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Restrictive Cardiomyopathy

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Restrictive obliterative cardiomyopathy, with emphasis on amyloid infiltration of the heart, is discussed. The presence of right-sided failure associated with low-voltage electrocardiographic complexes may simulate constrictive pericarditis. Intractable congestive heart failure is the most frequent presentation of amyloid heart disease, and the average survival from diagnosis is 14 months. Digitalis sensitivity and fatal arrhythmias are notoriously common. Other important, although less common, restrictive cardiomyopathies include 1) hemochromatosis, which is the only reversible cause of heart failure in this group; and 2) endomyocardial fibrosis, which is rarely seen in temperate zones but which is amenable to surgical palliation. Many questions regarding the pathogenesis and management of restrictive myocardial disease remain unanswered. (Henry Ford Hosp Med J 1986;34:168-73)

Restrictive cardiomyopathy, one of the three major clinicophysiologic divisions first suggested by Goodwin (1-3), is characterized hemodynamically by "stiffness" and lack of compliance of the ventricles in diastole. Systolic contractile function may be normal, but usually shows varying degrees of impairment. The restrictive cardiomyopathies include 1) endomyocardial fibrosis, which occurs mostly in Africa and tropical regions; 2) Loeffler's endomyocardial fibrosis with eosinophilia, which is seldom seen in temperate zones; and 3) infiltrative diseases of the myocardium such as amyloidosis, hemochromatosis, sarcoidosis, glycogen storage disease, Fabry's disease, and neoplastic infiltration. Of the latter category, amyloid heart disease is the most common in North America and presents the typical features of the restrictive group.

Case Reports

The patients in the following cases demonstrate many of the presenting, clinical, and diagnostic features of patients with amyloid heart involvement. These cases also demonstrate the poor prognosis for these patients following diagnosis.

Case 1

A 58-year-old man presented with a three-year history of progressive dyspnea, weight loss, memory loss, increasing fatigue, and hoarseness. He had been evaluated previously and diagnosed as having hypertrophic nonobstructive cardiomyopathy and paroxysmal atrial fibrillation. Coronary arteries were normal at angiography. He was started on propranolol hydrochloride and sodium warfarin.

On admission the patient's pulse rate was 70 beats/min and regular, with a blood pressure of 100/70 mm Hg. Respiratory rate was 30 breaths/min. Jugular venous pressure was markedly elevated. The tongue was not enlarged. The thyroid gland was diffusely enlarged and firm. The first and second heart sounds were normal with an S4 gallop. There were no murmurs or pericardial rub. The lungs were clear to percussion and auscultation, and there was 2 to 3+ pitting ankle edema bilaterally.

Laboratory studies showed a normal WBC count, a hemoglobin of 12 to 13 g%, and a serum creatinine of 1.8 mg%. Antinuclear antibody and serum complement tests were normal. There was 2+ proteinuria. The electrocardiogram (ECG) demonstrated sinus rhythm and first degree atrio-ventricular block of 0.24 seconds, intraventricular conduction delay, and low voltage. Poor R-wave progression in the chest leads suggested old anterior myocardial infarction. Generalized cardiomegaly, small bilateral pleural effusions, but normal pulmonary vasculature were noted on the chest X ray. An M-mode and two-dimensional echocardiogram revealed markedly hypertrophied right and left ventricles with a glistening appearance of the myocardium compatible with amyloid heart involvement. There was a moderate-to-large pericardial effusion and enlargement of both right and left atria. Echogram of the kidneys demonstrated normal-sized kidneys with increased echogenicity suggestive of amyloid involvement.

Hospital course—With the patient under local anesthesia, 500 mL of pericardial fluid was drained through the pericardial window, and a myocardial biopsy was obtained. The myocardial biopsy and subsequent rectal biopsy showed amyloid deposition when stained with thioflavin-T and Congo red. The patient had a progressive downhill course with increasing heart failure and died six months later. An autopsy was not performed.

Case 2

An 86-year-old man presented with a three-to-four month history of progressive weakness, decreased appetite, weight loss, and difficulty in swallowing food.

On admission the patient was noted to be cachectic. His temperature was 37°C, pulse 70 beats/min and regular, and blood pressure 124/70 mm Hg. Multiple ecchymotic and petechial lesions were present on the arms, back, and mouth. Neck veins were flat. Carotid pulse upstroke was normal. A grade II/VI ejection murmur was heard at the second right intercostal space radiating to the carotids. Breath sounds were diminished over both lung bases, and there was 2+ pitting ankle edema bilaterally.

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Pertinent laboratory studies revealed normal WBC count, hemoglobin of 10 g%, and a serum creatinine of 1.6 mg%. Serum antinuclear antibodies and urinalysis were negative.

