Life-Threatening Tumors of the Heart in Fetal and Postnatal Age

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Objectives To evaluate the role of histology in diagnosis and management of biologically benign heart tumors causing life-threatening symptoms and even death in children and fetuses. The clinical impact of a multidisciplinary approach including 2-D echocardiography, histology, genetics, and cardiac surgery has not yet been fully elucidated.

Study design Forty-one consecutive antenatal (n = 17) or postnatal (n = 24) detected cardiac masses were evaluated by 2-D echocardiography (in alive patients) or at autopsy, and 12/41 cases with definite histologic diagnosis of primary and benign cardiac tumor were entered in this study.

Results Rhabdomyomas (n = 6), hemangiomas (n = 3), central fibrous body chondroma (n = 1), fibroma (n = 1), or left arterial myxoma (n = 1) were histologically diagnosed in 4 fetuses and in 8 children. Death occurred in 6 patients showing diffuse or infiltrative tumors, 2/6 experiencing intrauterine death or sudden and unexpected infant death. Seven patients underwent surgery, 4/7 are alive and well at >5 years follow-up, whereas 3 deaths followed partial tumor resection. Two fetuses with extensive tumor/s were aborted. Tuberous sclerosis complex gene mutations were seen in patients with rhabdomyomas.

Conclusions Histology represents the best diagnostic approach in life-threatening pediatric cardiac tumors allowing definite diagnosis in cases other than rhabdomyoma and in sudden deaths, influencing clinical management and counselling. 2-D echocardiography remains the main tool for early clinical diagnosis and follow-up. A multidisciplinary approach is advisable because of rarity, difficult management, and possible associations with inheritable diseases. *(J Pediatr 2012; ■: ■-■).*

Cardiac tumors in children are rare with a reported prevalence ranging from 0.027% to 0.08% in pediatric series and approximately 0.14% during fetal life.[1-4] The types of pediatric heart tumors differ from those seen in adults. The most common primary tumor of the heart is rhabdomyoma (more than 60% of all primary cardiac tumors) in infants and children, and cardiac myxoma (50% of all primary heart tumors) in adults. Most pediatric cardiac tumors are biologically benign and may regress, such as rhabdomyomas that only occasionally require surgical excision in cases with clinical manifestations. Nevertheless, they may represent a life-threatening condition because of their site (eg, involving the conduction system), obstructive symptoms, or an infiltrative growth pattern causing severe impairment of cardiac output or contractile function, respectively.[5-7] We investigated 41 consecutive cases of pediatric cardiac tumors from patients between 20 gestational weeks and 11 years of age examined at 2 referral centers over a 10-year period.

Methods

Forty-one consecutive cases of antenatal (n = 17) or postnatal (n = 24) detected cardiac masses were investigated at 2 referral pediatric centers (Turin, Catania; **Table I**). The institutional review board approved the study. In all cases, the following data were collected: age at presentation, number of tumors, site, dimension, any associated cardiac or extra-cardiac anomaly, and family history. Five- to 10-year follow-up was available in alive cases. In 12 patients with cardiac compromise, histologic analysis of tumors was performed (**Table II**). Histology was performed in all 12 cases undergoing surgery and/or autopsy. Heart tumors were classified histologically according to updated diagnostic criteria.[3-5,8] Surgical specimens were totally sampled and a complete autopsy was performed in all fatal cases. In the latter group, both extra-cardiac and cardiac causes of death were investigated, the heart was thoroughly examined, and appropriate sampling was performed after gross analysis. Samples were formalin fixed and paraffin embedded, and

CFB	Central fibrous body
IUD	Intrauterine death
IVS	Interventricular septum
SENs	Sub-ependymal nodules
TSC	Tuberous sclerosis complex

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Table I. Clinical characteristics of the overall population (n = 41)

