CLINICAL PROGRESS

Cardiac Amyloidosis

By ROBERT S. ELIOT, M.D., HUGH J. McGEE, M.D.,
AND S. GILBERT BLOUNT, JR., M.D.

AMYLOIDOSIS was first described by Wilks in "The Guys Hospital Report" of 1856. It was referred to at that time as "lardaceous disease," obviously because of the physical similarity of amyloid to lard. Very few cases were reported until 1908 when Beneke and Bönning reported their experience. In 1929 Lubarsch reported three cases and suggested the criteria for diagnosis, but by 1930 only 10 cases were in the literature.

Very little appeared in the English or American writings until the mid 1930's. By 1950 Higgins and Higgins had collected 71 cases from the literature and added their own experience. Since their report, many other cases have been added and the concept of its rarity has faded in the light of these recent reports. The question of etiology remains to be answered, as well as the problem of terminology and classification. The lack of clarity in both these areas is demonstrated by the following terminology: atypical amyloidosis, paramyloidosis, unusual amyloid deposits, idiopathic amyloid disease, primary amyloidosis, and tumor-forming amyloid. This problem in terminology has made it difficult to review with accuracy the literature on this subject.

Perhaps the most workable classification is that suggested by Reimann, Koucky and Eklund: (1) primary amyloidosis—in which no concomitant disease or explanation is found; (2) secondary amyloidosis—which occurs in conjunction with chronic suppurative, malignant, or other wasting diseases; (3) localized tumor-forming amyloidosis; (4) amyloidosis associated with multiple myeloma. To date this classification has not been uniformly accepted.

So-called primary amyloidosis more commonly involves the heart than any other organ. Its presence is rarely suspected ante mortem and thus it represents a problem in cardiac diagnosis that has not as yet been thoroughly elucidated.

Mulligan recently reported 17 cases of cardiac amyloidosis and reviewed the literature. Subsequently, an unusual patient with this condition came to our attention and brought to mind the problem of diagnosis from a clinical and laboratory standpoint. None of our patients was diagnosed ante mortem.

The purpose of this paper is to present 20 cases of cardiac amyloidosis (19 from the University of Colorado Medical Center and one from the Denver VA Hospital); to report an unusual case; to review 82 additional cases from the literature, and to emphasize certain electrocardiographic findings. It is the hope that emphasis on certain findings will aid in predicting the type of patient in whom cardiac amyloidosis is to be suspected, so that more cases may be studied ante mortem.

First a patient is presented who is believed to have the largest amyloid heart ever reported.
X-ray reveals air under the diaphragm, gross cardiomegaly, and prominent vascular markings.

Case Report

A.B. was a 76-year-old Negro man who was admitted to the Denver VA Hospital with complaints of abdominal and chest pain for 3 days and dyspnea, ankle edema, and progressive weakness of 6 months duration. The past history revealed digitalis and diuretic treatment for 3 years, but elaboration on this and other historical data was impaired by his near terminal state.

Physical examination revealed an emaciated elderly, ill Negro with a blood pressure of 80/20 and an irregular heart rate of 80 per minute. The neck veins were distended beyond the angle of the jaw, the heart was enlarged beyond the midaxillary line, and basilar rales and 2 to 3 plus pitting edema were present. The abdomen was rigid and tender, with maximal point tenderness to the left of the umbilicus. Rectal examination revealed a guaiac-positive stool.

The admission white blood cell count was 3,800; the hemoglobin was 16 Gm. per cent; the serum glutamic oxaloacetic acid transaminase was 72 units. Serum electrolytes were within normal limits. Chest roentgenogram revealed a grossly enlarged heart and free air under the diaphragm (fig. 1). The electrocardiogram is shown in figure 2.

At surgery a 3-mm. perforation in an anterior gastric ulcer was closed and 1,500 ml. of cloudy yellow fluid were removed. Following the procedure, the patient failed to breathe well, ventricular fibrillation developed, and death ensued, despite procaine anide and precordial pounding, which temporarily restored normal sinus rhythm.

