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LETTER TO THE EDITORS

Neonatal myocardial infarction: substantial improvement of cardiac function after autologous bone marrow-derived cell therapy

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Sirs:

In children, congestive heart failure is mainly caused by different forms of cardiomyopathies or congenital heart disease. In contrast to adults, myocardial infarction in neonates is a rare disease [3-5]. The causes of myocardial infarction remain unclear in most paediatric patients, the management strategies of myocardial infarction in neonates are not standardised and mortality is still high [6].

An 18 days old male child (body weight 3.5 kg, length 58 cm) was admitted to our paediatric heart centre with a diagnosis of dilated cardiomyopathy with progressive deterioration of his clinical condition (NYHA IV, intubated and ventilated, on amiodarone for ventricular arrhythmias). Initial MRI showed highly reduced left ventricular function (EF 18%, EDVi, 3.8 ml/kg, ESVi 3.1 ml/kg), an akinetic posterior wall of the failing left ventricle with suprasystemic right ventricular pressure, and thrombus formation in the left atrium (2.2 × 0.5 cm). The ductus arteriosus (PDA) was reopened and stented with a 3.5 mm Integrity Stent to ensure systemic blood flow via right–left shunting over the duct. During the same catheterisation, the anatomical malformation of an anomalous left coronary artery from pulmonary artery was ruled out, as well as myocarditis was ruled out by biopsies. Haemostaseological work-up uncovered a heterozygote mutation in MTHFR gene (C677T), a frequent risk factor for thrombophilia. Therefore, we speculate that a myocardial infarction has occurred perinatal resulting in an akinetic posterior wall with a corresponding late enhancement documented in the MRI. By the time of heart catheterisation, the thrombus was already solved due to systemic anticoagulation.

After slight stabilisation of the clinical situation the child was extubated after 7 days in our centre. However, clinical condition and heart function deteriorated again (NYHA IV). Due to the desperate situation with an akinetic posterior left ventricular wall after 33 days of inotropic treatment without any signs of clinical recompensation, the decision for autologous bone marrow-derived cell therapy as compassionate treatment was made. Heart transplantation was also discussed.

The local ethics committee was informed and written informed consent was obtained from both parents. 6 ml of bone marrow was aspirated from the tibia; autologous BMCs were separated as previously described [13] (33, 84×10^6 cells) and administered via intracoronary bolus injection with stop-flow technique into the Ramus posteromarginalis and the Ramus circumflexus (3 ml each). (Fig. 1). BMCs were administrated without any adverse events. Thereafter, the clinical condition of the patient improved slowly but steadily. The reopened PDA was closed with an ADO II AS device 23 days after intracoronary cell therapy and the catecholamine therapy was ended 25 days after cell therapy.

Anticongestive treatment with Lisinopril and Propranolol was initiated. The patient was discharged 27 days after

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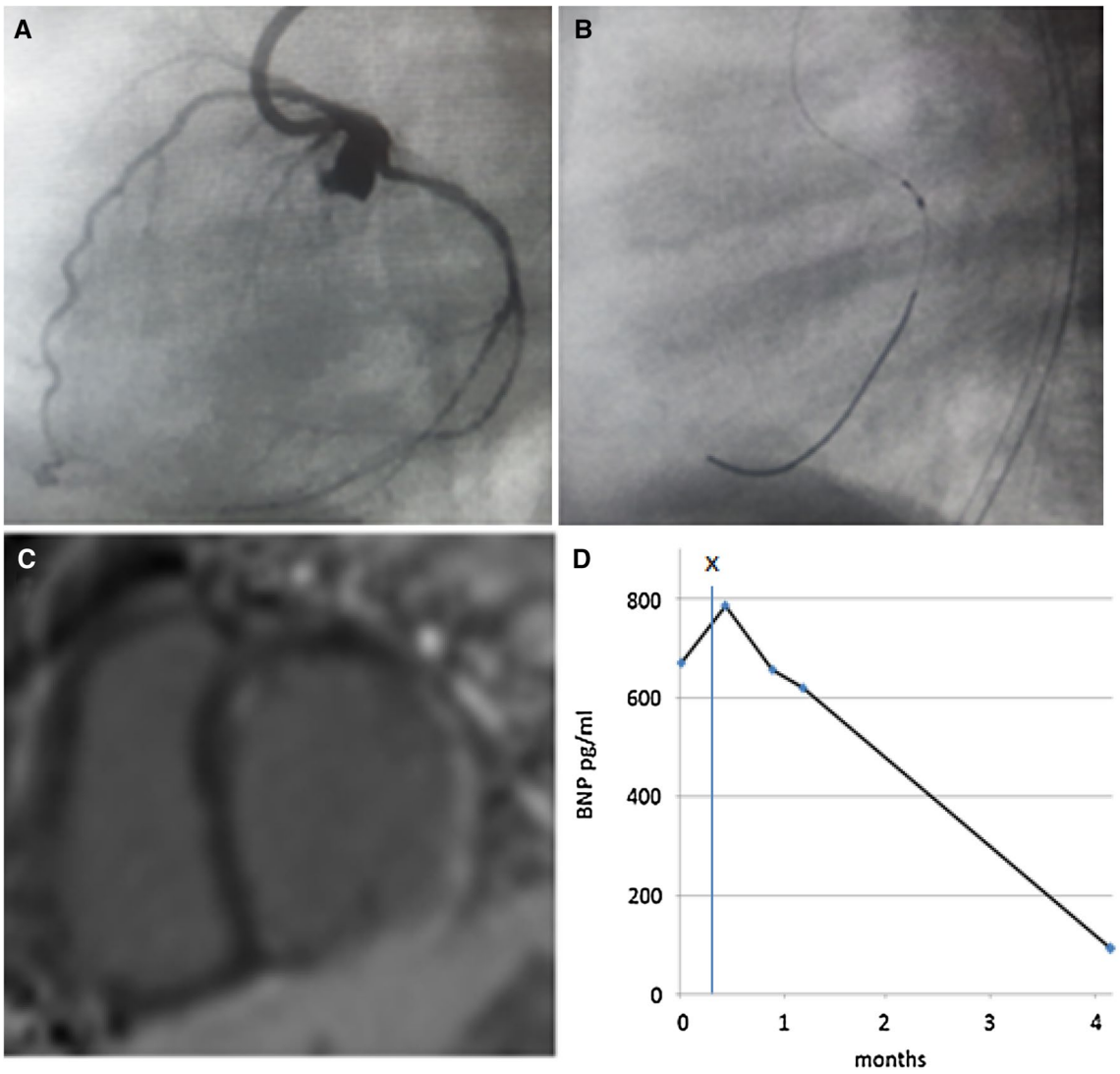

