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Case report

Steroid-induced hypertrophic cardiomyopathy following stem cell transplantation in a neonate: a case report

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Summary:

We report a case of severe left ventricular outflow tract obstruction complicating steroid therapy in an infant undergoing allogeneic transplant in the first few weeks of life for treatment of Krabbe's disease. While this complication is well known to those treating premature infants, it has not been reported in the stem cell transplant setting. For young infants undergoing allogeneic transplant who require steroid therapy, cardiac monitoring after 2–3 weeks of therapy is recommended. *Bone Marrow Transplantation* (2001) **27,** 1105–1108.
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Pre- and perinatal diagnosis and the rapid availability of cord blood for stem cells have resulted in a subset of very young patients undergoing stem cell transplantation. There are several characteristics that are unique to this cohort, including altered drug kinetics and immaturity of organ function, which may result in complications of therapy usually not seen in older cohorts undergoing similar treatment.

We report a case of severe ventricular hypertrophy and outflow obstruction as a cardiac complication due to steroid therapy. This complication is well known in the neonatal experience, but not previously reported in the context of stem cell transplantation.

Case report

A fetus was diagnosed as having Krabbe's disease (globoid cell leukodystrophy) based on chorionic villi sampling performed in a nondiabetic mother with a positive family history of the disease. In the absence of a suitable family member donor, a 4/6 antigen matched cord blood from an unrelated donor was identified before birth. At birth, after 38 weeks gestation, cord blood was tested for glucocerebrosidase activity (Dr Wenger, Jefferson Medical College, Philadelphia, PA, USA) and the diagnosis of Krabbe's disease was confirmed. Repeat HLA typing confirmed the prenatal result. At 10 days of age the infant was started on an Institutional Review Board-approved cord blood transplant protocol (collaboration with Dr Joanne Kurtzberg, Duke University, Durham, NC, USA): busulfan (1 mg/kg four times daily p.o. on days −9 to −5), cyclophosphamide (50 mg/kg once daily i.v. on days −5, −4, −3, and −2), and antithymocyte globulin (ATGAM) (30 mg/kg once daily i.v. on days −3, −2, and −1). Busulfan pharmacokinetics were performed after the first dose and revealed an area under the curve (AUC) level of 459 μM.min. The dose was increased to 1.5 mg/kg for doses 7–16 to achieve a target AUC of 900–1100 μM.min. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin (3 mg/kg i.v. continuous infusion starting day −2) and methylprednisolone (0.5 mg/kg twice daily i.v. days 0 to +4, then 1 mg/kg twice daily i.v. days +5 to +20). A pretransplant echocardiogram was done on day −11, showing normal structure, chamber dimensions, wall thickness, and function of the heart (Figure 1 and Table 1). The post-transplant course was uneventful. The patient was discharged home on day +13, with early evidence of count recovery, and without any evidence of GVHD. Discharge medications were cyclosporin and prednisone (2 mg/kg/day).

On day +25, the patient presented to the outpatient clinic with symptoms of poor feeding effort, post-feeding emesis, and decreased urine output. Physical examination revealed a new onset grade II/VI ejection systolic murmur at the left mid-parasternal border, a gallop, and cardiomegaly on chest roentgenogram. An echocardiogram showed moderate biventricular hypertrophy (Table 1), systolic anterior motion of the mitral leaflet with moderate mitral regurgitation and dynamic left ventricular outflow tract (LVOT) obstruction with a peak pressure gradient of 145 mmHg (normal $<$5 mmHg) (Figure 2). This resulted in left ventricular hypertension with an estimated systolic pressure of 165 mmHg (normal $<$112 mmHg for age). In the absence of a known association of Krabbe's disease with hypertrophic cardiomyopathy, and with no family history, structural heart defects, or hypertension to account for it, steroid-induced hypertrophic cardiomyopathy was considered as the probable diagnosis. Prednisone was discontinued. Furosemide (1 mg/kg/day) was used to treat congestive heart