The body was poorly nourished, was 62 inches long, and weighed 90 pounds. The heart weighed 1,090 Gm. and occupied nearly half of the thoracic space. This heart weight is particularly remarkable in relation to the total body weight of 41 Kg. in that it represented 2.7 per cent of body weight or more than five times normal. Anteriorly the epicardium was mottled red and elsewhere slightly roughened and marked by opaque gray plaques ranging from 1 to 10 mm. in diameter. The myocardium was firm and rubbery, and the chambers failed to collapse when emptied of blood. The cut surfaces of the myocardium were pale yellow-brown and gray mottled, waxy, and semitranslucent. In the anterior portions of the right and left ventricles and interventricular septum, dark red blood dissected among muscle bundles and separated them. The endocardium of the atria was thickened, yellow-tan, and marked by myriads of yellow-gray nodules, which projected slightly above the surface and averaged less than 0.5 mm. in diameter. The nodules did not extend onto the atrial surfaces of the valves, which were intact except for slight fibrous thickening at their free margins. The chordae tendineae were slightly thickened. The endocardium of the ventricles was focally thickened, opaque and gray-white to pale yellow-tan, and showed no nodules (figs. 3 and 4). The coronary arteries were patent and generally normal, except for slightly elevated yellow intimal plaques that moderately narrowed the lumen. The remainder of the gross examination was essentially negative, except for a recently closed, 1.5-cm. gastric peptic ulcer and a diffuse purulent peritonitis.

Microscopically, masses of amyloid had infiltrated diffusely among the muscle fibers and capillaries of all chambers. Amyloid was present in the media and intima of all arteries and veins, sometimes forming masses that bulged into the lumen (fig. 5). In the endocardium of the atria, masses of amyloid were present just beneath the endothelium and elevated it. Deposits were less prominent and more diffuse in the endocardium of the ventricles. Amyloid focally encased fat cells in the epicardium or was deposited in large plaques. In the myocardium most of the amyloid was diffusely deposited in the interstitial tissue among the muscle fibers (fig. 5). Often it formed definite rings about fibers. In most severely involved areas, muscle fibers were decreased in size and some had disappeared. In other areas the muscle fibers were considerably enlarged and had swollen irreg-
An electrocardiogram reveals left axis deviation with prolongation of the QRS (0.14 second), uniformly flat or inverted T waves, QS in II, III, and aVF. The major T vector is 180° from the major QRS vector. Without previous tracings, the diagnosis is obscure. Left bundle-branch block and parietal block are possibilities. No P waves are seen in any lead, and atrial fibrillation was believed to be present.

6. Left axis deviation, ventricular conduction disturbance, and low voltage QRS, ventricular premature contractions, and, finally, ventricular fibrillation.

7. A very enlarged heart without good explanation: The weight of 1,090 Gm. is larger than the largest amyloid heart found in the literature, particularly in relation to the patient's weight of 41 Kg. The heart weight was 2.7 per cent of total body weight, or five times normal.

8. Maximum involvement of the heart rather than other organs.


10. No evidence of coexisting chronic illness.

Discussion

Age Distribution

Sixteen of our 20 patients were between 80 and 90 years of age. Three were in their 70's and one was 90 plus. The range in the literature is from 20 to 101 years. More than 50 per cent are 70 years or older.

Sex Distribution

The male-to-female ratio, by virtue of the number of males autopsied, is 2.5 times the number of females.
Figure 4

Incisions through the anterior wall of the left ventricle demonstrate the extensive infiltration of amyloid and the prominent hypertrophy.

greater than the number of females at this institution. This may vary in other institutions as well. Josselson31,32 reported a sex ratio of 1.64 in 44 cases and Husselmann,65 1.75 in 40 cases. No conclusions are drawn from our study, since selection is involved.

Race

Amyloidosis has been reported in both white and Negro races. One patient in our series was Negro. Jones and Frazier38 reported 14 Negro cases of cardiac amyloidosis. Picking up one case from Ohliger42 and another from Golden,66 we know of at least 17 cases of 102 in the Negro. We are unaware of reports of this disease in the oriental races.

Incidence of Amyloidosis as a Primary Cause of Death

Amyloidosis was the primary cause of death in 11 of our 20 cases. In these instances, congestive failure was uniformly the cause of death, with a probable effect in two cases from ventricular arrhythmias. Amyloidosis played a secondary role in the remaining nine cases.

Incidence of Congestive Failure

Nine of our patients presented with refractory congestive failure; 19 of the 20 had definite findings of congestive failure at one time or another. Left ventricular failure was present first in all but three cases. Once heart failure developed, death ensued within 6 months to 2 years. It is significant that the failure was uniformly persistent and progressive, despite all therapeutic measures. The incidence of these symptoms and findings in our cases was higher than in the cases reviewed by Higgins and Higgins.82

Incidence of Gastrointestinal Complaints

Three of our patients (15 per cent) presented with perforated peptic ulcer; six others had various gastrointestinal complaints such as dyspepsia and postprandial distress making a total of nine patients, or 45 per cent.

