Left Atrial Myxoma

A Morphologic and Histogenetic Study

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SUMMARY

Seven cases of excised left atrial myxoma are described. These are compared with organizing and organized thrombi. The tumors occurred at ages ranging from 13 to 48 years with male preponderance. There were distinct histological and histochemical differences between myxomas and thrombi. Myxomas were lobulated, soft and gelatinous. The cells were arranged singly, in syncytium, or in gland like manner and around blood vessels. Scant to abundant acid mucopolysaccharide rich stroma with strong metachromasia was present. The cells on histochemical staining revealed a wide range of differentiation and contained small amounts of neutral mucopolysaccharides. Thrombi, on the other hand, were firm, laminated, and the cells were arranged in several stratified layers. Metachromasia was absent. Neutral polysaccharides were absent within the cells of thrombi. These features support the concept that cardiac myxoma is a neoplasm and arises possibly from multipotential mesenchymal cells.

Additional Indexing Words:

Thrombus

CARDIAC myxomas have been recognised as a distinct morphologic entity over 200 years.¹⁾ This is a rare tumor, but accounts for 1/3rd of primary cardiac neoplasms.²⁾ Most have occurred in the left atrium in relation to the fossa ovalis, but there is no evidence that the tumors arise from remnants of endocardial myxoid tissue in this region.³⁾ Multiple cardiac myxomas have also been recorded.⁴⁾ They may occur at any age, ranging from a stillborn infant⁵⁾ to 95 years,⁶⁾ but are most frequently found between the ages of 30 to 60 years.⁷⁾

Now that the surgery of the heart and removal of neoplasms has become a rather commonplace procedure, it appears to be even more important to recognize the morphologic variants of cardiac myxoma in order to distinguish them from other cardiac neoplasms of more serious import. Studies have generally stressed the clinical manifestations of the tumor and rarely have their

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morphologic aspects been accorded.^{8),9)}

In a brief span of 5 years, we encountered 7 cases of this rare tumor. This paper reports a detailed morphologic study of cardiac myxomas and their comparison with thrombi. An attempt will be made for appraisal of their histogenesis.

MATERIALS AND METHODS

Seven cases of cardiac myxoma collected in the department of Pathology of the All India Institute of Medical Sciences, New Delhi from 1976 to 1980 were studied. These cases had undergone cardiac surgery for removal of the tumor at this hospital. Paraffin sections were stained with hematoxylin and eosin, and on selected sections from all cases phosphotungstic acid hematoxylin (PTAH), Masson trichrome, Verhoeff's Van Gieson (VVG), Wilders reticulin, periodic acid Schiff reaction (PAS), iron and toluidine blue stains were performed. Six cases of organizing and organized thrombi were also studied by the above mentioned stains. Tissue from fossa ovalis and from an area nearby was examined from some post mortem cases for the existence of myxomatous "rests".

RESULTS

Patients ranged in age from 13 to 48 years. There were 5 males and 2 females.

All the tumors encountered by us were located in the left atrium in the region of the atrial septum. The patients were class III to class IV symptomatic and the duration of their complaints ranged between 6–24 months.

All the tumors were lobulated, grayish pink, gelatinous masses varying in dimensions from $5 \times 4 \times 3$ cm to $8 \times 5 \times 2$ cm, with the weight varying from 19 to 21 Gm. All but one had a stalk which varied in thickness and length from 0.5 cm to $2 \times 1.5 \times 0.2$ cm. The cut surface was smooth or bosselated and was variegated red, gray and yellow. All the tumors were soft and mucoid (Fig. 1a, b).

The thrombi were grayish brown, opaque, granular, laminated, and firm.

Microscopic features of all tumors were essentially similar, varying principally in the proportion of cells to myxoid intercellular stroma, the amount of fibrous tissue, elastic tissue and the number of vascular channels.

The common cellular denominator in all cases was a round or polygonal cell generally arranged in groups of two or more, in close apposition to capillaries or in irregular compact varying-sized clusters, some times separated from one another by irregular spaces (Fig. 1c). Their nuclei were generally uniform. Mitoses were not noted. The cytoplasm was moderately eosinophilic and was evenly distributed about the nucleus or streaming from one or both

Fig. 1a. Gross specimen of left atrial myxoma. External surface is lobulated, gray white with areas of hemorrhage (right). The cut surface is hemorrhagic (left). Stalk is also seen (arrow).

Fig. 1b. Gross specimen of atrial myxoma of another case. The tumor is gray white, gelatinous and lobulated.

Fig. 1c. Photomicrograph showing tumor cells arranged in groups of two or more and in irregular, varying sized clusters. These are separated by wide expanses of stroma. Hematoxylin and eosin (HE) $\times 130$.

Fig. 1d. Tumor cells with moderate amount of cytoplasm evenly distributed around the nucleus. Cytoplasmic boundaries are indistinct. Inflammatory cells distributed singly and in small groups in the stroma are also seen HE $\times 500$.