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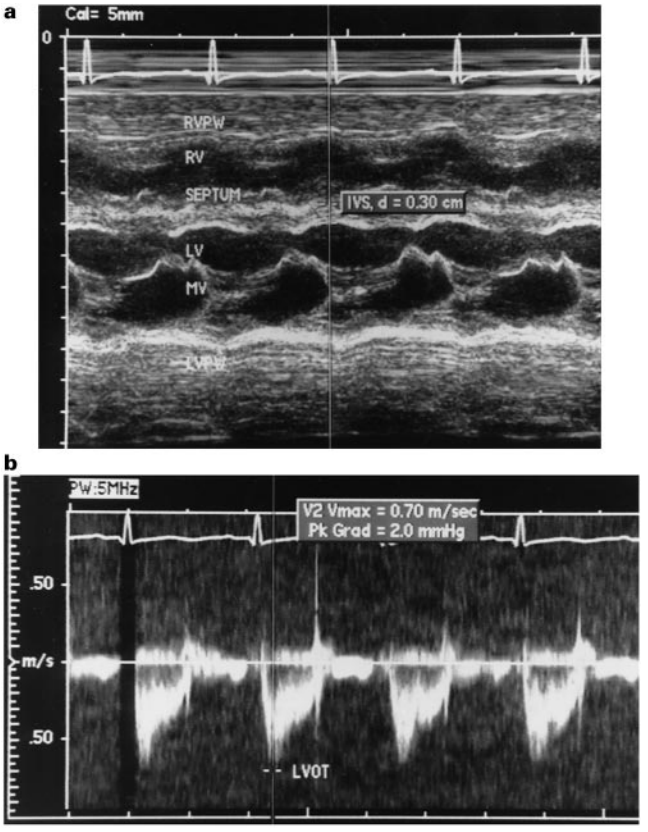

Figure 1 (**a**) A pre-transplant M-mode echocardiogram showing normal dimensions of the ventricular cavities and thickness of the free ventricular walls and interventricular septum. The two leaflets of the mitral valve are normally close to each other during systole (time period just after QRS of the ECG in the Figure) and separate during diastole. (**b**) Doppler interrogation across the left ventricular outflow tract shows a normal pressure gradient (<5 mmHg). AW = anterior wall; IVS = interventricular septum; LV = left ventricle; LVOT = left ventricular outflow tract; MV = mitral valve; PW = posterior wall; RV = right ventricle.

failure. Within a few days she developed grade III GVHD (skin and gut), which was managed by continuing cyclosporin and adding anti-interleukin-2 receptor antibody (Zenapax, Roche US Pharmaceuticals, 1 mg/kg once every 4 days for five doses) with marked clinical improvement.

Since the patient had critically high left ventricular pressures and congestive heart failure, initially betablocker (propranolol) and then calcium channel blocker (nifedipine) therapy was initiated (Table 1). At the time of discharge (day +33), the dynamic LVOT obstruction was mild (peak pressure gradient 25 mmHg), ventricular hypertrophy was less (Table 1), and there was no gallop or pleural effusion. Follow-up serial echocardiography at 2 and 6 weeks from discharge showed unchanged obstruction. Nifedipine was discontinued, and she was started on verapamil, which was titrated up to 1.75 mg/kg/day while monitoring her blood pressure. By 6 months of age ($4\frac{1}{2}$ months after steroid was discontinued), the mitral regurgitation and obstruction were resolved (Table 1), and verapamil was discontinued. At 8 months of age the ventricular wall thickness and cavity dimensions were completely normal (Figure 3). Subsequent cardiac evaluations have been normal.

Table 1 Echocardiographic findings prior to and following steroid therapy

Time sequence (weeks)	*Pre-transplant*	*Post transplant steroid therapy*					
		After initiation	*After discontinuation*				
		4	*1*	*4*	*8*	*16*	*32*
LVPWDT							
actual (mm)	3	6	7	5	5	4	3.8
% of normal	67	152	149	106	106	98	92
IVSDT							
actual (mm)	4	9	13	9	8	6	4.2
% of normal	90	187	260	191	163	122	100
LVEDD							
actual (mm)	18	14	13	15	16	19	20
% of normal	100	78	56	62	69	80	85
SAM-MV	– – –	+	+	+	+	– – –	– – –
MR	– – –	++	+	+	+	– – –	– – –
LVOT peak PG (mmHg)	<5	145	64	38	35	<5	<5

LVPWDT = left ventricular posterior wall diastolic thickness; IVSDT = interventricular septal diastolic thickness; LVEDD = left ventricular diastolic diameter; SAM-MV = systolic anterior motion of the mitral valve, '– – –' = absent, '+' = present; LVOT peak PG = left ventricular outflow tract peak pressure gradient; MR = mitral regurgitation; % of normal = percentage of the value at the upper end of the normal for body surface area.