Incidence of Cardiac Murmur

Twelve of our patients (60 per cent) were reported to have systolic murmurs (usually grade I or II) located at the left sternal border or apex. Insufficient data were available to define these murmurs further. No diastolic murmurs were recorded. In the literature we found murmurs recorded in-
Incidence of Coronary Atherosclerosis

Atherosclerotic involvement of the coronary arteries was graded as minimal, moderate, or severe with infarction. Only four patients had associated severe coronary atherosclerosis. Three had moderate atherosclerosis, but the remainder were minimally involved. Six patients recorded in the literature but none of our series had angina.

Incidence of Hypertension

One of our patients had a diastolic blood pressure greater than 110 mm. Hg. Only four patients with a diastolic pressure greater than 110 mm. Hg were found in 82 cases in the literature.

Average Heart Weight

The heart weight was noted in 76 of the 82 cases reviewed in the literature. In these patients the average weight was 472 Gm., and almost all had clinical cardiac disease. In our series (not including the 1,090-Gm. heart) the average was 414 Gm.; including the above case, our average would be 442 Gm., but it is considered that the latter is not a representative figure (table 1). In general, hearts that were minimally involved (microscopic evidence only) had normal weights and no abnormality of the axis. Hearts that were grossly involved were heavier and demonstrated left or right axis deviation in a high percentage.

Electrocardiographic Findings

For this study, only those patients from the literature who were analyzed in which photographs of electrocardiograms were in-

<table>
<thead>
<tr>
<th>Electrocardiographic Findings</th>
<th>Summary of literature</th>
<th>Our experience</th>
<th>Per cent or average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low voltage</td>
<td>11</td>
<td>14</td>
<td>80%</td>
</tr>
<tr>
<td>Normal axis</td>
<td>3</td>
<td>4</td>
<td>22.5%</td>
</tr>
<tr>
<td>(a) Average heart weight</td>
<td>301 Gm.</td>
<td>283 Gm.</td>
<td>900 Gm.</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>7</td>
<td>9</td>
<td>52.0%</td>
</tr>
<tr>
<td>and parietal block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline left axis deviation</td>
<td>0</td>
<td>2</td>
<td>6.4%</td>
</tr>
<tr>
<td>Left axis deviation and pericardial block</td>
<td>1</td>
<td>0</td>
<td>3.2%</td>
</tr>
<tr>
<td>Total with left axis deviation</td>
<td>8</td>
<td>11</td>
<td>61.6%</td>
</tr>
<tr>
<td>(a) Average heart weight</td>
<td>588 Gm.</td>
<td>415 Gm.</td>
<td>463.4 Gm.</td>
</tr>
<tr>
<td>(b) Number of infarcts</td>
<td>1</td>
<td>1</td>
<td>6.4%</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>4</td>
<td>1</td>
<td>16.0%</td>
</tr>
<tr>
<td>(a) Average heart weight</td>
<td>486.6 Gm.</td>
<td>400 Gm.</td>
<td>469.2 Gm.</td>
</tr>
<tr>
<td>First degree A-V block</td>
<td>7</td>
<td>4</td>
<td>34.3%</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>1</td>
<td>1</td>
<td>6.4%</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>1</td>
<td>2</td>
<td>9.6%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>4</td>
<td>29.0%</td>
</tr>
<tr>
<td>Ventricular premature contractions</td>
<td>6</td>
<td>4</td>
<td>32.0%</td>
</tr>
<tr>
<td>T-wave abnormalities</td>
<td>6</td>
<td>4</td>
<td>32.0%</td>
</tr>
<tr>
<td>Definite myocardial infarction</td>
<td>1</td>
<td>1</td>
<td>6.4%</td>
</tr>
<tr>
<td>Inverted QRS V1-V3</td>
<td>8</td>
<td>8</td>
<td>52.0%</td>
</tr>
</tbody>
</table>

*Heart weights do not include the 1,090-Gm. heart
Large deposits of amyloid are present beneath the intima of the coronary sinus. A few hypertrophied muscle fibers are present among the amyloid which diffusely infiltrates around the muscle fibers. Hematoxylin and eosin stain.

A section through the contusion in the anterior wall of the left ventricle.

The amyloid appears to be deposited as a coating upon the fractured, irregularly swollen reticulum fibers. Crystal violet and Wilder reticulum stain.

Right axis deviation was observed in four cases in the literature and in one of our cases. Because these cases lacked an R' in V_{3R} or V_{1}, the true S_{1}S_{2}S_{3} syndrome could not be established. The right axis deviation in our single case was unexplained. No definite conclusions could be drawn from the other four cases, except that the right axis deviation was more frequently associated with amyloid hearts weighing more than 450 Gm.

