

Pediatric heart tumors

Introduction

Pediatric heart tumors are comprised primarily of non-neoplastic hamartomatous lesions. These include two lesions of cardiomyocyte derivation, namely rhabdomyoma and histiocytoid cardiomyopathy (sometimes designated Purkinje cell hamartoma). Cardiac fibroma is the most commonly excised pediatric tumor, is sometimes also found in adults, and like rhabdomyoma is likely not a true neoplasm. Germ cell tumors may involve the pericardium or, less commonly the myocardium, and are generally of the non-seminomatous type, most typically immature teratoma or yolk sac tumor. Mesenchymal proliferations of the myocardium, other than fibroma, are extremely rare in the pediatric age range. Embryonal rhabdomyosarcomas primary in the heart is a tumor of children and young adults; alveolar rhabdomyosarcoma may occur in the heart as a metastatic lesion. Recently, inflammatory myofibroblastic tumors have been described as originating from the endocardium. The precise nature (reactive / neoplastic) of cardiac IMFT remains undetermined.

Rhabdomyoma

Cardiac rhabdomyoma is highly associated with tuberous sclerosis complex (TSC). Two disease genes have been identified: TSC-1 at chromosome 9q34, and TSC-2 at chromosome 16p13. Over 50% of patients have sporadic mutations. The familial form of TSC exhibits autosomal dominant inheritance. The TSC-1 gene encodes hamartin, and TSC-2 tuberlin, proteins involved in tumor suppression. Loss of heterozygosity is often found at the TSC-1 and TSC-2 loci in tumors from patients with tuberous sclerosis. The precise roles of TSC-1 and TSC-2 in the development of cardiac tumors and regulation of embryonic and neonatal cardiomyocyte growth remain to be elucidated. More than 50% of patients with tuberous sclerosis have cardiac hamartomas. Multiplicity of tumors is especially associated with TSC.

Rhabdomyomas are most commonly diagnosed tumor of the prenatal period by fetal echocardiography. Intrauterine as well as sudden death after birth has been attributed to them. Clinical and hemodynamic findings are related to the number, position, and size of tumors. Symptoms include those related to valve obstruction or occlusion of chamber cavities, arrhythmias, and fetal hydrops. The tumors may cause infant respiratory distress, congestive heart failure, or low cardiac output. Right-sided tumors that cause obstruction may cause cyanosis, or features suggestive of tetralogy of Fallot or pulmonary stenosis. Left-sided tumors may present as subaortic obstruction or hypoplastic left heart syndrome. They can be associated with structural cardiac defects.

Echocardiography is a sensitive modality for the diagnosis of rhabdomyomas and shows relatively homogeneous well-circumscribed echo-bright intramural or intracavitary masses that can be found virtually anywhere in the heart, but most commonly in the

ventricles. Cardiac MRI is reserved for selected patients in whom tumor type is questionable after echocardiography or when additional anatomical or functional information is required. Rhabdomyomas appear as well-circumscribed masses, usually in the ventricles but they can be found anywhere in the heart, with hyperintense signal on T1- and T2-weighted spin echo images. Compared with the signal from uninvolved myocardium, the masses are hypointense on post-gadolinium imaging. MRI is often used in patients with rhabdomyomas to evaluate the brain, liver, and kidneys for evidence of tuberous sclerosis.

Cardiac rhabdomyomas are well-demarcated nodules of enlarged cardiac myocytes with cleared cytoplasm. In some cells, strands of eosinophilic cytoplasm stretch from a central nucleus to the cell membrane giving rise to cells that resemble a spider (“spider cells”). The majority of cells show vacuolization with sparse myofilaments. There is a strong reaction with periodic acid-Schiff reagent, reflecting the glycogen content of rhabdomyoma cells.

Immunohistochemical studies document the striated muscle characteristics of rhabdomyoma cells, which express myoglobin, desmin, actin, and vimentin. Tumor cells do not express cell proliferation markers, indicating that the lesions are more likely hamartomas as opposed to neoplasms.

By electron microscopy, the cells resemble altered myocytes. They possess abundant glycogen, small and sparse mitochondria, and cellular junctions resembling intercalated disks surround the cell periphery. In contrast, the intercalated disks of differentiated myocytes are located exclusively at the poles of the cell. Intercalated discs and myofibrils or collections of Z band material are present.

Rhabdomyomas have a natural history of spontaneous regression, and many patients are followed with surgery. However, serious symptoms may precipitate the need for surgical resection. When arrhythmias are the presenting symptom, treatment with anti-arrhythmic drugs is commenced. If drugs fail to control arrhythmias, surgical resection is indicated.

Fibroma

Most cardiac fibromas are discovered in children and often before 1 year of age, but the upper range of age at presentation extends into late adulthood. Approximately 3% of patients with Gorlin syndrome have cardiac fibromas. Gorlin syndrome results from germline mutations in the PTC gene, which maps to chromosome 9q22.3 and is homologous to the *Drosophila* patched (*ptc*) gene.