Overall population	Mean age	Sex M/F	Site	Growth pattern	Associated anomalies	<EF	Outcome	Clinical diagnosis
Prenatal diagnosis (n = 17)	29.7 ± 5.8 gestational wk	10/7	LV (n = 11) RV (n = 5) IVS (n = 4) Atria (n = 2) Other (n = 1) Multifoc 12	Diffuse (n = 11) Obst (n = 4) Infiltr (n = 2)	6/17 (35%)	10/17 (58%)	Born alive* (n = 14) IUD (n = 1) Abortion (n = 2) Postnatal outcome* Deaths (n = 2/14) Stable (n = 2/14) Improved (n = 10/14)	Rhabdomyoma (n = 16) Other (n = 1)
Postnatal diagnosis (n = 24)	14.7 ± 35.5 mo	12/12	LV (N = 19) RV (n = 8) IVS (n = 8) Atria (n = 3) Other (n = 6) Multifoc 14	Diffuse (n = 8) Obstr (n = 9) Infiltr (n = 7)	17/24 (71%)	3/24 (12%)	Alive† (n = 21) Death (n = 3) Cured by surgery† (n = 3) Stable† (n = 18)	Rhabdomyoma (n = 17) Other (n = 7)

<EF, reduced ejection fraction; *Infiltr*, infiltrative growth pattern; *LV*, left ventricle; *Multifoc*, multifocal tumors, *Obstr*, obstructive symptoms; *RV*, right ventricle.
*Postnatal outcome in born alive patients with prenatal diagnosis.
†Clinical outcome in alive patients with postnatal diagnosis.

serially sectioned for routine histology. Three-micron histologic sections were stained by hematoxylin-eosin, Masson's trichrome, and periodic acid-Schiff techniques. Additional poli-L-lysine coated slides were collected for immunohistochemistry and specific antibodies were used to characterize cardiac masses (Table III; available at www.jpeds.com). Briefly, after microwave antigen retrieval, primary antibodies were labeled with a biotinylated link antibody directed against mouse/rabbit antigen with the use of a peroxidase-based kit (LSAB; Dakopatts, Glostrup, Denmark) and visualized by 3′-diaminobenzidine substrate. Positive controls consisted of sections obtained from human lymph node, bowel appendix, adipose tissue, and myocardium. Negative controls were performed by replacing the respective primary antibodies by isotype and concentration matched irrelevant antibody.

Clinical and molecular genetic investigations were proposed to parents of children or fetuses with possible inheritable diseases, and genetic tests were performed in cases of rhabdomyoma/s on peripheral blood samples by using denaturing high pressure liquid chromatography and multiplex ligation-dependent probe amplification analysis of tuberous sclerosis complex (TSC)1 and TSC2 genes.[9,10]

Results

Clinical data of patients are represented in Table I. Comparison of fetal and postnatal cases is shown in Figure 1 (available at www.jpeds.com). Associated anomalies were found in 14 patients, consisting of either cardiac (patent ductus arteriosus, atrial septal defect, or interventricular septal defect, n = 6) or extracardiac (cortical tubers or subependymal nodules [SENs] of giant astrocytes, functional cerebral alterations consisting of epilepsy, learning difficulties, or behavioral problems, necrotizing enteritis, n = 8) abnormalities. On the basis of clinical follow-up and/or genetic analysis, tuberous sclerosis was diagnosed in 24 patients out of the 33 cases of rhabdomyoma, most of them (20) affected by multiple rhabdomyomas.