Two of our cases showed sufficient coronary atherosclerosis to suggest it as the cause for the axis deviation. Hearts with right or left axis deviation were, however, much heavier than those with normal axis. This observation emphasizes the importance of finding gross cardiomegaly before suggesting amyloidosis to account for clinical heart disease.

The uniformly low voltage QRS has been commented upon by many authors as well as P-R prolongation and frequent premature ventricular contractions. Atrial fibrillation in the absence of significant coronary atherosclerosis was present in almost 30 per cent of cases. It is probable that our patient with the 1,090-Gm. heart had atrial fibrillation, but this was not definitely established by the technically poor record.

Etiology

Neither the etiology nor the exact chemistry...
of amyloid is as yet understood. The theory that chondroitin-sulfuric acid is at least a building block in amyloid has not been substantiated.75, 78

Block79 recently reported the presence of an atypical serum protein component of five patients with familial primary systemic amyloidosis. It appears to be located between the alpha and beta globulins and he calls it an A2' globulin. This has apparently not been demonstrated in acquired cases as yet. Schneckloth and Page80 have recently reported a case with elevation of B1 lipoproteins as well as the A2 fractions, in a patient with nephrotic syndrome secondary to amyloidosis.

Mulligan24 has pointed out that "the apparent common denominators of amyloidosis of the heart are senility and malnutrition." Fifteen of our cases had impaired food intake due to gastrointestinal lesions (seven cases), cancer (three cases), and other causes (five cases). The low weight of the liver in these cases lends additional support to the thesis of malnutrition. He objected to the term "primary," indicating that in view of the associated findings this disease is probably always secondary, if only the cause were known. Whether it is reduced capacity for the synthesis of serum proteins81 or the synthesis of abnormal proteins,80 hypoalbuminemia, 33, 37, 80, 82 thiamine deficiency,74, 83-86 or some other unrecognized metabolic abnormality, remains to be clarified.

In 1948 King78 correlated the incidence of amyloid with age and proposed that amyloid disease was more common than had been suspected. Edwards87, 88 found amyloid in five of 100 consecutive autopsies of men in the ninth decade. Certainly, most patients are past 70 years of age.

Distribution in the Heart

Edwards88 reported that all cases of cardiac amyloidosis demonstrated gross lesions of the endocardium, of the right atrium, and often of the left atrium, and that these lesions were tiny translucent gray-to-pink elevations from pinpoint in size to 5 mm. in diameter. According to Dahlin and Edwards,88 87, 88 the atrial endocardium was the single location showing a uniform presence of amyloid.

Summary and Conclusions

A case of cardiac amyloidosis with a 1,090-Gm. heart is presented in detail. This is believed to be the largest amyloid heart reported, especially since the heart represented 2.7 per cent of the patient's total body weight, or five times the normal.

Eighty-two cases from the literature and 20 cases of our own have been analyzed, and the literature on cardiac amyloidosis has been reviewed.

Most patients are men over 70 years of age, in poor nutritional state, who have predominantly intractable left ventricular failure, a systolic cardiac murmur, minimal coronary atherosclerosis, cardiomegaly (av. 452 Gm.), variably positive Congoal tests, and cardinal involvement of the heart over other organs.

Electrocardiograms in 31 cases of cardiac amyloidosis are analyzed, and some useful correlations of special interest are made. Left axis deviation, parietal block, and a heart weight of 450 Gm. or more appear in a significant number of cases in which cardiac amyloidosis is the primary cause of death. Atrial fibrillation is frequently found in patients with cardiac amyloid with or without significant coronary atherosclerosis.

Acknowledgment

We are indebted to R. M. Mulligan, M.D., of the University of Colorado, Department of Pathology, for his constructive criticism; and to T. P. Sears, M.D. Chief of Medicine, Denver Veterans Administration Hospital, for his cooperation.

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Infinity

Alike in the external and the internal worlds, the man of science sees himself in the midst of perpetual changes of which he can discover neither the beginning nor the end. If, tracing back the evolution of things, he allows himself to entertain the hypothesis that the universe once existed in a diffused form, he finds it utterly impossible to conceive how this came to be so; and equally, if he speculates on the future, he can assign no limit to the grand succession of phenomena ever unfolding themselves before him.—Herbert Spencer. First Principles. New York, reprinted from the Fifth London Edition, The Home Library, 1880, p. 57.
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