Fibromas are generally single lesions and often cause symptoms necessitating surgical resection. The most common site of cardiac fibroma is the ventricular septum, but the free walls of the left and right ventricle are other common locations. Atrial fibromas are quite rare. Cardiac fibromas cause obstruction of blood flow, interference with valvular function, cause significant arrhythmias, syncope or sudden death. Magnetic resonance imaging shows the location, size, boundaries, and relations with adjacent structures, including the epicardial coronary arteries. On T1- and T2-weight standard or fast spin echo sequences cardiac fibroma appears as a well-defined, usually large, solitary intramyocardial mass with inhomogeneous signal intensity. Compared with the signal intensity of adjacent uninvolved myocardium, fibroma is slightly hypointense.

Gadolinium-enhanced MRA and first pass perfusion imaging demonstrate a hyperperfused tumor core that is readily distinguishable from the surrounding perfused myocardium.

Histologically, they resemble fibromatoses, with infiltrating margins. There are usually abundant elastic fibers. Cellularity may be quite marked in young infants, but usually decreases with age. Calcification is not uncommon.

Histiocytoid cardiomyopathy

Histiocytoid cardiomyopathy is a rare, arrhythmogenic disorder caused multifocal hamartomatous proliferation of cardiac cells with oncocytic features. The female:male ratio is 3:1. Approximately 5% of reported cases have occurred in families. Arrhythmias associated with histiocytoid cardiomyopathy include paroxysmal atrial tachycardia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, premature atrial contractions, premature ventricular contractions, Wolff-Parkinson-White syndrome, and right or left bundle branch block. Extracardiac anomalies occur in 17% of patients. The cause of death may be presumed SIDS until histologic evaluation of myocardial tissue is performed. Pathologically, there are typically subendocardial yellow-tan nodules or plaques. They can also be seen in the inner myocardium and subepicardial areas. The lesions may be grossly difficult to identify, but there is generally a subtle color difference separating the lesion from normal myocardium. The histologic findings are pathognomonic, with nests of foamy-appearing myocytes resembling macrophages.

For patients that are diagnosed pre-mortem, electrophysiological mapping is indicated if anti-arrhythmics are ineffective in ablating arrhythmias and allowing regression of the lesions. Treatment includes surgical excision or direct-vision cryo-ablation of the multiple small nodular tumors. Surgical intervention, electrophysiological mapping, and ablation of the arrhythmogenic foci result in a survival rate of approximately 80%. Rare patients have been treated with heart transplantation.

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumors (IMFTs) are proliferations of uncertain histogenesis, which vary in appearance from inflammatory, reactive-appearing proliferations to low-grade sarcomas. There is probably organ-specific variation in the histologic characteristics of IMFT. In the heart, they invariably arise from the endocardium, are variably cellular, but usually have abundant myxoid matrix and surface fibrin. Most lesions designated IMFT in the heart are likely non-neoplastic. However, embolic symptoms and sudden death from coronary occlusion may occur.

We have recently reported a series of cardiac IMFT-like lesions seen in consultation (see table).

Cardiac IMFT

#	Age, years	Sex	Race	Symptom	Previous medical history	Endocardial location	Other cardiac findings	Tumor maximal dimension, cm	Follow-up
1	5 weeks	M	Caucasian	Shortness of breath	None provided	Right atrium	None	6	Not available
2	2	F	Caucasian	Recurrent seizures	Seizures, recurrent cerebral infarcts (embolic)	MV anterior leaflet extending to the LV wall	None	4	Died 2 years
3	5	F	Caucasian	Right sided hemiplegia, seizure	None	MV, extending to LV wall	None	3	Not available
4	6	F	Caucasian	Syncope	Recent myocardial infarction of LV wall and IVS	MV at junction of posterior and medial leaflets extending down chordae tendineae of anterior papillary muscle	None	3	Explant
5	8	M	Caucasian	Chest pain/dyspnea=> Sudden death	None provided	Left coronary sinus with occlusion of LAD and LCA, and obstruction of R coronary ostium	Anomalous LCA arising from proximal RCA	2.5	Death
6	10	M	Hispanic	Heart murmur	None provided	Right ventricular outflow tract	None	1.5	Not available
7	12	M	None provided	Transient ischemic attack	None provided	Right ventricle	None	6.0	Not available
8	17	F	Hispanic	Incidental murmur, sports physical	None	Right ventricle, involving tricuspid valve	None	5.0	Not available
9	19	F	Not provided	Fever, myalgias (6 months)	None provided	Thin pedicle from the LV free wall	None	3.2	NED, 6 years, 9 months
10	21	F	Not provided	Fatigue, dyspnea (1 1/2 months)	Pulmonary hypertension	Interventricular septum in the right outflow tract extending to the pulmonic valve	Enlarged right atrium, moderate tricuspid regurgitation, moderate pericardial effusion	4.0	NED, 11 years

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