Myxoma of the Heart:

Clinical and Experimental Observations

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During the past 12 years, 13 patients with atrial (10 left and 3 right) myxoma have been treated. The tumors of the left atrium produced signs and symptoms of mitral valve obstruction and/or subacute bacterial endocarditis and those of the right atrium manifestations of tricuspid valve disease or of pulmonary embolus or hypertension. The diagnosis was established by angiocardiography in 8 patients, at surgery performed for suspected mitral stenosis in 3 patients, and at autopsy in 2 patients. Resection of the atrial myxoma alone in 5 patients or with atrial septum where the atrial myxoma was attached in 4 or with the whole right atrial wall where the atrial myxoma was attached in one patient was performed and all are doing well without evidence of recurrence. Studies of experimentally produced 1.5–3 cm in diameter left atrial thrombus in 30 dogs divided into 5 groups and followed cineangiocardiographically and sacrificed from 14 days to 6 months indicated that the implanted thrombus is absorbed over a 3 to 6 month period. These experimental and human left atrial thrombi were found to be histologically and histochemically different from human atrial myxomas. The electron microscopic studies performed on some of the resected atrial myxomas suggested that the atrial myxoma cells are active cells of endothelial origin. These observations suggest that atrial myxoma is a primary tumor of the heart which can mimic other clinical entities, and the results of its surgical treatment are gratifying and long lasting.

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MYXOMA OF THE HEART is the commonest intracavitary tumor accounting for more than half of all primary cardiac tumors.[1,11] The clinical manifestations of these tumors are variable and despite the increase of clinical awareness and improved diagnostic techniques, still their diagnosis occasionally appears as a surprise at surgery or autopsy.[2,3,19] Also, despite several histochemical[5,6,17] and structural studies[10,14,18,20] of cardiac myxomas, the cell of origin, and certain of the structural features of these tumors remain subject of controversy.

This communication is a review of our clinical experience and of the possible histogenesis of atrial myxoma.

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Material and Methods

Clinical Studies

During a 12-year period, 1962 to 1974, 13 patients (5 men and 8 women) with atrial myxoma were treated at Emory University and Grady Memorial Hospitals. Aspects of several of these patients have been reviewed previously.[16] Ten of the tumors arose from the left atrium and 3 from the right atrium, one of which protruded into the left atrium through an atrial septal defect. In 9 patients the presenting clinical picture was suggestive of mitral valve disease, in most of them of mitral stenosis, and two of them had, in addition, constitutional symptoms (malaise, fever, anemia, etc.) suggestive of subacute bacterial endocarditis. Left atrial myxoma was suspected in 3 of these patients initially and in 2 after unsuccessful treatment for bacterial endocarditis and was proved by angiocardiography. In the remaining 4 patients, an unexpected atrial myxoma was found in 3 at the time of thoracotomy for mitral commissurotomy and in one at autopsy while awaiting

"closed commissurotomy." One patient complained of dyspnea and his chest roentgenogram and angiocardiogram showed a calcified myxoma in the right atrium and one had chest pain and hemoptysis which were initially thought to be due to pulmonary embolus alone but later a right atrial myxoma was diagnosed angiocardiographically.

Another patient was seen with dyspnea, severe cyanosis and grade 2/6 systolic murmur. This clinical picture was initially thought to be the result of pulmonary hypertension, but angiocardiography revealed the cause to be a right atrial myxoma protruding into the left atrium through an atrial septal defect (Fig. 1).

One patient was admitted with clinical and electrocardiographic findings indicative of acute myocardial infarction and died shortly after admission. At autopsy, an unexpected left atrial myxoma was found in addition to the acute myocardial infarction.

Eleven of the atrial myxomas were globular or ovoid, pediculated, arising from the atrial septum in the vicinity of the fossa ovalis and two were botryoid with broad attachment site, one of which was attached to the whole right atrial wall.

Five of the operated upon patients had resection of their tumor only with its pedicle, four had resection of the tumor and of the atrial septum where the myxoma was attached and one had resection of the tumor, the intra-atrial septum and the right atrial wall because the tumor was attached to all these structures. (Fig. 2).

There was no operative mortality in the 10 patients who had resection of their atrial myxoma and all are doing well, without evidence of recurrence of the tumor, one to 12 years after surgery. One patient died while awaiting reoperation for resection of the left atrial myxoma diagnosed at the time of thoracotomy for suspected mitral stenosis. One patient died from myocardial infarction and another while awaiting "closed commissurotomy," and at autopsy an unexpected left atrial myxoma was found in both.

