Fetal and neonatal cardiac rhabdomyomas: clinical presentation, outcome and association with tuberous sclerosis complex

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Rhabdomyoma is the most common pediatric heart tumor. Cardiac rhabdomyomas (CRs) have a natural history of spontaneous regression and are closely associated with tuberous sclerosis complex (TSC). We aimed to evaluate the clinical presentation and outcome of CRs and their association with TSC. Patients with CRs diagnosed in last six years were retrospectively analyzed. A total of 25 tumors were identified in seven patients by echocardiography. Three patients were diagnosed prenatally by fetal echocardiography, three patients in the neonatal period and one patient in early infancy. The median follow-up period was two years (range: 5 months-6 years). Five patients (71%) had multiple tumors. Three patients had arrhythmias and two patients required surgery. Only 36% (9/25) of the tumors regressed. TSC was diagnosed in four patients during the follow-up. CRs may have different presentations and clinical course. Surgery is only necessary when hemodynamically significant obstruction is present. As CRs are associated with long-term development of TSC and other diagnostic features are not yet typically apparent in the prenatal and neonatal periods, careful evaluation and follow-up are essential to exclude TSC.

Key words: cardiac tumor, rhabdomyoma, tuberous sclerosis complex, echocardiography, fetal echocardiography.

Primary cardiac tumors are rare, with a reported incidence from 0.027% to 0.08% in pediatric autopsy series[1]. Rhabdomyomas constitute 45% to 80% of all primary cardiac tumors in children. Cardiac rhabdomyomas (CRs) have a natural history of spontaneous regression; however, they may cause arrhythmias, hemodynamically significant obstruction, heart failure, and sudden death[2].

Cardiac rhabdomyomas are highly associated with tuberous sclerosis complex (TSC) (MIM #191100), which is characterized by cortical tubers, subependymal nodules, epileptic seizures, mental retardation, renal angiomyolipomas, cysts, polycystic renal disease, renal carcinoma, and facial angiofibroma (adenoma sebaceum)[3]. Approximately 80% of children with CRs have clinical or radiologic findings or family history of TSC and 50% of TSC patients have CRs[4]. CRs may precede the skin, neurological and radiological signs of TSC by months or even years. The reported incidence of TSC in fetuses with CRs ranges from 51% to 86%[5].

We aimed to evaluate the clinical presentation and outcome of CRs diagnosed in our center and their association with TSC.

Material and Methods

We identified all CR patients diagnosed between 2003 and 2009 from the database in our unit. Clinical features of prenatally diagnosed patients were documented from obstetric records and postnatally diagnosed patients from pediatric records. Echocardiographic images were reviewed from the computer

database. Data included age at diagnosis, clinical presentation, physical examination findings (respiratory distress, cyanosis, murmur, arrhythmia, heart failure), electrocardiogram (ECG), 24-hour ECG recording results, initial and last echocardiographic findings (number of CRs, size, location, presence of inflow or outflow tract obstruction, myocardial dysfunction, valvular insufficiency), time and indication of surgery, outcome (partial or total regression, residual tumor), and follow-up period. For patients with prenatal diagnosis, gestational age at diagnosis, presentation, and fetal echocardiographic and magnetic resonance imaging (MRI) findings were also reviewed.

Patients with diagnosis of TSC were identified from patients who were initially diagnosed as having CRs. Diagnosis of TSC was based on criteria established at the 1998 TSC Conference[3]. Clinical and radiological findings of TSC patients (family history of TSC or CRs, hypopigmented macules, seizures, mental retardation, electroencephalogram, cranial MRI and abdominal imaging results) were evaluated. Informed consent was obtained from parents of the patients.

Results

A total of 25 tumors were identified in seven patients in the study period. Three patients were diagnosed prenatally by fetal echocardiography (Table I). Two patients had incidental finding of an intracardiac tumor during routine fetal ultrasonography (USG), and one patient presented with fetal arrhythmia (atrial premature contractions). None of the patients had hemodynamically significant obstruction or developed fetal hydrops. Routine fetal USG was normal except for cardiac tumors. Fetal cranial and abdominal MRI performed to exclude TSC was available in one patient (Case 2) and yielded normal results. Figure 1 shows fetal and postnatal echocardiographic images of Case 2.

Clinical features and outcome of all patients are presented in Table II. None of the patients had associated congenital heart disease. Four patients were diagnosed postnatally. The median age at diagnosis was 11 days (range: 3 days-3 months). Five patients were asymptomatic during their initial presentation, and echocardiography was performed for presence of murmur, cyanosis or arrhythmia. Seventy-one percent (5/7) of the patients had multiple tumors, and 88% (22/25) of these were located in the ventricles. Figure 2 shows the echocardiographic image of Case 4 with multiple CRs. The largest tumor diameter ranged between 22 to 70 mm (median: 26 mm). All patients had normal ECG except one (Case 1). 24-hour ECG recordings documented arrhythmia in three patients. Two of these patients (Cases 1 and 7) required antiarrhythmic therapy (oral propanolol). One patient had atrial premature contractions (Case 1) and two patients (Cases 5 and 7) had isolated monomorphic and polymorphic ventricular premature contractions. The follow-up period ranged between five months to six years (median: 2 years). Two patients (Cases 5 and 7) developed hemodynamically significant obstruction during the follow-up and required surgery. Case 5 initially presented with multiple CRs, one causing right ventricular outflow tract (RVOT) obstruction. Spontaneous regression did not occur and surgery was necessary at five months for severe RVOT obstruction. Figure 3 shows preoperative and postoperative echocardiographic images of this patient. Case 7 initially presented with a 70x65 mm tumor in the left ventricle that compressed the right ventricle, RVOT and pulmonary artery; spontaneous regression did not occur and surgery was necessary at five months. However, she had residual tumor which persisted for two years. Four patients had no tumor regression and three patients had partial regression. In our series, only 36% (9/25) of the tumors regressed.