Fig. 1e. Photomicrograph showing lobulated pattern of tumor that is lined by single or multiple layers of elongated flattened cells. Note the loose myxomatous stroma. HE $\times 130$.

Fig. 1f. Photomicrograph showing tumor cells and loose myxoid stroma. The cells are arranged in an epithelium like and/or gland like manner without a limiting basement membrane. HE $\times 130$.

ends of the cells. The cytoplasmic boundaries were frequently indistinct (Fig. 1d). The surface of all the tumors was covered in most areas by a single or multiple layers of elongated flattened cells with long, narrow nuclei and little cytoplasm to columnar cells that were sometimes seen to be in continuity with the underlying myxoma cells (Fig. 1e).

The ratio of the tumor cells to myxoid stroma was quite variable not only among different cases but also in different portions of the same tumor. In some areas, scattered, isolated, single or small groups of myxoma cells were surrounded by abundant polysaccharide rich stroma, while in other portions of the tumor, cells were abundant and assumed an epithelium like and/or gland like configuration without a demonstrable limiting basement membrane (Fig. 1f). Intercellular polysaccharide accumulation separated the tumor cells. Intracytoplasmic mucin in some areas was sufficient to distend the cell cytoplasm and produce a goblet cell appearance. Other cells noted were histiocytes laden with hemosiderin, plasma cells, lymphocytes, and fibroblasts (Fig. 1c, d).

The stroma showed strong metachromasia with toluidine blue. The elastic fibers were seen randomly distributed throughout the stroma, beneath the lining and at the base. Collagen fibers were present in small amounts in all tumors, extensive foci of dense collagen were seen particularly near the pedicles. Reticulin fibers formed a sparse but discrete network around some

Table I. Histochemical Staining

Cardiac Myxoma	PAS		Masson	VVG
	Cell	Stroma	Collagen	Elastic tissue
Case 1	+	Negative	+ to ++	+ (throughout the stroma)
Case 2	+	Negative	+ to ++	+ (at base)
Case 3	+	Negative	+ to ++	++ (at surface)
Case 4	###	Negative	+ to ++	+ to ++ (throughout the stroma)
Case 5	+	Negative	+	+ (focal)
Case 6	+	Negative	+	+ (focal) (throughout the stroma)
Case 7	+	Negative	+ to ++	+ (focal)

+ = scant; ++ = moderate; ### = abundant.

groups of tumor cells. An occasional fiber showed positive staining for muscle in 1 case and in 2 cases, tadpole cells were seen without any cross striations. PAS reaction of the stroma was uniformly negative in all the cases indicating absence of neutral polysaccharides. Contrary to this, positive PAS reaction was seen within the cells (Table I).

Organized thrombi by light microscopy showed several stratified layers of spindle or oval cells, granulation tissue with abundant capillaries, red blood cells, abundant hemosiderin pigment and no mucin. No gland like structures were seen. These were not lined by endocardial covering. Toluidine blue staining revealed complete absence of metachromasia within the stroma. PAS reaction was negative both within the cells as well as the stroma. The latter also showed fine reticulin fibers throughout. PTAH stain was negative. Thick bands of collagen were seen throughout the organized thrombi.

Tissues from the area of fossa ovalis and surrounding area showed loose fibrous tissue but so called myxomatous 'rests' were not seen.

DISCUSSION

Since the cardiac myxomas were first recognised, a controversy has existed regarding its nature as to whether it is a thrombus or a neoplasm.^{10),11)} The histogenesis of cardiac myxoma and the cellular epithelium-like and

Reaction in Cardiac Myxomas

Iron	Reticulin	PTAH	Toluidine Blue Metachromasia
++	+ to ++	Negative	+ to +++ (diffuse)
+	+ to ++	Negative	+ to +++ (diffuse)
+	+ to ++	Negative	++ to +++ (around groups of cells mainly)
++	+ to ++	Positive in occasional cell	-do-
++	+ to ++	Few tadpole cells No cross striations	-do-
++	+ to ++	Negative	-do-
+	+ to ++	Few tadpole cells No cross striations	+ (around groups of cells mainly)

gland-like tissues reported in some of the atrial myxomas¹¹⁾⁻¹³⁾ have received little attention. Fine et al (1968)¹¹⁾ have suggested an endocardial origin of myxoma. They further stated that the accompanying epithelial and gland-like tissues were derived from mesothelium or endoderm. However, the intimate relationship of the two types of tissue and the transition from the typical myxoma to the epithelial and gland like tissue which we have also observed, support a common cell origin as also reported by others.^{8),9),11),14)} The microscopic dissimilarity between the myxoma and mesothelioma of other areas, the absence of basement membrane in the gland-like portions of the myxoma, its endocardial location, and the absence of endodermal structures such as are seen in teratomas, are not in keeping with a mesothelial or endodermal derivation.¹¹⁾ An endocardial cell origin appears to be more likely in view of the tissue culture studies.¹⁵⁾ Silverber and Kay (1970)¹⁶⁾ pointed out that myxoma cells contain alkaline phosphatase a finding typical of endothelial tissue, and considered myxomas to be derived from endocardial cells.