In 12/41 cases histology was available (Table II and Figures 2 and 3). In 10/12 patients, cardiac masses were detected by prenatal (n = 6) or post-natal (n = 4) 2-D echocardiography showing single (n = 6) or multiple (n = 4) tumors localized to the cardiac chambers (atria and/or ventricles) (n = 8) or to the pericardium (n = 2). In the other 2 patients, a cardiac tumor was found only at the postmortem examination. Associated anomalies were found in 3 patients by 2-D echocardiography (atrial septal defect and interventricular septal defect in case # 10) or by post-mortem examination revealing necrotizing enteritis (case # 8) and histologic features of SENs (constituted by giant astrocytes and considered possible precursors of subependymal giant cell tumors in tuberos sclerosis) in case # 5 (Figure 2, G). Death occurred in 6 cases, including an intrauterine death (IUD), a sudden and unexpected infant death, 3 patients undergoing partial tumor resection, and an extremely premature newborn. Two fetuses were aborted after 2-D echocardiographic diagnosis of extensive single or multiple tumors consistent with rhabdomyomas. Seven patients underwent surgery because of severe hemodynamic impairment (n = 3), obstructive symptoms (n = 3), or cardiac tamponade (n = 1), with complete resection of the tumor in 3/7. At follow-up, 3 patients with partial resection of multiple rhabdomyomas (n = 2) or of diffuse infiltrating fibroma (n = 1) died soon (few days to 3 weeks) after surgery, the longest survivor (with fibroma) while awaiting cardiac transplantation. In the patient with cardiac tamponade, a hemolymphangioma was diagnosed after partial resection by an emergency procedure (Figure 3, A–C). He is alive and symptom-free at 11-year follow-up, although the yearly performed nuclear magnetic resonance and 2-D echocardiography have shown a 12-cm diameter residual tumor; he has refused further surgery. The 3 patients with complete tumor resection are alive and well at >5 year follow-up and lacking any evidence of tumor relapse.

In the case of IUD, autopsy disclosed a rhabdomyoma of the interventricular septum (IVS) in a fetus at 20 weeks

Table II. Clinicopathologic characteristics of patients with histologic diagnosis

No.	Age	Sex	Symptoms-signs	Site/tumor growth	Surgery	Size (mm)	Histology	Outcome
1	20 g.wk	F	None	IVS/InM	No	8	Rhabdomyoma	I.U.D.
2	20 g.wk	F	Prematurity	IVS, RV, LV/InM-InCav	No	15	Rhabdomyoma	Death
3	22 g.wk	F	Diffuse Involvement	IVS, LV, RV/InM-InCav	No	22	Rhabdomyoma	Abortion
4	22 g.wk	F	Hygroma	RA/InM	No	10	Rhabdomyoma	Abortion
5	1 d*	M	Low CO	Aa, Vs, IVS/InM-InCav	Partial resection	18	Rhabdomyoma	Death
6	4 d	M	Arrhythmias	CFB/InM	No	20	Chondroma	SUID
7	6 d	F	Hydrops, resp fail	Pericardium/InCav	Complete resection	28	Hemangioma	Clin. well NED
8	9 d*	M	Low CO	LV, IVS/InM-InCav	Partial resection	40	Rhabdomyoma	Death
9	3 mo	M	Low CO	LA, Vs, IVS/InM	Partial resection	30	Fibroma	Death
10	12 mo	M	TV Obstr	RA/InCav	Complete resection	20	Hemangioma	Clin. well NED
11	11 y	M	Cardiac Tamponade	Pericardium/InCav	Partial resection	120	Hemolymphangioma	Clin. well
12	11 y	M	MV Obstr	LA/InCav	Complete resection	30	Myxoma	Clin. well NED

Aa, atria; *Clin.*, clinically; *CO*, cardiac output; *InM*, intramural; *InCav*, intracavitary; *LA*, left arterial; *MV Obstr*, mitral valve obstructive symptoms; *NED*, no evidence of disease; *RA*, right arterial; *resp fail*, respiratory failure; *SUID*, sudden and unexpected infant death; *TV Obstr*, tricuspid valve obstructive symptoms; *Vs*, ventricles.
*Cases with fetal echocardiographic diagnosis.

gestational. Finally, in a 5-day male newborn who was referred to our center for a postmortem examination, a central fibrous body (CFB) chondroma was diagnosed (Figure 3, F). This patient developed sudden and untreatable heart failure with rhythm disturbances after an uneventful delivery. By histology, mature cartilaginous tissue was found within loose connective tissue (Figure 3, G).

Rhabdomyomas were the most frequent tumors (n = 6), followed by hemangiomas (n = 3) and myxoma, fibroma, and CFB chondroma (1 case each). The tumors were single or multiple in 7 and 5 patients, respectively, and variously localized to atria, ventricle/s, or pericardium with an intramural and/or intracavitary growth pattern (Table II).