Discussion

Hypertrophic cardiomyopathy is a well-known complication of steroid therapy in premature infants, developing with steroid courses of 2–3 weeks duration or longer.[1,2] It is less common but has been reported in full-term infants and children.[3,4] However, hypertrophic cardiomyopathy has not been reported in the context of stem cell transplant, which frequently includes relatively prolonged steroid therapy for GVHD prophylaxis or treatment.

Steroid-induced hypertrophic cardiomyopathy is characterized by the concentric thickening of the interventricular septum and free walls of the ventricles and reduction in the intracavity dimensions. Prolonged steroid therapy in young infants and premature neonates induces increased protein synthesis in myocytes, leading to hypertrophy. Such changes are transient in premature infants, as they resolve within 1–2 weeks after discontinuation of the steroids.[1,2] In older infants and children, the course of resolution of ventricular hypertrophy may be longer, as demonstrated by our and other case reports,[3,4] emphasizing the need for a longer follow-up. Severe septal hypertrophy causes a Venturi effect, drawing the anterior mitral leaflet against the ventricular septum, resulting in left ventricular outflow obstruction and a pressure gradient. This was present in our case and has been reported in only a few other cases of steroid-induced hypertrophic cardiomyopathy.[5] The resultant left ventricular hypertension may cause myocardial ischemia and congestive heart failure, which developed in our case and has been only occasionally reported by others.[6] These clinical and hemodynamic developments warranted medical intervention in our case to relieve the ventricular outflow tract obstruction and the signs and symptoms of heart failure.

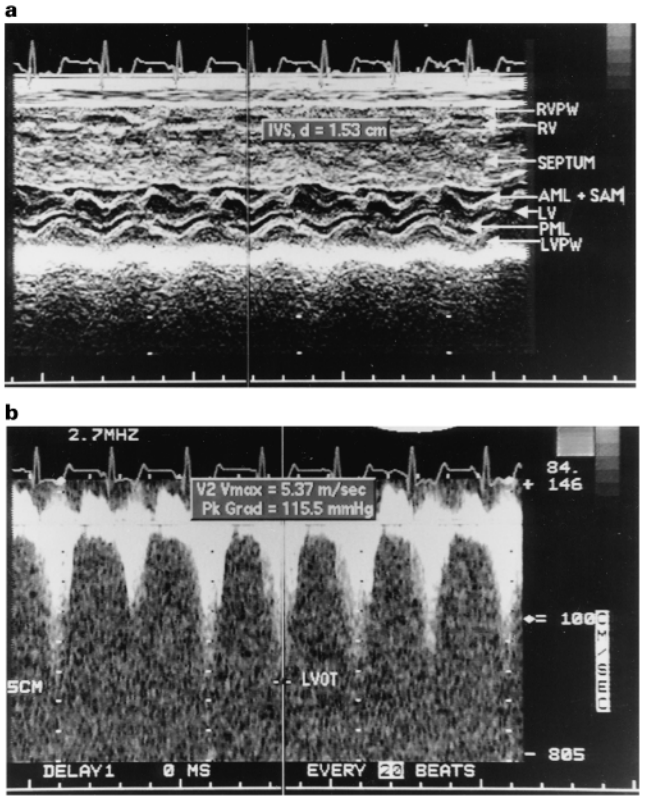

Figure 2 (**a**) A post-transplant M-mode echocardiography 27 days after steroid therapy, showing gross thickening of the intraventricular septum (1.53 cm, normal for the age ⩽4 mm), reduction in the cavity dimensions of the left and right ventricles, and mild thickening of the left ventricle posterior wall. The anterior and posterior leaflets of the mitral valve are separated during systole due to systolic anterior motion of the anterior leaflet. (**b**) The dynamic pressure gradient across the left ventricular outflow tract is of severe degree and is depicted by the characteristic tapering spectral profile. AML and PML = anterior and posterior mitral leaflets, SAM = systolic anterior motion of the anterior mitral leaflet, other abbreviations as in Figure 1.

