Myxomatous Degeneration of Cardiac Valves*

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A retrospective study of ten patients with myxomatous degeneration of cardiac valves revealed two patients with “floppy valve syndrome” and eight patients with isolated myxomatous change of apparently diverse etiology. The myxomatous degeneration can be seen in a minor degree in normal valves and to a greater extent in clinical and experimental diseases of unknown etiology. The difficulties encountered in the surgical treatment of patients with myxomatous degeneration of the cardiac valves are related to the friability of the aorta and the valve annulus.

While Marfan1 first described musculoskeletal abnormalities and unusual elongation of extremities in a young patient, the first autopsy on a patient with the Marfan syndrome was done by Salle,2 who noted myxomatous change in the gross appearance of cardiac valves. Recently, Read and associates3,4 described myxomatous transformation of cardiac valves (floppy valve syndrome) without characteristic musculoskeletal or ocular stigmata of the Marfan syndrome in a group of patients. These patients had pure mitral or aortic insufficiency due to myxomatous degeneration without evidence of calcification, commissural disease, or inflammation. They were considered as formes frustes of the Marfan syndrome. Subsequent studies have validated their claim.5,6 A review of our own experience with ten patients showing myxomatous degeneration of cardiac valves is reported.

MATERIALS AND METHODS

The records of all patients with insufficiency of cardiac valves who were operated upon, or on whom autopsy was performed in the last six years at the Veterans Administration and University of Tennessee affiliated hospitals were reviewed. Those patients with histologic evidence of rheumatic fever were excluded. All available tissue was reexamined and only those patients showing myxomatous degeneration of valves were selected. Eight cases were selected from a group of 400 patients who were operated upon, and two cases from a group of 3,200 patients who were subjected to autopsy. The interpretation of myxomatous degeneration of the mitral valve in one patient was confirmed by the Armed Forces Institute of Pathology. The other cases were not submitted because of the same histologic appearance. Subsequently, the histologic features of the affected valves were carefully compared with those of patients dying of noncardiac causes.

Findings

The ten patients may be divided into two groups (group 1 and 2). The details of the patients are summarized in Table 1. The first group (case 1 and 2) showed not only myxomatous transformation of the aortic valves and cystic medionecrosis of the aorta, but some of the musculoskeletal features of the Marfan syndrome. They were similar to the patients described by Read and co-workers.3,4 Case 1 reported below is representative of this group. The second group of eight patients did not have any stigmata of the Marfan syndrome or any known inherited connective tissue disease. Of these, two were examined solely at autopsy and six were operated upon. Among the latter, five were between the ages of 12 and 39 and one patient was 59 years old. Unusual friability of tissues was noticed by the surgeon at the time of operation in all cases. Dehiscence of the suture line of the implanted valve

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Table 1—Summary of Clinical Data (Ten Patients)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Isolated Stigmata</th>
<th>Marfan Syndrome</th>
<th>Nature of Valve at Operation or Autopsy</th>
<th>Complication of Operation</th>
<th>Operation</th>
<th>Result</th>
<th>Associated Disease or Complications</th>
<th>Associated Findings</th>
<th>State of Aorta</th>
<th>Group</th>
<th>Duration of Heart Disease (years)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>F</td>
<td>Aortic incompetence (AI) + Aortic incompetence (AD)</td>
<td>Femoral artery aneurysm</td>
<td>Endocarditis</td>
<td>Thrombus formation</td>
<td>Thin</td>
<td>SE</td>
<td>Alive</td>
<td>Thin</td>
<td>Medioneocrosis</td>
<td>1</td>
<td>Striking arachnodactyly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>Aortic incompetence (AI) + Aortic incompetence (AD)</td>
<td>Endocarditis</td>
<td>Endocarditis</td>
<td>Aspergillus endocarditis</td>
<td>Thin</td>
<td>SE</td>
<td>Died 1 month</td>
<td>Aspergillus endocarditis</td>
<td>Medioneocrosis</td>
<td>1</td>
<td>Family history suggestive of Marfan's Aspergillus endocarditis postoperatively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>F</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>5 mo.</td>
<td>Myocardial infarction (MI)</td>
<td>Dehiscence of valve</td>
<td>Thin</td>
<td>Died 3 days</td>
<td>Death</td>
<td>Dehiscence of valve</td>
<td>Thin</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Heart failure during pregnancy</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>Many</td>
<td>VP</td>
<td>Operative death</td>
<td>Thickened</td>
<td>Died 20 days</td>
<td>Death</td>
<td>Operative death</td>
<td>Thickened</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Mitral incompetence secondary to AI</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>18</td>
<td>Myocardial infarction (MI)</td>
<td>Dehiscence of valve</td>
<td>Thickened</td>
<td>Died 20 years</td>
<td>Death</td>
<td>Dehiscence of valve</td>
<td>Thickened</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Mitral incompetence secondary to AI</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>3</td>
<td>Myocardial infarction (MI)</td>
<td>Dehiscence of valve</td>
<td>Thickened</td>
<td>Alive 3 years</td>
<td>Death</td>
<td>Dehiscence of valve</td>
<td>Thickened</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Progressive heart disease since age</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>2</td>
<td>SE</td>
<td>Operative death</td>
<td>Thickened</td>
<td>Died 2 months</td>
<td>Death</td>
<td>Operative death</td>
<td>Thickened</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Ascending aorta aneurysmal</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>Hypertensive</td>
<td>7</td>
<td>SE</td>
<td>Arrhythmia</td>
<td>Thickened</td>
<td>Died 2 months</td>
<td>Death</td>
<td>Arrhythmia</td>
<td>Thickened</td>
<td>Medioneocrosis</td>
<td>2</td>
<td>Hypertension—7 year</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>M</td>
<td>Hypertensive</td>
<td>20</td>
<td>None</td>
<td>None</td>
<td>Thickened</td>
<td>Died 2 months</td>
<td>Death</td>
<td>None</td>
<td>Thickened</td>
<td>Hypertension, 18 year old endocarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>M</td>
<td>Aortic incompetence (AI) - Aortic incompetence (AD)</td>
<td>7</td>
<td>None</td>
<td>Multiple fenestrations</td>
<td>Thickened</td>
<td>Died 2 months</td>
<td>Death</td>
<td>Multiple fenestrations</td>
<td>Thickened</td>
<td>Sudden death due to pulmonary edema</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD—aortic diastolic murmur; AS—aortic systolic murmur; MD—mitral diastolic murmur; SE—Starr-Edwards valve; MS—mitral systolic murmur; McG—McGovern valve; VP—valvuloplasty; AI—aortic incompetence; MI—mitral incompetence