Tuberous sclerosis was diagnosed in 3/6 patients with fatal rhabdomyoma/s (multiple tumors in one case) on the basis of genetic tests. In another case it was suspected on the basis of histologic investigations showing cerebral lesions consistent with SENs.

In the overall population (n = 41), genetic counseling was proposed to parents in all 33 cases with

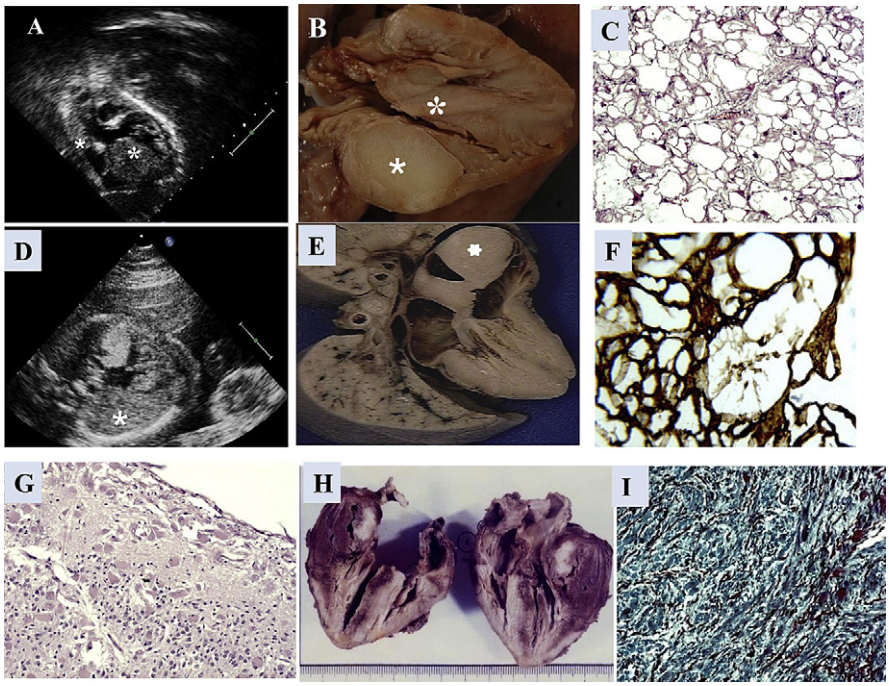

Figure 2. 2-D echocardiography **A,** showing inter-ventricular and left ventricle (subchostal view) rhabdomyomas (*) in a newborn baby (case #8); **B,** corresponding gross and **C,** microscopic (spider cell proliferation) features (hematoxylin and eosin, original magnification 10×). **D,** 2-D echocardiography (transverse four chamber view, case #4) and **E,** gross features of a right atrial rhabdomyoma (*) in a 22-week fetus; **F,** intense immunostaining for desmin in spider cells of another fetal rhabdomyoma (case #1; original magnification 20×). **G,** SENs of giant astrocytes (*) in the frontal lobe of a newborn baby with multiple rhabdomyomas and genetically proven tuberosclerosis (case #5, hematoxylin and eosin, original magnification 20×). **H,** Gross and **I,** microscopic features of a diffuse fibroma (case #9; **I,** Masson's trichrome staining, original magnification 10×).