During the follow-up, TSC was diagnosed in 4/7 (57%) patients (Table III). The median time lapse between diagnosis of rhabdomyoma and diagnosis of TSC was 3.5 months (range: 50 days-4.5 years). Three patients had a family history of TSC, and all patients had multiple CRs and cerebral pathology consistent with TSC based on cranial MRI. Seizures and neurodevelopmental delay were present in one patient (Case 5) who responded successfully to anticonvulsive therapy. During screening of the parents for presence of CRs by echocardiography, the father of Case 1 was found to have multiple CRs and was diagnosed as TSC after demonstration of cortical and subcortical tumors on cranial MRI and a giant renal tumor on USG.

Table I. Clinical Features of Patients with Prenatal Diagnosis of Cardiac Rhabdomyomas

Case	Diagnosis (GA)	Sex	Presentation	Family History of TSC	Number	Tumor Location	Largest Tumor Diameter	Hemodynamic Obstruction	Fetal Arrhythmia	Fetal Hydrops	Fetal MRI	Outcome
1	28 weeks	M	Fetal arrhythmia	+	Multiple	RA, RV, LV	25 mm	-	+	-	NA	Alive
2	25 weeks	F	Fetal USG-Intracardiac tumor	-	Single	LV	26 mm	-	-	-	Normal	Alive
3	35 weeks	F	Fetal USG-Intracardiac tumor	+	Multiple	RA, RV	21 mm	-	-	-	NA	Alive

F: Female; GA: Gestational age; LV: Left ventricle; M: Male; MRI: Magnetic resonance imaging; NA: Not available; RA: Right atrium; RV: Right ventricle; TSC: Tuberous sclerosis complex; USG: Ultrasonography.

Fig. 1a: Fetal echocardiographic image of antenatally diagnosed patient (Case 2), at 31 gestational weeks; arrow shows the rhabdomyoma (R) in the left ventricle. **1b:** Postnatal echocardiographic image of the same patient at two months with no regression in tumor size. AO: Aorta.

Discussion

Echocardiography has been established as the primary diagnostic tool for the evaluation of cardiac tumors in children[2]. Rhabdomyomas appear on ultrasound as round, homogeneous,

Fig. 2: Echocardiographic image of the patient (Case 4) with multiple rhabdomyomas (R) in the right and left ventricles. AO: Aorta.

Table II. Clinical Features of the Patients with Cardiac Rhabdomyomas

Case	Diagnosis	Sex	Presentation	Postnatal physical examination	Number of tumors	Tumor location	Largest tumor diameter	Hemodynamic obstruction	Arrhythmia	Surgery	Tumor regression	Follow-up period
1	Prenatal, 28 weeks	M	Fetal arrhythmia	Arrhythmia Murmur Cyanosis	Multiple	RA, RV, LV	25 mm	-	+	-	-	5 months
2	Prenatal, 25 weeks	F	Fetal USG-Intracardiac tumor	Murmur	Single	LV	26 mm	-	-	-	-	3 months
3	Prenatal, 35 weeks	F	Fetal USG-Intracardiac tumor	Normal	Multiple	RA, RV	22 mm	-	-	-	+ (partial)	2 years
4	15 days	M	Asymptomatic	Murmur	Multiple	RV, LV	34 mm	-	-	-	+(partial)	1 year
5	3 days	F	Asymptomatic	Arrhythmia Murmur	Multiple	RA, RV, LV	33 mm	+	+	+	+ (partial)	2.5 years
6	6 days	M	Cyanosis	Cyanosis	Multiple	RV, LV	24 mm	-	-	-	-	6 years
7	3 months	F	Asymptomatic	Murmur	Single	LV	70 mm	+	+	+	-	2.5 years

F: Female; LV: Left ventricle; M: Male; RA: Right atrium; RV: Right ventricle; TSC: Tuberous sclerosis complex.

Table III. Clinical and Radiological Findings of Cardiac Rhabdomyoma Patients Diagnosed as Tuberous Sclerosis Complex

Case	Diagnosis of cardiac tumor	Diagnosis of TSC	Family history of TSC	Cardiac Tumors	Three or more hypomelanotic macules	Seizures	Cortical/ subcortical tubers	Subependymal nodules	Renal lesion
1	Prenatal	4 months	Father, nephew	Multiple	-	-	+	+	-
3	Prenatal	3 months	Father	Multiple	-	-	+	+	-
5	9 days	50 days	-	Multiple	+	+	+	+	-
6	6 days	4.5 years	Paternal uncle, nephew	Multiple	+	-	+	-	-

TSC: Tuberous sclerosis complex.