Chest X ray showed cardiomegaly with bilateral pleural effusions larger on the left than on the right side. An M-mode and two-dimensional echocardiogram revealed marked hypertrophy of the left and right ventricles with a glistening appearance of the myocardium compatible with amyloid infiltration of the heart. Echocardiographic evidence of pulmonary hypertension and right and left atrial enlargement was also present. There was minimal aortic sclerosis without stenosis. Barium swallow showed abnormal coordination of the hypopharyngeal muscles with considerable difficulty in swallowing contrast material. An ECG demonstrated sinus rhythm with marked first degree atrioventricular block, low voltage, and nonspecific ST-wave changes. Biopsy of the skin lesion and staining with Congo red were positive for amyloid.

The patient was treated with furosemide, multivitamins, and folic acid. He died two months later of severe heart failure and malnutrition. An autopsy was not performed.

Discussion

General features of amyloid restrictive cardiomyopathy

Amyloid, initially used by Virchow in 1853 (4) to define the “starch-like” substance deposited in the liver and other organs, has now been demonstrated to result from the deposition of aggregates of twisted β-pleated sheet fibrils of proteins (5). The conditions caused by the deposition of these proteinaceous fibrils have been separated into two major groups: 1) primary amyloidosis or “immunocytic amyloidosis” (5) in which the fibrils consist mainly of light chains (amyloidosis) of either the λ or κ light chain class, and 2) a secondary type or “reactive systemic amyloidosis” in which the fibrils consist primarily of protein A (amyloid A protein) (4). Amyloid fibrils are insoluble, resist proteolytic digestion, replace or destroy normal tissues, and thus give rise to a great variety of clinical syndromes.

Diagnosis—The antemortem diagnosis has improved from 26%, as reported in 1956, to 96% as reported in 1983 (6,7). Factors that helped improve the earlier diagnosis include the increased awareness of the protean systemic features; the presence of predisposing associated illnesses such as multiple myeloma, rheumatoid arthritis, chronic infections, and neoplasms; the more liberal use of biopsies of bone marrow, skin, rectal submucosa, gum, tongue, kidney, liver, and endomyocardium; and the use of appropriate stains such as Congo red and fluorescent thioflavin-T (8).

Macroglossia, an important clinical clue in the diagnosis of amyloidosis, has been reported in as many as 20% of patients, mainly those with “primary amyloid” (6-8). The skin is involved in 25% to 40% of patients with systemic amyloidosis, and a simple needle biopsy of the subcutaneous fat may prove diagnostic (9). Ecchymosis, another diagnostic clue, is caused by light rubbing of the skin, valsalva maneuvers, or postural changes and results from the increased fragility of the superficial arterioles affected by the amyloid deposits.

In patients with suspected heart involvement, myocardial scans with technetium-99 m-pyrophosphate (10,11) have shown abnormally high uptake. Although nonspecific, this test may have diagnostic value. Echocardiography has proven useful, showing increased thickness of the ventricular walls, hypokinesis, small ventricular cavities, and a “granular sparkling” appearance of the myocardium on two-dimensional echocardiograms (12-14).

Although the average age of patients with amyloidosis is 50 years, a 21-year-old patient was reported to have cardiovascular involvement (15), and two children had primary amyloidosis (16,17). Cardiac amyloidosis occurs more frequently with advancing age, and the term “senile amyloidosis” has been suggested by several authors (18) to define the typical small nodules of amyloid visible in the atrial endocardium and small vascular deposits in other viscera of elderly patients (19). The immunological composition of senile amyloidosis differs from other types of amyloidosis.

Cardiovascular manifestations

The cardiovascular manifestations of amyloidosis depend on the amount and location of the deposits giving rise to a variety of clinical syndromes (20) of which restrictive cardiomyopathy and refractory congestive heart failure are most frequently recognized. Presentation with features of ischemic heart disease, orthostatic hypotension, hypertrophic cardiomyopathy, dyssrhythmias, and cerebral amyloid angiopathy has also been seen.

Restrictive cardiomyopathy

Cardiac amyloidosis may mimic constrictive pericarditis on clinical, electrocardiographic, and physiologic grounds (21-23), and patients have been subjected to exploratory thoracotomy with this presumptive diagnosis. In the past the so-called “square root” sign in the ventricular pressure curve configuration (Fig 1) with a ratio between the systolic pressure and the diastolic plateau in the ventricle of more than 1/3 (0.3%) was considered diagnostic of pericardial constriction. This dip-plateau configuration is now generally considered to be a nonspecific hemodynamic finding also encountered in cardiomyopathies of the noncompliant or restrictive types. The hemodynamic findings of a low cardiac index, moderately severe pulmonary hypertension, and the presence of a gradient between the left and right atrial pressure in excess of 9 mm Hg would favor the diagnosis of cardiomyopathy as was suggested by Wood (24) 25 years ago. Whereas Chew et al (12) confirmed

![Fig 1 — Pressure tracings from a 63-year-old man with restrictive amyloid cardiomyopathy in the left ventricle (LV), right ventricle (RV), and right atrium (RA). A dip-plateau configuration of the LV and RV diastolic pressure can be noted as well as elevated pressures (23 mm Hg) throughout.](image-url)
these results and found the left ventricular end-diastolic pressure to exceed that in the right ventricle by at least 10 mm Hg, these values are nearly equal in constrictive pericarditis. Other authors (20,25) have made similar observations, but exceptions showing equal left-sided and right-sided diastolic pressures do occur (Fig 1).