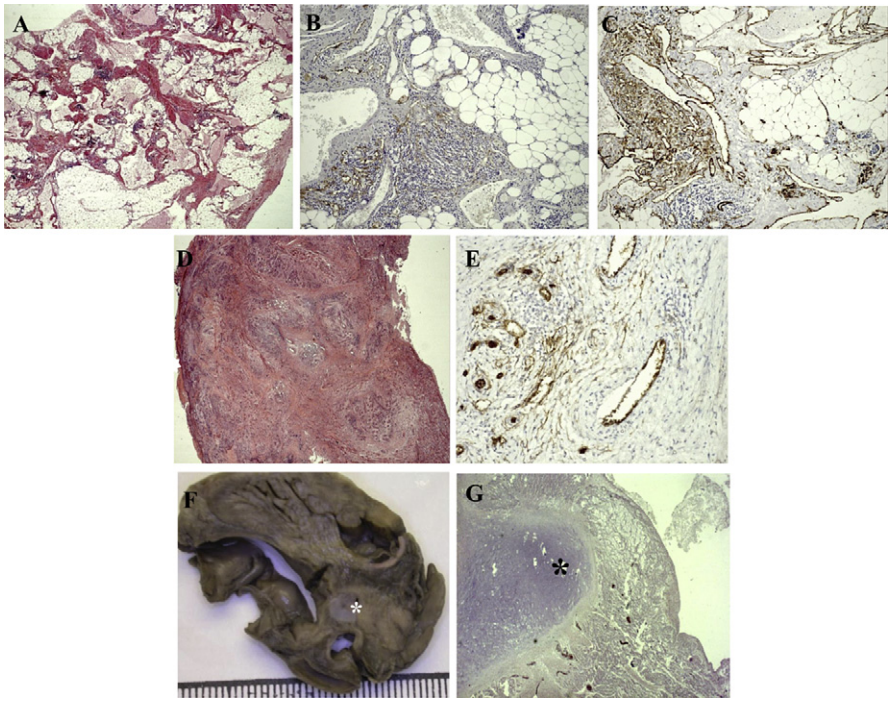

Figure 3. **A–C,** The hemolymphangioma (case #11) showing proliferation of lymphatic and hematic vessels (**A,** hematoxylin and eosin, original magnification 5×; **B,** D2-40 immunostaining for lymphatic vessels; **C,** CD 31 immunostaining for endothelial cells; original magnification 10×). **D** and **E,** hemangioma (case #10) with proliferation of small and intermediate vessels (**D,** hematoxylin and eosin, original magnification 5×; **E,** CD31 immunostaining of endothelial cells, original magnification 10×). **F,** Gross and **G,** microscopic features of the CFB chondroma (*), case #6; (**G,** hematoxylin and eosin, original magnification 5×).

rhabdomyoma/s; in 22/33 of cases, genetic tests were accepted and demonstrated family or sporadic mutations of TSC1 (n = 6, 4 sporadic and 2 family mutations) or TSC2 gene (n = 14, 8 sporadic and 6 family ones) with 2 cases negative for known mutations. In the selected population of the present study (n = 12), genetic tests were performed in 3/6 cases with histologically confirmed rhabdomyomas. Mutations of TSC1 (sporadic, n = 1, case #1) or TSC2 (n = 2, cases #4, 8 family and sporadic, respectively) genes were seen.

In the child with cardiac myxoma, clinical data allowed the exclusion of an inherited Carney complex. There were no signs, symptoms of endocrine over-activity, skin lesion, or other tumors found at the time of surgery. Family history was silent for related diseases.

Discussion

In the evaluation of the previously published literature, large cardiac tumors ($P < .0001$), fetal dysrhythmia ($P < .0001$), and hydrops ($P < .0001$) have been shown to be strong predictors of neonatal outcome.[11-14] In fetuses, tumor size ≥ 20 mm ($P = .009$, with relative risk = 20.6, 95% CI, 2.2-195.9), hydrops, and fetal dysrhythmia ($P = .001$; relative risk = 13.6, 95% CI, 2.9-62.3) were significantly associated with neonatal morbidity. TSC was significantly associated with multiple cardiac tumors ($P < .0001$) and family history of TSC ($P = .02$).[9,10,14] Size and location of tumor in the heart influenced prognosis in childhood is greater than that in adults.[1,2,4,15] Finally, in a pediatric surgical series, benign tumors such as rhabdomyomas and fibromas were associated to lack of recurrence after partial resection, with less risky tumor debulking being effective in these histotypes.[16]