AD—Aortic incompetence; MI—Mitral incompetence; MD—Mitral diastolic murmur; SE—Starr-Edwards valve; McG—McGovern valve; VP—Valvuloplasty; AS—Aortic incompetence.
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in two patients, disruption of valvuloplasty in one, and rupture of the aorta at the site of application of vascular clamp in another substantiate this observation. Only one patient out of six survived the operative correction. This high percentage of complication and mortality was in marked contrast with that of other patients with valvular disease in whom operative correction was attempted. A representative of this group of operated cases is case 5 which is reported in some detail. Two of the non-operated cases belonging to group 2 were both 73 years old, and lived an almost normal life span. Case 9 is believed to represent this subgroup.

CASE REPORTS

CASE 1

A 54-year-old Negro woman was admitted to the hospital with a four-year history of increasing dyspnea on mild exertion. Past history revealed emergency left iliac and right femoral arterial surgery for ruptured aneurysms, which were reported as arteriosclerotic aneurysms. She was 5 feet 9 inches tall and weighed 126 pounds. There was striking arachnodactyly and myopia but arching of the palate was not unusual. No other musculoskeletal characteristic or family history of the Marfan syndrome was present. Blood pressure was 190/120 mm Hg. There was a grade IV/Vi diastolic murmur over the aortic area, to the left of the sternal border, and at apex of the heart. Aortogram confirmed massive aortic regurgitation and dilatation of the ascending aorta. At operation the aortic cusps were thin with edges rolled back. Microscopic examination revealed myxomatous degeneration with destruction of the architecture of cusps and replacement with basophilic material (Fig 1). A No. 13 Starr-Edwards prosthesis was implanted. Patient continued to do well for more than a year after operation.

CASE 5

A 25-year-old Negro man was admitted to the hospital because of progressive dyspnea to accustomed exertion. He was first seen 18 years prior to this admission and the diagnosis was rheumatic aortic incompetence. However, previous records failed to show evidence for rheumatic etiology. He was 73 inches tall and weighed 200 pounds. His blood pressure was 130/70 mm Hg. A diastolic thrill and a grade I/V murmur were heard in the aortic area. There was also a grade III pansystolic murmur heard at the apex, which was conducted to the axilla. The liver was palpable two inches below the costal margin and there was minimal pedal pitting edema. At operation, a large and dilated heart was seen. Both the aortic annulus and ascending aorta were greatly dilated. The mitral annulus was also greatly dilated. The aortic cusps were thin and prolapsed into the ventricle. The mitral annulus was also greatly dilated. The aortic valve was removed and the largest size McGovern valve was implanted. The removed valve showed evidence of myxomatous de-
generation. The patient did well in the immediate postoperative period, but died 20 days later of pulmonary edema due to separation of the valve from the aortic annulus. There was no evidence of rheumatic activity or aortic dissection at autopsy. Histologic examination of the mitral valve was not done.

CASE 9

A 57-year-old Negro man was seen in 1949 because of epistaxis and minimal exercise intolerance. There was no previous history of rheumatic fever. The patient weighed 171 pounds and was 71 1/4 inches tall. There were no stigmata of the Marfan syndrome. Blood pressure was 145/100 mm Hg, and the point of maximal impulse was in the left sixth intercostal space outside the midclavicular line. A grade III pansystolic murmur was heard at the apex and was conducted to the axilla. He was discharged after symptomatic treatment of epistaxis. In 1955, he was given digitals elsewhere, because of the same symptoms. In 1964, he was readmitted for back and joint pains, and at this time was placed on medications for his hypertension. He continued to have minimal symptoms until December, 1965, when he was admitted to the hospital because of high fever and signs of heart failure. Electrocardiograms at this time showed left ventricular hypertrophy and strain pattern. B-hemolytic Streptococcus was cultured from the blood twice on this admission. Treatment with high doses of penicillin, digitalis, and hypotensive drugs controlled his symptoms until the patient's sudden death, two years later, at the age of 73 years.