The light microscopic study of all resected tumors revealed abundant mucoid stroma, varied cellularity, from area to area along with areas of fibrosis and hemorrhage. The myxoma cells, singly or in clumps, lay in pools of mucoid stroma and they varied in shape from round to spindle to stellate.

Electron microscopic studies were performed in three of the resected myxomas, all of which showed the myxoma cells with fairly distinct nucleolus, often dilated endoplasmic reticulum, intercytoplasmic filaments, fat droplets with glucogen and plentiful collagen around the cells. In numerous cells, multiple Golgi apparatuses and prominent mitochondria were present.

The histochemical studies of 4 of the examined myxomas showed that the tumors ground substance was composed of only hyaluronic acid and chondroitin-4 or chondroitin-6 sulfate.

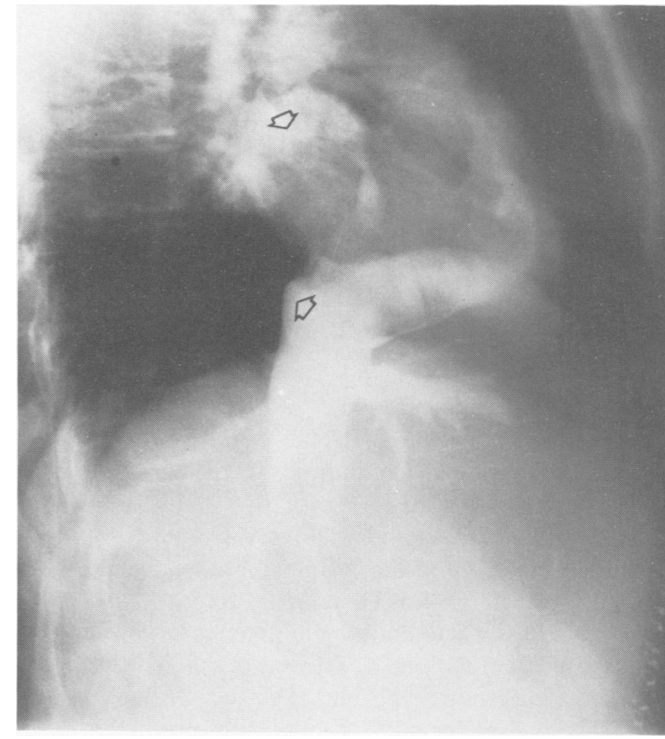


FIG. 1. Posteroanterior and right lateral biplane angiocardiograms showing a large filling defect in the right atrium and an early opacification of the left atrium by contrast material traversing the atrial septal defect.

Animal Studies

In 30, healthy, adult mongrel dogs, under inflow cavae occlusion, right atriotomy and atrial septotomy a 1.5–3 cm in diameter Surgicel* ball appropriately constructed was sutured in the left atrium at the superior margin of the fossa ovalis.

At ten days after operation and at monthly intervals thereafter, serial cineangiocardiograms were obtained injecting into the main pulmonary artery 20 ml of Renovist† at 200 p.s.i.

The dogs were sacrificed and autopsied: group I, 10 dogs, 2 to 14 days after operation; group II, 5 dogs, one month; group III, 5 dogs, 2 months; group IV, 6 dogs, 3 months and group V, 4 dogs, 4 to 6 months after operation. The Surgicel thrombus with the adjacent septum was removed at the time of autopsy and histological and histochemical studies were performed.[4]

The cineangiocardiograms showed, with the passage

* Oxidized regenerated cellulose, Johnson & Johnson, New Brunswick, New Jersey 08903.

† Renovist, E. R. Squibb & Sons, 909 Third Avenue, New York, New York.

