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 atrial 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 2013;162:964-9)*.

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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The authors declare no conflicts of interest.

0022-3476/$ - see front matter. http://dx.doi.org/10.1016/j.jpeds.2012.10.055

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