Fig. 1 **a** Selective angiogram of the left main coronary artery, which supplies the area suggestive to be ischemic on ECG and MRI. **b** Intracoronary bolus injection of BMCs in the R. posterior marginalis via low-pressure inflation of a 1.5×20 mm Emerge Push-Ballon (2–4 atm). **c** Late enhancement with the affected left ventricular posterior wall. **d** BNP development over the period of 4 month. (X) Application date of autologous bone marrow-derived cell therapy

cell therapy. Because of the C677T mutation in the MTHFR gene, we continued anticoagulation therapy with heparin until the thrombus in the left atrium was dissolved; afterward therapy was continued with ASS. The patient was regularly seen in our out-patient clinic. 4 months after cell therapy the BNP had decreased from peak values of nearly 800 pg/ml at the time of the cell therapy to 93 pg/ml (Fig. 1), the EF increased to 42%, the EDVi and the ESVi decreased to 3.3 and 1.9 ml/kg, respectively (MRI) and the general clinical condition had also increased significantly (NYHA I, Ross-Score 3/12).

Cardiac regeneration capacity is preserved in zebrafish [12], some adult amphibians and young mammals [11]. Furthermore cardiac recovery potential is documented in several clinical courses in young children [15]. An example is given by children with ALCAPA who present in a poor clinical condition with ECG signs of infarction, elevated troponin and CKMB levels indicating significant cardiomyocyte loss. After surviving surgical correction most of these children show normalization of severely reduced cardiac function [9]. Another example is given by a functional recovery after myocardial infarction as described before [8]. In contrast to the published report, in the present case, the heart function and the clinical condition have been worse and did not recover for > 1 months.

In the last years many clinical trials have evaluated safety [1, 10] and clinical effects of cardiac cell therapy in adults. Most meta-analyses seem to agree that the potential

beneficial effect of cell therapy for heart failure and acute myocardial infarction is inconclusive [7]. Several case reports [13, 18] and case series [2, 14] are published suggesting a beneficial effect of cell therapy for children. A clinical Phase 2 Trial (PERSEUS) shows moderate positive effects from intracoronary injection from cardiosphere-derived cells in children with a single ventricle physiology and global dysfunction [16]. Progenitor and stem cells secrete an enormous variety of extracellular vesicles and cytokines and these endocrine factors mediate antiapoptotic, angiogenic and antifibrotic actions [17].

In the present case, a toddler with severely reduced cardiac function and critical clinical condition was treated with autologous BMC therapy to support endogenous regeneration capacity. In the follow–up, a significant increase of the cardiac function in line with a significant increase of the clinical condition was documented. This clinical course serves as another challenging example of cardiac regeneration capacity in children. Because of some preserved regeneration capacity in very young children, intracoronary cell therapy could be a more viable option for children than for adults, especially for very young children as presented in this case.

Based on the knowledge that regenerative capacity is partly preserved in the paediatric population, a toddler suffering from myocardial infarction presenting in a prolonged unstable clinical condition was treated with intracoronary autologous bone marrow-derived cell therapy. Intracoronary cell therapy was technically feasible and safe. The clinical condition of the child improved significantly in the follow-up.

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