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Benign cardiac tumors of the pluripotent mesenchyme

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Among benign primary cardiac tumors, myxomas and papillary fibroelastomas are the most common. Cardiac myxomas arise from pluripotent mesenchymal cells and are seen as intracardiac, glistening polypoid masses arising most frequently from the interatrial septum in the left atrium. They are composed of stellate to polygonal myxoma cells in a mucopolysaccharide-rich matrix. These tumors can be sporadic or familial. On the other hand, papillary fibroelastomas are sporadic, seen as a mass of delicate papillary fronds ("sea anemone"-like) arising from a slender stalk, commonly located on diseased left-sided valves. They are lined by plump endothelial cells, which rest on stalks composed of mucopolysaccharides enclosing a collagen- and elastin-rich core. Embolism is often the mode of presentation for both of the tumors; myxomas are also associated with obstructive and constitutional symptoms. In contrast, neurogenic tumors (paraganglia or nerve sheath tumors) are exceedingly rare and occur as epicardial and infrequently as intracardiac masses. The tumors are often incidentally diagnosed by the usual echocardiography, but magnetic resonance imaging is useful for further characterization of the tumors. The tumors are, in general, treated by surgical resection, but may require a little or at times more significant reconstruction. Among these tumors, the myxomas are associated with a higher rate of recurrences.

Cardiac myxomas

Among the various primary tumors of the heart, recognized as exotic forms of cardiac disease since the 16th century, cardiac myxomas are by far the most common. They account for more than half of the primary cardiac neoplasms,[1] and their designation stems from the gelatinous or "myxoid" gross appearance produced by a mucopolysaccharide-rich extracellular matrix. The myxoma is a benign tumor, and its neoplastic nature has been proved beyond doubt by detection of chromosomal abnormalities and abnormal DNA content.[2] Despite its benign nature, the myxoma can run a turbulent course in some patients due to cardiac dysfunction, effects of tumor embolism, and postoperative recurrences,[3] which could mistakenly suggest malignant biologic behavior. The contemporary noninvasive cardiac imaging techniques have made the diagnosis of cardiac tumors in general and myxomas in particular a lot easier and frequent, even in asymptomatic patients.

Incidence

The cardiac myxoma is an uncommon tumor with an overall incidence of about 0.5/million/year and accounts for 50% to 70% of all primary cardiac tumors. Most myxomas manifest themselves between the fourth and seventh decades of life in adults, especially women.[4] The tumors are rare in the pediatric population, occurring occasionally in teenagers, and are even rarer in fetuses and neonates[5]; they are also identified in the geriatric population.[6]

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Table 1 Syndromic cardiac myxomas

Syndrome	Manifestations
1. Carney's Complex	Cardiac myxomas
	Lentigines or nevi
	Myxomatous mammary fibroadenomas
	Testicular tumors
	Primary nodular adrenal cortical disease
	Pituitary adenomas
2. LAMB	**L**entigines
	Atrial myxoma
	Blue nevi
3. NAME	**Nevi**
	Atrial myxoma
	Myxoid neurofibroma
	Ephelides

Most myxomas are sporadic in nature, and in about 90% of these cases, they are solitary. In approximately 75% of the tumors, the classic or typical location is the interatrial septum on the left atrial aspect; myxomas located elsewhere in the left atrium and in the other chambers have been designated as atypical myxomas.[7] Such atypical locations include other parts of the left atrium, right atrium (15% to 20%), left and right ventricles, or even valves.[1,8-11]

In comparison to sporadic tumors, familial cardiac myxomas, constituting about 7%, present as nonsyndromic familial tumors[12] or as part of a syndrome (syndrome myxoma). Syndromic cardiac myxoma is constituted by the Carney complex, an autosomal dominant disorder wherein myxomas are accompanied by other extracardiac abnormalities (Table 1).[13] Certain other groups of findings, referred to as the LAMB and NAME syndromes (Table 1) are now included under the common umbrella of the Carney complex.[14] In these situations, the tumors tend to occur in younger patients, at multiple sites and/or atypical locations, and have a greater frequency of recurrence.[15] Most individuals with the Carney complex have a mutation in the PRKAR1A gene, which encodes the regulatory R1 alpha subunit of protein kinase A. The mutation results in an increased propensity for tumor development; such mutations may not be associated with sporadic myxomas.[16] In some cases of sporadic myxomas, *Herpes simplex virus* type 1 antigens have been demonstrated at immunohistochemistry (IHC), suggesting tumorigenesis through chronic smoldering inflammation of the endocardium.[17] There have also been reports of tumors occurring after radiation therapy for other malignant tumors.

Genesis

The histogenesis of myxomas has been shrouded in controversy. The belief that myxomas represent a variant form of organized thrombi had persisted for a long time,[8] and hopefully has now been laid to rest. In a large study of 100 interatrial septa by Acebo and coworkers,[18] the origin of myxomas from Prichard's structures (minute endothelial age-related lesions) has been disproved, as only 12% of the septae had shown these structures. Variable expression of proteins by IHC has suggested an epithelial, endothelial, myogenic, myofibroblastic, or even neural origin, suggesting activation of primitive pluripotent mesenchymal cells.[8,19] In a more recent study, using an array of diagnostic modalities, Orlandi and coworkers[20] have documented a probable origin from remnants of the endocardial cushion cells since the phenotypic expression is akin to those seen during the "endothelial–mesenchymal" transformation taking place at the atrioventricular junction.

Gross features

Most of the myxomas are located in the left atrium, attached to the interatrial septum in the vicinity of the fossa ovalis, by a broad-based connection or a short fibrovascular stalk (Figures 1 and 2). The average size of the tumor ranges from 4 cm to 8 cm, and they exhibit two morphologic subtypes. The solid type may be globular (Figures 1 and 2) or elongated with a smooth, shiny, fibrous, and sometimes undulant surface and firm consistency.[2,21] On the other hand, the papillary type (Figure 2), as its name suggests, has a papillary or villous surface, rarely resembling a cauliflower with a friable and gelatinous consistency.[2,21] The tumors have a variegated cut surface. In most instances, the cut surfaces appear gelatinous and greenish-yellow, punctuated by variable areas of hemorrhage (Figure 2), cystic degeneration, collagenization, calcification, or even rare ossification. Larger foci of hemorrhage may be seen in tumors with a high vascular density as myxomas are known to elaborate and possess receptors for vascular endothelial growth factor[22]; these tumors also tend to be smaller.[19] Extensive cystic change can at times even simulate a hydatid cyst.[23] Fibrocalcific or fibro-osseous changes usually take place in older individuals, long-standing myxomas, or right-sided neoplasms.

Histological features

At microscopy, the characteristic tumor components are best appreciated on the endocardial aspect, which is largely devoid of secondary changes. Polygonal, spindle-shaped, or syncytial stellate myxoma cells, also called lepidic cells, are distributed in abundant, eosinophilic myxoid matrix (rich in chondroitin-6-sulfate and hyaluronic acid) either singly, in groups, or cords (Figure 3). The cells have abundant eosinophilic cytoplasm, round to ovoid nuclei, and inconspicuous nucleoli; occasional multinucleation may be present.[24] A conglomeration of thick-walled and tortuous blood vessels can be seen, most commonly at the base of the tumor. This is said to predict a solid phenotype[21] or even antedate the occurrence of the myxoma.[25] Toward the surface, the cells are often associated with blood vessels (Figure 3). They form classical ring-like structures where a single or multiple concentric layer of cells surround capillaries. Sometimes,