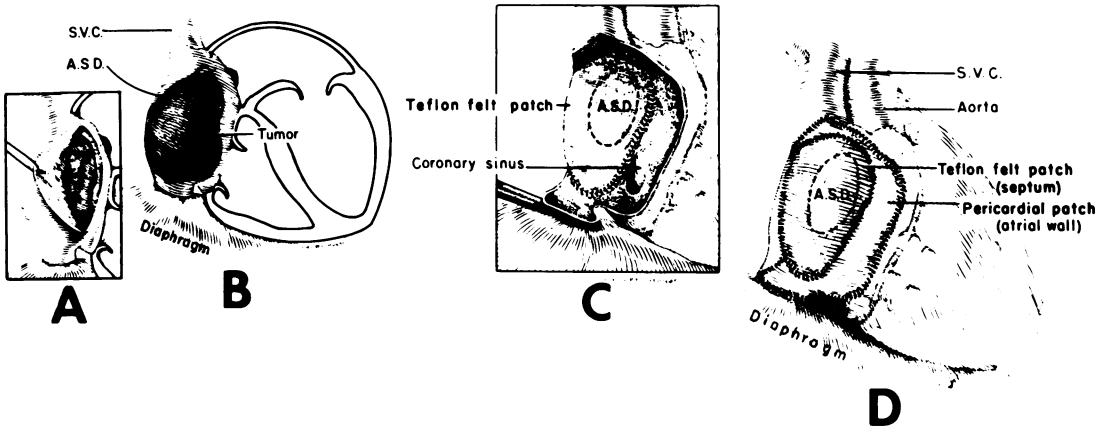


FIG. 2. Drawings, a) and b) of the right atrial tumor and c) and d) of the technique employed to reconstruct the new right atrium.

of time, progressive diminution of the filling defect in the left atrium (Fig. 3).

The implanted Surgicel ball was examined grossly and histologically: in group I dogs there was a large ball of thrombus; in group II dogs a somewhat smaller thrombus with smooth endothelial-like surface, which on histological examination, was a well-organized thrombus (Fig. 4a); in groups III and IV the thrombus was progressively smaller and an increasing prominent connective tissue developed around the thrombus and invaded it (Figs. 4b and 4c). In group V dogs fibrous tissue had replaced the thrombus (Fig. 4d).

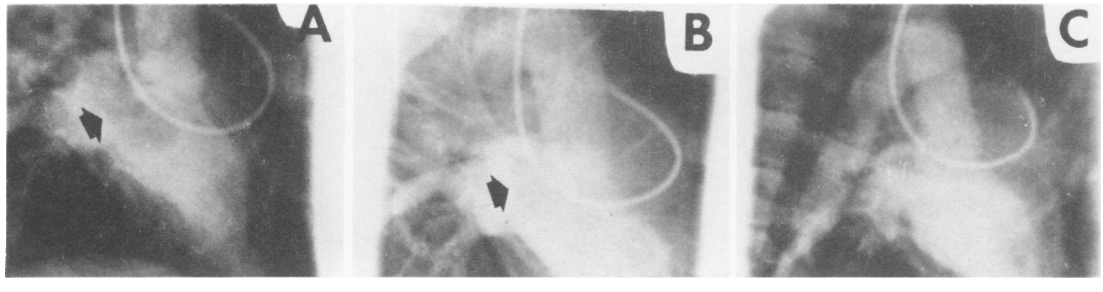
The histochemical studies of the implanted aging thrombus suggest the presence in the ground substance, in addition to hyaluronic acid, chondroitin-4 and chondroitin-6 sulfates, other glycosaminoglycans, such as dermatan sulfate, keratan sulfate, or heparan sulfate.

Discussion

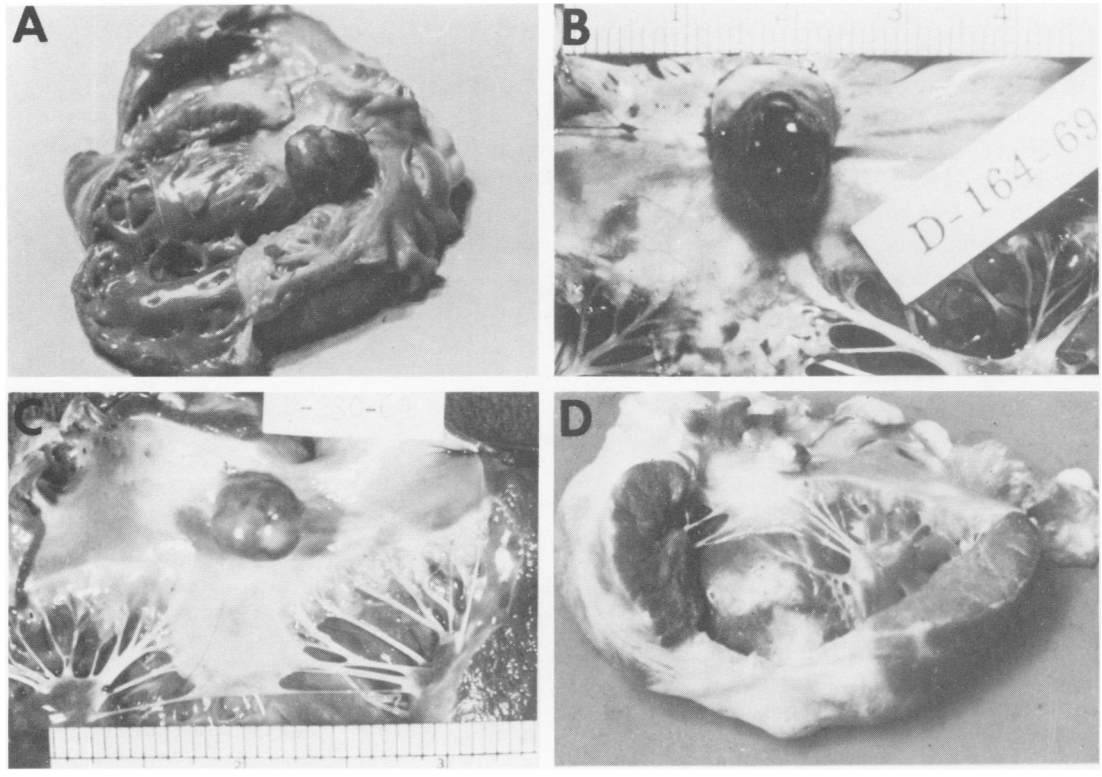
Myxoma of the heart can now be successfully treated but the success is obviously dependent upon the correct diagnosis and treatment prior to development of catastrophic complications such as sudden death, embolism or cardiac failure. Awareness, therefore, of this cardiac tumor, familiarity with its various clinical manifestations, and prompt and proper treatment are essential for the successful treatment.