Diagnosis and treatment of pediatric cardiac tumors may be challenging because of their rarity, the possible association with inheritable diseases, and the clinical complexity in many cases.[1,2,4,6,11-21] The tumors of the present series were biologically and histologically proven to be benign tumors, although the term "benign" is misleading as they caused death in 6/12 (50%) of the patients because of their growth pattern and site. Mortality in patients undergoing surgery (3/7) was attributable to unresectable tumors with infiltrative or obstructive growth. IUD or sudden and unexpected infant death was the presenting symptom in other patients, very likely related to arrhythmogenic disturbances. Another patient with multiple rhabdomyomas died of extreme prematurity (born at 20 gestational weeks). Cardiac transplantation was advocated in the case with diffuse and unresectable fibroma, but the patient died 2 weeks after palliative surgery, awaiting transplantation.[12] Thorough histopathologic investigations of autopsy cases may also disclose additional lesions that are useful to diagnosis and counseling in complex and/or syndromic diseases.

Genetic counseling is advisable in patients with pediatric heart tumors such as rhabdomyomas or myxomas that may be part of a syndrome or inheritable disease.[9,10,22,23] Our series of genetic studies of both patients and parents represented a valuable tool for early diagnosis of tuberous sclerosis and counseling of families. Cardiac rhabdomyoma is often the earliest sign of tuberous sclerosis in utero, but this disease has highly variable and unpredictable phenotypes, including cardiac rhabdomyomas, mental retardation, seizures, and multi-organ (brain, kidney, pancreas, retina, and skin) hamartoma, many clinical features becoming evident after 3 years of age. Tuberous sclerosis is an autosomal dominant disorder with an estimated prevalence of 1 in 6800-17 300 and a heterogeneous genetic basis. TSC2 mutations are more frequent, with only 10% to 30% of tuberous sclerosis cases being attributable to TSC1 mutations. TSC1 mutations account for 15%-30% of family cases and 10%-15% of sporadic cases, whereas the frequency of TSC2 mutations in sporadic cases ranges from 75% to 80%.[24] Fifty-eighty percent of childhood cases are considered to result from spontaneous mutations.[9,10] About 15%-20% of patients have no identifiable mutations, which may be attributable to mosaicism.[24] A multidisciplinary approach to these patients, including genetic tests in index patients and in parents, and thorough clinical and histopathologic investigations in affected patients, is advisable.

Rhabdomyomas represented the most frequent tumor types (6/12, 50%),[1-4] as is reported in the literature. They were localized either to atria, ventricular free wall, and/or IVS, and they caused death in 4 patients because of either infiltrative or obstructive pattern of growth or very likely arrhythmic disturbances. Rhabdomyomas are hamartomas spontaneously regressing from the 30th week of gestational age. They do not usually require surgery, but surgery is recommended if there is significant outflow obstruction or if medical anti-arrhythmic treatment is not successful.

The second most frequent group of tumors was hemangiomas. These tumors are exceptionally rare in the heart with 1%-2% incidence in overall series of benign heart neoplasms.[3,4] They are usually circumscribed and asymptomatic, and are an incidental finding at echocardiography, computed tomography, nuclear magnetic resonance, or at autopsy. They may rarely cause arrhythmias, pericardial effusions, congestive heart failure, right ventricular outflow tract obstruction, embolic episodes, myocardial ischemia, and sudden death.[25] They may occur in any part of the heart, but more commonly in the right heart chambers. In the present series, obstructive symptoms and cardiac tamponade were cured by surgery, but only in 2 hemangiomas the surgical excision was complete. Cardiac fibromas are benign tumors that usually occur in the ventricular free wall and/or the IVS, mainly in children <1 year of age as in the case of the present series.[1,2] Nevertheless, the slow and continuous growth may cause conduction defects, arrhythmias, obstruction of atrioventricular inflow or arterial outflow and, if the mass is inoperable, cardiac transplantation with or without pre-transplant surgical palliation may be indicated.[4,12] This tumor is exceptionally rare and may be rather considered heterotopia or ectopic tissue tumor.[26] The cardiac myxoma did not histologically differ from the much more common adulthood counterpart.[3]