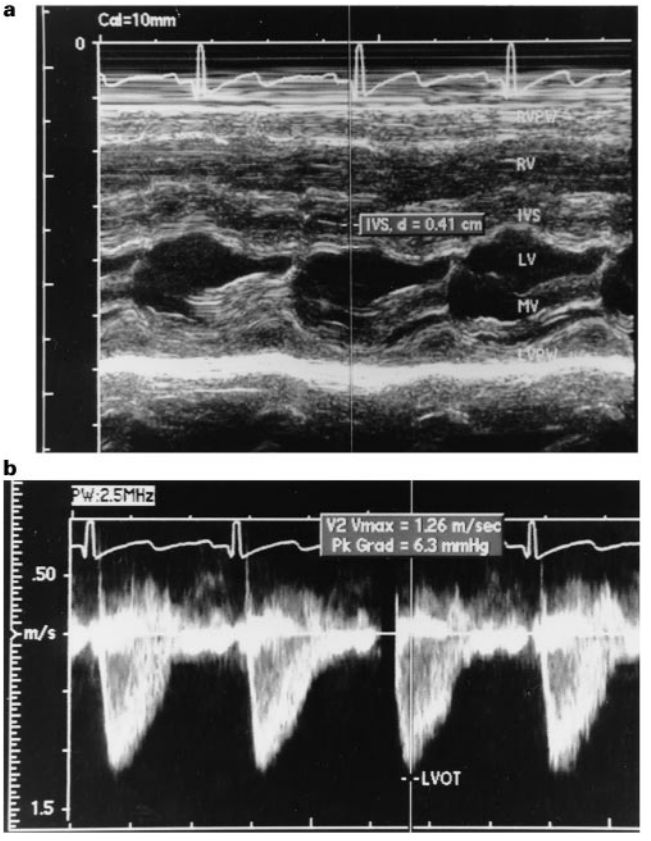

Figure 3 (**a**) A post-transplant M-mode echocardiography 4.5 months after stopping the steroid therapy, showing complete normalization of the dimensions of the ventricular cavities and wall thickness of the free ventricular walls and the septum. The systolic anterior motion of the mitral valve has resolved. (**b**) The dynamic pressure gradient across the left ventricular outflow tract has resolved (normal ⩽10 mmHg for age). Abbreviations as in Figures 1 and 2.

Hypertrophic cardiomyopathy is usually a familial disorder due to mutation in several genes coding for both light and heavy chain myosin cardiac protein. Its manifestation in infancy is rare. There was no positive family history in our case. Many secondary causes of hypertrophic cardiomyopathy have been identified and include various inborn errors of metabolism, systemic hypertension, iatrogenic factors (such as steroids), and being the infant of a diabetic mother. In our case, the absence of a family history of cardiomyopathy or gestational diabetes, the onset of cardiac hypertrophy within 2 weeks of steroid therapy, its resolution within months of steroid discontinuation (while continuing on the same dose of cyclosporin), no reported association between Krabbe's disease and cardiac hypertrophy, and the absence of systemic hypertension prior to the development of cardiac hypertrophy were all supportive of the diagnosis of steroid-induced hypertrophic cardiomyopathy. In the setting of a relatively prolonged course of steroid therapy, a steroid-induced hypertrophic cardiomyopathy should be considered, particularly with the development of a new heart murmur and cardiomegaly during the course of the treatment. Cardiologic evaluation and serial echocardiographic monitoring should be undertaken to discern the presence of left ventricular outflow obstruction and the need for medical intervention.

As stem cell transplants are performed in younger/premature infants, the use of methylprednisolone and other steroids may be associated with abnormal cardiac hypertrophy, which may be life-threatening. In addition to a pre-transplant echocardiogram, we recommend a repeat echocardiogram at 2–4 weeks after starting steroids in young infants undergoing transplantation.

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