Myxoma of the heart is the commonest primary cardiac tumor most frequently occurring in the left atrium at the fossa ovalis. The right atrium or both the right and left atrium and the left or right ventricle are other sites of origin of this tumor. Myxoma of the heart occurs in all ages from newborns to 80 years old; but most commonly it is found between 30 and 60 years of age, and it is more frequent in women. The presenting clinical picture of the cardiac myxoma is most variable and is dependent to a certain extent on the location of the tumor.[9] Symptoms and signs of mitral valve lesion, usually mitral stenosis with or without symptoms of subacute bacterial endocarditis are the most common manifestations of left atrial myxoma, resulting not infrequently in the erroneous diagnosis of mitral stenosis or subacute bacterial endocarditis. Symptoms of tricuspid stenosis and pulmonary hypertension are the frequently seen clinical manifestations, of right sided, usually right atrial myxoma. Systemic embolization from left atrial myxoma and rarely pulmonary embolization from a right one may also be part of the clinical picture emphasizing the need for consideration of this clinical entity when there is no apparent explanation of these embolizations and for the histological examination of the extracted emboli.

In many patients cardiac myxoma provokes constitutional manifestations characterized by weight loss, fatigue, fever, anemia, high sedimentation rate and elevated serum immunoglobulin concentration, leukocytosis, thrombocytopenia, clubbing, Raynaud's phenom-



FIGS. 3a to c. Cineangiocardiograms, a) shortly after implantation of the left atrial thrombus; b) 40 days later, and c) 70 days later.



FIGS. 4a to d. Experimental left atrial thrombus, a) one month old, b) two months old, c) three months old, and d) six months old.

enon, and breast fibroadenomata. In addition, right atrial myxoma has been the cause of polycythemia and cyanosis.

The diagnosis, therefore, of atrial myxoma should be suspected in a patient who has various features of classic triad of atrioventricular valvular obstructive disease, of embolism and of constitutional manifestations. This is especially true in patients with clinical findings of heart disease and history of syncope or dizziness and a marked postural effect on the severity of symptoms and especially if recumbency relieves dyspnea or with variable auscultory findings with position changes or change from one examination to the next or with early diastolic sound termed as "tumor plop".[8] The diagnosis, however, can be only established with echocardiography[13] and especially with angiocardiography, although these tests will not differentiate atrial myxoma from thrombus.

Angiocardiography should be done in all patients suspected of having myxoma of the heart. In order to avoid provocation of tumor embolization, the radiopaque material should be injected into the cavae for visualization of right atrial myxoma and into the pulmonary artery for the diagnosis of myxoma of the left atrium.[15]

Once the diagnosis of left atrial myxoma has been made, the patient should be operated upon as soon as possible before undesirable complications, embolization or sudden death occur. An 8% mortality has been reported in patients awaiting operation following definitive diagnosis.

The cardiac tumor should be removed under direct vision and total cardiopulmonary bypass. Both left or right atrial myxomas are approached through right anterolateral or midsternotomy incision and moderate hypothermia. In order to prevent undue handling of a right atrial myxoma in some patients, the inferior vena cava might need to be drained through femoral vein cannulation and the superior vena cava through the axygos vein or through a high incision of the right atrial wall. Gentle handling of the heart during cannulation, constant decompression of the left ventricle through apical vent, electrical fibrillation after initiation of cardiopulmonary bypass and before any manipulation of the tumor, en bloc removal of the myxoma without fragmentation, and irrigation and aspiration of the atrium and ventricle with saline to wash out any tumor fragments are of paramount importance to prevent catastrophic embolization of tumor debris.