Although heart tumors are very rare, clinicians and pathologists must be aware of this rare cause of cardiac compromise. 2-D echocardiography is the main tool for diagnosis and follow-up of cardiac masses, but histology can play a role for both therapeutic decisions and prognosis in cases that do not spontaneously regress and that require surgery. A multidisciplinary approach is strongly recommended because of the rarity, difficult management, and possible associations of pediatric heart tumors with inherited diseases. ■

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References

1. Becker AE. Primary heart tumors in the pediatric age group: a review of salient pathologic features relevant for clinicians. Pediatr Cardiol 2000; 21:317-23.
2. Isaacs H Jr. Fetal and neonatal cardiac tumors. Pediatr Cardiol 2004;25: 252-73.
3. Burke A, Virmani R. Tumors of the heart and great vessels. In: 3rd Series, Atlas of Tumor Pathology, Fascicle 16. Washington, DC: Armed Forces Institute of Pathology; 1996. p. 78-86.
4. Burke A, Jeudy J Jr, Virmani R. Cardiac tumors: an update. Heart 2008; 94:117-23.
5. Butany J, Nair V, Nassemudin A, Nair GM, Catton C, Yau T. Cardiac tumors: diagnosis and management. Lancet Oncol 2005;6:219-28.
6. Freedom RM, Lee KJ, MacDonald C, Taylor G. Selected aspects of cardiac tumors in infancy and childhood. Pediatr Cardiol 2000;21:299-316.
7. Zhou QC, Fan P, Peng QH, Zhang MH, Fu Z, Zhang CH. Prenatal echocardiographic differential diagnosis of fetal cardiac tumors. Ultrasound Obstet Gynecol 2004;23:165-71.
8. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. WHO Classification of Tumours- Pathology and Genetics-Tumours of the lung, pleura, thymus, and Heart. Lyon: IARC Press; 2004.
9. Milunsky A, Shim SH, Ito M, Jaekle RK, Bassett LL, Brumund MR, et al. Precise prenatal diagnosis of tuberous sclerosis by sequencing the TSC2 gene. Prenat Diagn 2005;25:582-5.
10. Habbu JH, Hayman R, Roberts LJ. Tuberous sclerosis in an antenatally diagnosed cardiac rhabdomyoma. J Obstet Gynaecol 2005;25:193-4.
11. Miyake CY, Del Nido PJ, Alexander ME, Cecchini F, Berul CI, Triedman JK, et al. Cardiac tumors and associated arrhythmias in pediatric patients, with observations on surgical therapy for ventricular tachycardia. J Am Coll Cardiol 2011;58:1903-9.
12. Gazit AZ, Gandhi SK. Pediatric Primary cardiac tumors: diagnosis and treatment. Curr Treat Options Cardiovasc Med 2007;9:399-406.
13. Gulati G, Sharma S, Kothari SS, Juneja R, Saxena A, Talwar KK. Comparison of echo and MRI in the imaging evaluation of intracardiac masses. Cardiovasc Intervent Radiol 2004;27:459-69.
14. Chao AS, Chao A, Wang TH, Chang C, Chang YL, Hsieh CC, et al. Outcome of antenatally diagnosed cardiac rhabdomyoma: case series and a meta-analysis. Ultrasound Obstet Gynecol 2008;31:289-95.
15. Cina SJ, Smialek JE, Burke AP, Virmani R, Hutchins GM. Primary cardiac tumors causing sudden death: a review of the literature. Am J Forensic Med Pathol 1996;17:271-81.
16. Padalino MA, Vida VL, Boccuzzo G, Tonello M, Sarris GE, Berggren H, et al. Surgery for primary cardiac tumors in children: early and late

