dilated cardiomyopathy. Left ventricular ejection fraction increased from 20% before stem cell transplantation to 41% at 4 months of follow-up.

Keywords: Cardiac insufficiency; stem cells; transplantation

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DILATED CARDIOMYOPATHY IS RARE AMONG children, however, with significant morbidity and mortality and constitutes the principal indication for cardiac transplantation in childhood.[1–3] Therefore, it is imperative to develop novel strategies for optimising non-transplant treatment of children with cardiac failure attributable to dilated cardiomyopathy.

Cardiac stem cell transplantation has become a promising therapy to treat myocardial infarction and cardiac failure in adults;[4,5] however, very few data are available on cardiac stem cell transplantation in children.[6] To our knowledge, there are no reports about direct intramyocardial cardiac stem cell transplantation in early age children. We hypothesised that cardiac stem cell therapy could represent an option before cardiac transplantation in children with severe cardiac failure caused by dilated cardiomyopathy.

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Case report

A 3-month and 2-week-old female child (body weight 5.7 kilograms, 37.5 percentile) diagnosed with dilated cardiomyopathy was admitted to our paediatric cardiac centre with rapid deterioration of her clinical condition (New York Heart Association functional class III–IV). Initial echocardiography confirmed the diagnosis and the reduced left ventricular function (ejection fraction – 25–28%, shortening fraction – percent, end diastolic diameter – 30 millimetres). Aortic coarctation and anomalous left coronary artery arising from the pulmonary artery or anomalous right coronary artery arising from the pulmonary artery were excluded with echocardiography. Anticongestive treatment was immediately adjusted (enalapril, digitalis, furosemide, spironolactone, and nitrates); however, the condition of the patient continued to deteriorate and therapy with catecholamine (dobutamine), complete sedation, and mechanical lung ventilation in assisted control mode were begun. Despite the clinical condition of the patient remaining critical, the dimensions of the left

Table 1. Echocardiographic and clinical characteristics.

	Before mononuclear cell transplantation	At discharge	At 3-month follow-up	At 4-month follow-up
Ejection fraction (%)	20	25	40	41
Shortening fraction (%)	12	18	19	20
End diastolic diameter (mm)	44	40	40	40
Mitral regurgitation	II	II	II	II
Weight (kg)	5.3	5.5	7.2	8.0

ventricle continued to increase and those of cardiac function to decrease (ejection fraction – 20%, shortening fraction – 12%, end-diastolic diameter – 44 millimetres, mitral regurgitation – II). The patient was oedematous with optimal urine production (under furosemide therapy) and normal serum creatinine levels as well as showed continuous body weight reduction (body weight 5.3 kilograms, 10 percentile). On account of this desperate situation with continuously worsening clinical condition despite optimal available therapy (cardiac transplantation and ventricular assist devices are not available for small children in our country), the decision for cardiac stem cell therapy with autologous bone marrow mononuclear cells was made as a possible therapeutic option. The local ethics committee approved the procedure and written informed consent was obtained from parents. On the day of bone marrow mononuclear cell transplantation, the child was 4 months and 1 week old.

A total of 1 millilitre of bone marrow was aspirated into heparin-treated syringes from the iliac crest with the use of local anaesthesia. The bone marrow aspirate was shipped at room temperature to the central cell-processing laboratory and diluted with sterile 0.9% NaCl (1:5), filtrated through a 70 microns cell strainer (BD Biosciences, Bedford, MA, USA), and the bone marrow mononuclear cells were isolated and enriched by density gradient with the use of Ficoll – Paque Premium (GE Healthcare Bio-Sciences AB, Uppsala, Sweden; manufactured according to GMP standards, Density 1.077 g/ml Lot 1001768) according to the manufacturer's instructions, with minor modifications. Mononuclear cells were washed two times with 45 millilitres 0.9% NaCl containing 10 unit per millilitre heparin. A total of 20 million bone marrow mononuclear cells were suspended in 2 millilitres of X VIVO (LOT 8MB152) 10 medium LOT 8MB152 without phenol red and gentamicin (Lonza Verviers S.p.r.l., Belgium; serum-free medium containing pharmaceutical-grade human components).

The left ventricle wall was punctuated in a transcutaneous, transapical way in echocardiography control and mononuclear cells were injected directly into the left ventricle wall.

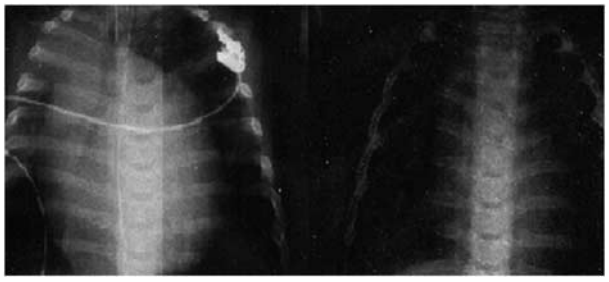

Figure 1.
Thoracic X-rays on the day after stem cell transplantation and at four months of follow-up.

The child's general clinical well-being improved dramatically after intramyocardial stem cell transplantation. The child was discharged 3 weeks later. The clinical condition improved further during the following months. The patient was regularly seen in our outpatient clinic; the ejection fraction increased from 25% at discharge to 47% 3 months after therapy and to 41% 4 months after bone marrow mononuclear cell therapy. During this observation period, the child showed significant signs of development, increased in body weight (8.0 kilograms, 37.5 percentile) as well as learned to crawl. The echocardiographic and clinical characteristics are summed up in Table 1. Figure 1 shows the child's thoracic X-rays on the day after stem cell transplantation and at 4 months of follow-up.

No adverse reaction occurred in the present case.

Discussion

Recent evidence shows that cellular cardiomyopathy has a potential fundamental regenerative capability, and it has already been introduced in clinical trials with adult patients using bone marrow mononuclear cells.[7] To our knowledge, this is the first case in which bone marrow mononuclear cells were transplanted directly intramyocardially in an early age child with dilated cardiomyopathy.

The cardiac regeneration capacity in children might be much better than in adults. In addition, paediatric failure has a good prognosis if casual therapy is possible. For example, early age children with anomalous left coronary artery arising from the

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pulmonary artery, who represent the patient subgroup with severe reduced ventricular function due to chronic ischaemia, recover after operation in most cases and show a normal ventricular function over time.[8] However, dilated cardiomyopathy still has limited therapeutic options.

In this case, the recovery of cardiac function, clinical status, and the child's development were observed. However, given the well-known spontaneous improvements in children with dilated cardiomyopathy at this age, we cannot exclude that similar recovery would have been observed even without intramuscular stem cell administration.

Conclusions

The present case illustrates that autologous bone marrow mononuclear cell therapy, which has become a promising therapy in adults, might also represent a therapeutic approach in children with dilated cardiomyopathy. However, multi-centre randomised trials have to determine the safety and efficacy of intramuscular stem cell therapy in small children with dilated cardiomyopathy.

Further research will be orientated to evaluate the possible progress of cardiac function at 6 and 12 months of follow-up. Multi-slice, three-dimensional echocardiography, magnetic resonance tomography, and multi-conduction electrocardiogram are planned.

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