Fig. 3a: Preoperative echocardiographic image of the patient (Case 5) with right ventricular outflow tract (RVOT) obstruction. Arrow shows tumor near the pulmonary valve. **3b:** Postoperative echocardiographic image of the same patient with complete resection of the tumor. AO: Aorta.

hyperechogenic, intramural or intracavitary masses, mostly involving the ventricles, sometimes multiple, and rarely in the atrium or pericardium[6]. Other cardiac tumors include fibroma, myxoma, teratoma, and hemangioma[2]. Differential diagnosis between rhabdomyoma, fibroma and myxoma using USG for a single cardiac mass remains difficult. Fibromas are hyperechogenic, but associated with calcifications and cystic degenerations, and myxomas are usually soft and moderately echogenic masses. Teratomas are extracardiac masses located in the pericardial cavity, always with pericardial effusion. Hemangiomas have complex echogenicity, with cystic and solid parts with calcifications, and are usually found in the right atrium[9].

The clinical findings of CRs are related to the number, position and size of the tumors. Tumors may cause arrhythmias, hemodynamically significant obstruction, heart failure, and even

sudden death[2]. Patients may also present without obvious clinical findings, despite multiple or large tumors, as seen in our five asymptomatic patients who had murmur or arrhythmias on physical examination.

The prenatal diagnosis of a cardiac tumor was first reported by DeVore et al.[7] Rhabdomyoma is the most common fetal heart tumor and has a 4-6% risk of fetal death [8]. Rhabdomyomas are usually identified in the midtrimester and most regress beyond the third trimester[9]. Fetal arrhythmias have been reported to be present in 16% to 47% of the cases. In our series, none of the fetal CRs regressed in size *in utero*.

Cardiac rhabdomyomas are known to have a benign course. It has been reported that more than 80% of CRs have complete resolution within infancy and early childhood[8,9]. However, in our series, only 36% (9/25) of the tumors regressed during a median follow-up of two years, and two patients required surgical resection. Two of nine of the regressed tumors were located in the atrium and 8/9 of the regressed tumors were less than 8 mm. We propose that most tumors in our series did not regress during the follow-up because of their larger tumor size.

In a recent meta-analysis of 138 antenatally diagnosed CR cases, large tumor size (diameter ≥20 mm) and fetal dysrhythmia were found to be significantly associated with increased perinatal and neonatal morbidity[6]. Despite the fact that all our antenatally diagnosed patients had large tumor size (diameter >20 mm) and one patient had fetal dysrhythmia, we observed no significant perinatal or neonatal morbidity. A family history of TSC and presence of multiple fetal CRs were found to be highly associated with diagnosis of TSC[4,6]. Our patients with diagnosis of TSC also had multiple CRs and three had a family history of TSC. However, patients with a single CR may have TSC as well[2,8].

Tuberous sclerosis complex is an autosomal dominant multisystemic disorder with highly variable phenotype, with an incidence from 1:10,000 to 1:6,000 births. Fifty to eighty percent of cases are caused by *de novo* mutation[3]. TSC is caused by gene mutations and deletions at two loci: TSC1 (9q34) and TSC2 (16p13-3)>[10,11]. The gene products, hamartin (TSC1) and tuberin (TSC2), act as tumor suppressors. The precise roles of TSC-1 and TSC-2 genes in regulation of embryonic and neonatal cardiomyocyte growth and development of cardiac tumors remain to be elucidated.

The age-dependent nature of the characteristic features of TSC has presented challenges for the diagnosis in the first year of life[12]. Hypomelanotic macules may be present in infancy, but facial angiofibromas and Shagreen patches usually do not occur until puberty and renal angiomyolipomas occur in adults. Cortical and subcortical tubers develop before birth and are responsible for the epilepsy[13]. CRs may be the earliest finding of TSC *in utero* and may precede the detection of brain or kidney lesions and can be symptomatic in the fetus and newborn[8]. In our series, cardiac tumors were present before the cerebral pathology in TSC patients. In a recent study of 41 patients diagnosed with TSC in the first year of life, 23 patients (56%) initially presented with a CR, 14 (34%) presented with seizures, six (15%) presented with hypomelanotic macules, and five (12%) had a family history of TSC (12). Neuroimaging confirmed the diagnosis of TSC in 95% of the patients. The study concluded that the imaging studies in the fetus and neonate will facilitate the early diagnosis of TSC. The value of fetal cerebral MRI in sonographically proven CR was emphasized in another study, but a normal fetal cerebral MRI does not guarantee there will be no postnatal development of TSC[6,14].

In summary, CRs may have different presentations and clinical course. Surgery is only necessary when hemodynamically significant obstruction is present. As CRs are associated with long-term development of TSC and other diagnostic features are not yet apparent in the prenatal and neonatal periods, careful evaluation and follow-up are essential to exclude TSC.

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