results in a multicenter European congenital heart surgeons association study. Circulation 2012;126:22-30.
17. Beroukhim RS, Prakash A, Valsangiacomo Buechel ER, Cava JR, Dorfman AL, Festa P, et al. Characterization of cardiac tumors in children by cardiovascular magnetic resonance imaging. A multicenter experience. JACC 2011;58:1044-54.
18. Padalino MA, Basso C, Milanesi O, Vida VL, Moreolo GS, Thiene G, et al. Surgically treated primary cardiac tumors in early infancy and childhood. J Thorac Cardiovasc Surg 2005;129:1358-63.
19. Akyildiz EU, Tolgay E, Oz B, Ylmaz R, Koc S. Cardiac myxoma: an unusual cause of sudden death in childhood. Turk J Pediatr 2006; 48:172-4.
20. Gunther T, Schreiber C, Noebauer C, Eicken A, Lange R. Treatment strategies for pediatric patients with primary cardiac and pericardial tumors: a 30-year review. Pediatr Cardiol 2008;29:1071-6.
21. Thomas-De Montpreville V, Nottin R, Dulmet E, Serraf A. Heart tumors in children and adults: clinicopathological study of 59 patients from a surgical center. Cardiovasc Pathol 2007;16:22-8.
22. Carney JA. Differences between nonfamilial and familial cardiac myxoma. Am J Surg Pathol 1985;9:53-5.
23. Mahilmaran A, Seshadri M, Nayar PG, Sudarsana G, Abraham KA. Familial cardiac myxoma: Carney's complex. Tex Heart Inst J 2003;30:80-2.
24. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008; 372:657-8.
25. Burke A, Johns JP, Virmani R. Hemangiomas of the heart. A clinicopathologic study of 10 cases. Am J Cardiovasc Pathol 1990;3:283-90.
26. Ramsay AD, Malone M, Sheppard MN, RoebucK D, Elliott MJ. Massive cardiac chondroma presenting with heart failure and superior vena cava obstruction in a teenage boy. Fetal Pediatr Pathol 2004; 23:325-31.

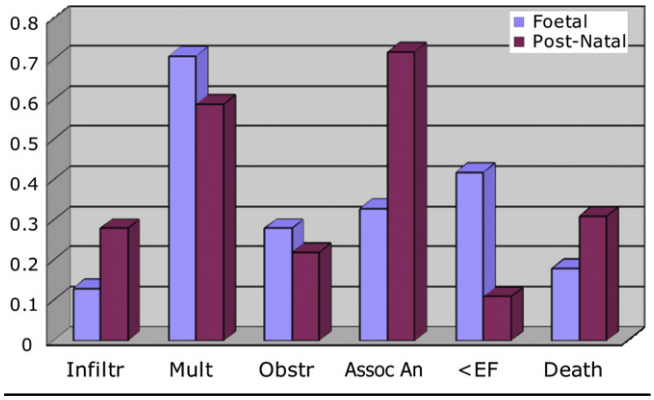

Figure 1. Comparison of main clinical characteristics in fetuses (n = 17) and pediatric patients (n = 24) with clinical diagnosis of cardiac mass/masses: Infiltrative pattern of growth (Infiltr); multiple (Mult) (≥2) cardiac masses; obstructive symptoms (Obstr); associated anomalies (Assoc An); reduced ejection fraction (<EF).

Table III. Antibody panel for immunohistochemistry

Antibody	Clone/species	Company	Staining	Tumor
a-SMA	1A4/mouse	Sigma	Smooth muscle cells	Myxoma, Hemangioma
Calretinin	Dak-Calret 1/mouse	Dakopatts	Lepidic cells	Myxoma
CD31	JC70A/mouse	Dakopatts	Endothelial cells	Hemangioma, Myxoma
Desmin	D33/mouse	Dakopatts	Spider cells	Rhabdomyoma
D2-40	D2-40/mouse	Dakopatts	Lymphatic vessels	Lynphangioma
S100	(S100B)/rabbit	Dakopatts	Lepidic cells	Myxoma
Vimentin	V9-monoclonal mouse	Dakopatts	Various cells	Fibroma
Ki-67	MIB-1/mouse	Dakopatts	Proliferation index	Various

a-SMA, anti-smooth muscle antibody.