By light microscopy, several workers^{8),11),17)} observed the various types of cellular aggregates that we found in this study. Fine (1968)¹⁸⁾ concluded that myxomas are slow growing tumors that arise from mesenchymal cells. Matsuyama and Ooneda (1967)¹⁴⁾ found myxomatous tissue not only in the tumor mass, but also in the endocardium and in the muscular layer of the interatrial septum to which the tumor was attached. They also observed a few cross striated, tadpole shaped tumor cells that resembled those observed in embryonal botryoid rhabdomyosarcoma. They considered the cardiac myxoma to be a neoplasm derived from embryonal undifferentiated mesenchyme and thus related to embryonal botryoid rhabdomyosarcoma. However, Fisher and Hellstrom (1960)¹⁹⁾ did not find myxomatous 'rests' near the fossa ovalis. Our findings are also in keeping with the latter study.

Merkow et al (1969)²⁰⁾ observed a variety of cellular arrangements in a left atrial myxoma and emphasized the occurrence of vasoformative elements. Electron microscopically, cytoplasm of myxoma cells contained fine filaments that measured from 85 to 125 Å in diameter, and intra and extracellular membrane-bound, elongated, filamentous dense bodies with a periodicity of 80 Å. These structure were also observed by others.^{8),21),22)} Merkow et al (1969)²⁰⁾ considered the cytoplasmic filaments of 85 to 125 Å as being in the same size range as those of smooth muscle cells. They believed, therefore, that myxoma cells should be classified as a myoid type of endocardial cell. However, others^{9),16),21),22)} believed that myxomas represent a benign tumor of the ubiquitous subendothelial vasoformative reserve cell. Numerous studies indicate that, in the early proliferative intimal reserve cell response to injury, the subendothelial smooth cells are characterized by the production of muco-

polysaccharides.²³⁾⁻²⁵⁾ According to Ferrans and Roberts (1973)⁸⁾ endothelial cells, fibroblast like cells, macrophages and mature and immature smooth muscle cells are derived from myxoma cells. So, they concluded that cardiac myxomas arise from multipotential mesenchymal cells.

Williams et al (1970)²⁶⁾ suggested that myxoma cells have a secretory function directed towards synthesis of the tumor stroma. They observed that these cells contain numerous cisterns of rough surfaced endoplasmic reticulum, prominent Golgi cisterns and vesicles, and small, single membrane limited bodies with electron dense content. These observations suggest that stromal material is synthesized in the endoplasmic reticulum and Golgi zone, which are known to be the site of synthesis of acid mucopolysaccharides and glycoproteins in other cells,^{27),28)} and that this material is then segregated into membrane bound bodies that function as secretory granules. An alternative explanation for the formation of the stroma is that after synthesis in the endoplasmic reticulum and Golgi zone, the stromal material is transported outside the cells by the small Golgi vesicles with an electron dense content.⁸⁾ It must be remembered that the most typical feature of cardiac myxomas is their gelatinous, mucopolysaccharide rich stroma. Unfortunately, this stroma does not show any unique ultrastructural features.⁸⁾ On biochemical analysis of the stroma,²⁹⁾ it has been found that myxomas contained approximately 3 mg of hexosamine containing macromolecules per 100 mg dry fat free tissue, out of which about 66% was glycosaminoglycans. Chondroitin

Table II. Distinguishing Features of Myxoma and Organized Thrombi

Features	Myxoma	Organized thrombus
Location	Left atrium	Ventricles, atrial appendages and atria
Gross	Lobulated, glistening transparent soft and mucoid	Opaque, granular, firm, laminated
Surface	Continuous endocardial lining	Surface not covered by endocardial lining
Cells	Variable in number, single or syncytial, at places forming gland like structure	Several stratified layers. No gland formation.
Mucin -stroma -cells	Abundant, metachromasia PAS positive	Metachromasia absent PAS negative
Elastic fibres	Thin to moderately thick bundles, beneath the surface, at the base and in focal areas in the stroma	Few
Reticulin fibres	Arranged around groups of cells	Few without any arrangement
Collagen	Thin to moderately thick bands.	Thick bands
Muscle cells	Occasional tadpole like cells in stroma. No cross striation seen	Absent
Hemosiderin	Moderate to abundant	Variable, scanty

4 and/or 6 sulfates were predominant, constituting over 75% of the total glycosaminoglycans. Hyaluronic acid constituted 16%. Dermatan sulfate was absent. The high content of chondroitin 4 and/or 6 sulfates and complete absence of dermatan sulfate suggest that cardiac myxomas are neoplastic in nature.

The feature supporting the contention that myxomas (reported here) are neoplastic and not thrombi are presented in Table II.

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