After excision of the tumor, the adjacent to it mitral and tricuspid valve should be evaluated for any abnormality and both atria examined for multicentric myxoma. Although the excision of the area of the septum where the myxoma is attached has been a controversial point, many authors now feel it is preferable and provides protection against the rare incidence of recurrence of the myxoma.[7] Read et al.[12] found 8 reports and described 3 of their own cases with recurrence of this cardiac tumor.

Since cardiac myxoma was first recognized, a controversy has existed regarding its histogenesis, thrombotic[4] or neoplastic in origin. The histochemical, light

and electron microscopic findings of the present study show no evidence to support the contention that myxoma of the heart evolves from cardiac thrombus nor that its cells are modified muscle cells. Although there is electron microscopic evidence that precollagent may be synthesized by the myxoma cells, the production of mucoprotein rich matrix does not help in identifying the cell or origin, since many cells are capable of synthesizing these substances. The presence, however, of numerous intracytoplasmic fibrils favors an endothelial or basoformative cell origin. This cell origin is strengthened even more by the existence of lipid droplets within the cytoplasm of the cells concerned.

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Discussion

Dr. Harris B. Shumacker, Jr. (Indianapolis): Dr. Symbas and his colleagues have made a significant contribution by relating their clinical experiences with this interesting, life-threatening, and operatively curable intracardiac tumor, and by describing their pertinent experimental observations.

All of our treated cases have been recognized preoperatively, and have done well, and have exhibited no evidence of recurrence.

As Dr. Symbas has mentioned, patients harboring these lesions ordinarily obtain professional aid because of cardiac dysfunction. In rare instances, however, they seek medical, and soon surgical help, because of other manifestations, as was the case with one of our patients, who suddenly developed frightening visual disturbances consequent to a retinal arterial embolus from a partially calcified myxoma.

Sometimes, too, the lesion can be identified by old and simple methods. If the tumor is pedunculated and contains calcium, one can, on the ordinary fluoroscopic screen, see it flip from atrium to ventricle and back again with each heart beat.

In my judgment, the greatest advance in the management of myxomas has perhaps been medical, rather than surgical. I refer to their precise, almost instant recognition by the simple bedside technique of echocardiography.

My institution was among the first to explore the use of ultrasound as a cardiac diagnostic tool, and I feel confident in saying that since the first myxoma was so studied, each one has been identified positively by this technique. So certain am I of its accuracy that I would operate with confidence on any lesion so diagnosed, without any other studies such as cardiac catheterization if operative intervention were fairly urgent. This has proven a life-saving measure. I recall well one patient, practically moribund when first seen, in whom immediate operation could be carried out after promptly establishing the diagnosis in this way. It is almost certain that she would not have survived long enough for other studies to have been done, such as cardiac catheterization.

Dr. Gilbert S. Campbell (Little Rock, Arkansas): Dr. Symbas and his associates are to be commended for their elegant experimentation and careful clinical studies, which clearly demonstrate the neoplastic nature of cardiac myxomata. Even though in half of their cases the tumor was just plucked, they report that all obtained a "gratifying and long-lasting" result. Others have not had such a happy experience.

Thus, as my colleague, Dr. Raymond Read reported last year, 16 patients are now known to have suffered 19 recurrences, after what was thought to be "successful" removal of the left atrial myxomata.

(Slide) This shows the resected tumor in one of our patients. You can see from the photograph that quite a bit of the atrial septal wall was removed with the tumor. He returned nine years later with obvious metastases in the chest wall. The following year he had parascapular metastases, and one year later he died. Autopsy revealed metastasis to the tongue, lungs, more tumor in the heart, and in the thoracic wall.

Another of Dr. Read's patients has had two local recurrences in the left atrium, and is now doing well nearly two years after his last operation, which was followed by a course of Adriamycin. We recommend radical excision of the atrial septum to reduce recurrence from multicentric foci. Extraseptal myxomata are more likely to recur, and on histological study these recurrences have what appears to be a progressively more malignant nature.

Strong efforts should be made to prevent myxomatous emboli, since they can invade locally. These tumors may be multiple and can spread to other heart chambers. Therefore, other chambers of the heart should be inspected at the first operative procedure. Since the malignant potential of these neoplasms has been established, postoperative study with echo cardiography is an excellent non-