There was moderate left ventricular enlargement seen at autopsy. The aortic and mitral valves showed redundant floppy leaflets. The posterior leaflet of the mitral valve was approximately three times the normal thickness and had a large bulbous mass at the free edge of the cusp. On the anterior leaflet, there was an area of perforation about 0.4 cm in diameter. The chordae tendineae were thin and markedly stretched. Microscopically, the valve leaflets showed myxomatous degeneration with marked loss of elastic fibers and increase in mucopolysaccharide ground substance and fibrous tissue. These findings were confirmed by the Armed Forces Institute of Pathology.

COMMENT

The patient lived a normal life span in spite of a 20 year history of mitral insufficiency. He was considered suffering from rheumatic mitral disease, but no evidence of previous rheumatic activity was present at any point in his course. The gross appearance and histologic picture were strikingly different from rheumatic valvular disease. The evidence of bacterial endocarditis is interesting in the light of known propensity for this disease in patients with the Marfan syndrome. McKusick thinks that myxomatous degeneration is the basis for that association.5

DISCUSSION

All patients in this study showed myxomatous transformation of aortic or mitral valves. The histologic appearance of myxomatous degeneration seen in group 1 or group 2 was indistinguishable from the other. In group 1, both patients had cystic medionecrosis of the aorta as well as stigmata of the Marfan syndrome. The similarity of myxomatous degeneration of the valve cusps to the medionecrosis in the aorta has been pointed out by Tobin and colleagues,7 Tung and Liebow,8 and Castleman and Sprague.9

In group 2, two patients had cystic medionecrosis of the aorta and myxomatous degeneration of the aortic valves without any stigmata of the Marfan syndrome. Though isolated Erdheim's cystic medionecrosis is apparently unrelated to the Marfan syndrome, the histologic appearance of the affected aortae are indistinguishable.5,7 Histologically, the same appearance is seen in the coarctation of the aorta,10 and in the Ehler-Danlos syndrome6 as well.

It is known that myxomatous degeneration of the cardiac valves and cystic medionecrosis may be seen in diseases of apparently unrelated etiology, affecting connective tissue, particularly elastic fibers. Thus, in some cases of fibroelastosis11 and in the Hurler syndrome,12 myxomatous change in cardiac valves may be seen. Fenestration of aortic cusps, described by Castleman and Sprague,9 was associated with a similar change in histologic appearance of the aortic cusps. Similar cases were reported by Mathews and Darvill.12

O'Brien and co-workers18 reported two cases of spontaneous aortic cusp rupture, associated with valvular myxomatous transformation. Symbas and colleagues14 described fenestration of aortic cusps in two cases which were the seat of “mucinous degeneration.” Their photomicrographs are consistent with myxomatous transformation. Neville and others15 reported nine patients with mitral insufficiency unassociated with the stigmata of the Marfan syndrome, the basis of which was myxomatous degeneration. Review of all these cases, including our own, leads us to conclude that histologic appearance of myxomatous degeneration in cardiac valves can be seen in patients whose only obvious abnormality is in their cardiac valves or in the aorta and cardiac valves.

Experimentally, myxomatous changes of cardiac valves and cystic medionecrosis of the aorta can be produced by giving aminonitriles in rats.16,17 Copper deficient diets produce medionecrosis of the aorta in swine,18 turkeys,19 and chicks.20 In turkeys, low protein diet, estrogen administration, or aminonitriles produce medionecrosis. The histologic appearance of medionecrosis in these animals is similar though not identical with that of man. However, increase in myxomatous tissue in the affected aortae is evident. That different mechanisms are involved.
in the production of medionecrosis by different agents is suggested by the fact that collagen abnormality seen in aminonitrile fed rats is not seen in swine fed copper deficient diets.

The support for the concept of nonspecificity of myxomatous change is shown by many older observations, and a recent review published after preparation of this paper.11 Mortitz22,23 describing cystic medionecrosis of the aorta, quotes Schultz23 who believed that myxomatous degeneration was an aging phenomenon seen in animals and man. Castleman and Sprague9 mention myxomatous change in cardiac valves of normal individuals over the age of 30. Our own observations showed that an occasional focus of myxomatous change could be seen in cardiac valves of otherwise normal patients. However, the extent of myxomatous change seen in either group 1 or 2 was never seen unassociated with disease.

CONCLUSIONS

Myxomatous transformation of the cardiac valves is not specific to the Marfan syndrome or to the so-called “floppy valve syndrome.” It is seen in minor degree in normal valves and in clinical and experimental diseases of unknown etiology. The difficulties encountered in the treatment of patients with myxomatous degeneration of the cardiac valves9,14,24 are related to friability of aorta and valve annulus.

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CHEST, VOL. 57, NO. 6, JUNE 1970