In amyloid heart disease the left ventricular angiogram frequently shows the characteristic "stiff heart syndrome" (12) with decreased ventricular excursion, increased ventricular wall thickness with prominent papillary muscles, and a small left ventricular cavity (Fig 2).

The echocardiogram is important in differentiating amyloid heart disease from other cardiomyopathies and from constrictive pericarditis (12-14). In amyloidosis left ventricular diastolic size may be normal, and generalized decreased contractility and diffusely increased thickness of both ventricular walls, septum, and valves occurs (26). A small-to-moderate pericardial effusion is common (Fig 3). Additional echocardiographic findings commonly shared with other infiltrative cardiomyopathies include a diminished rate of early diastolic mitral valve closure with marked flattening of the anterior leaflet diastolic slope secondary to decreased ventricular compliance. The "granular sparkling" (Fig 4) appearance of thickened ventricular walls and septum is striking on two-dimensional images (27). In contrast, constrictive pericarditis may show paradoxical septal motion,

Fig 2—Representative frame of angiocardiograms with contrast material outlining, a very thick left ventricular wall (LV) in a 72-year-old man with amyloidosis (LA = left atrium and RA = right atrium).

Fig 3—M-mode echocardiogram of left ventricle and mitral valve of a patient with amyloidosis showing increased thickness and decreased contractility of the ventricular septum (VS) and posterior wall (PW) and mild to moderate pericardial effusion (PE). (RVW = right ventricular wall, and MV = mitral valve.)
and the increased thickness of the free left ventricular wall and septum is not seen. Recently, the determination by ECG and echocardiography of an inverse voltage/mass relation was helpful in distinguishing amyloidosis from constrictive pericarditis (28). The magnitude of the increase of the mean left ventricular wall thickness and the reduction in its shortening have value in predicting survival (29). On occasion amyloid heart disease may mimic hypertrophic cardiomyopathy by showing asymmetric septal hypertrophy and systolic anterior motion of the anterior mitral leaflet (30,31); the differential diagnosis is of importance since calcium blockers are contraindicated in the former. Computed tomography has confirmed the echocardiographic findings showing diffuse myocardial thickening on post-contrast tomograms (32).

Refractory congestive heart failure

Refractory congestive heart failure is the most frequent manifestation in patients with extensive cardiac amyloid deposits. Rukavina et al (6) found 92 of 142 patients (64.7%) with significant congestive failure. In a review of 42 patients, Cohen (33) found clinical cardiac disease in 80% with primary amyloid and 60% with secondary amyloid. Buja et al (15) found significant congestive heart failure in 46% of 339 cases, and Kyle and Greipp (7) found significant congestive heart failure in 34% of 229 patients. Generally, this group of patients requires large doses of diuretics and frequent thoracenteses. They are highly susceptible to digitalis toxicity and soon become totally unresponsive to treatment. Newer modalities of preload and afterload reduction therapy have to be approached carefully, if at all, in view of the tendency toward postural hypotension, impaired vascular reactivity, and normal or small left ventricular diastolic volume. A typical example of this clinical presentation, a 72-year-old man who died after ten months of progressive intractable failure, is shown in Fig 5.

Prognosis—The prognosis for patients with amyloid heart disease remains poor. Average survival ranges from 12 to 14.7 months after histologic diagnosis (7). No effective treatment is available. The prognosis in secondary amyloidosis is somewhat better, depending on control of the underlying disease. One report (34) shows that eight of nine patients with “secondary amyloidosis” survived for 24 months following diagnosis.

Fig 4—Two-dimensional apical four chamber view. Both right and left ventricular walls are markedly hypertrophied with glistening appearance of intraventricular septum (arrow). The right and left atrial chambers are dilated, and a small amount of pericardial effusion is present. (PE = pericardial effusion, IVS = intraventricular septum, LA = left atrium, LV = left ventricular chamber, LVW = left ventricular wall, RA = right atrium, RV = right ventricular chamber, RVW = right ventricular wall, MV = mitral valve, and TV = tricuspid valve.)
Less common causes of restrictive cardiomyopathy

Among the other restrictive-infiltrative cardiomyopathies, cardiac involvement in hemochromatosis is common. Heart failure secondary to the congestive dilated type was found as the cause of death in nearly one-half of the cases reported in a large series in 1955 (35). Although only a few cases presenting as the restrictive type have been reported, the importance of keeping this etiology in the differential diagnosis cannot be overemphasized since it is the only reversible cause among this group (36).

Myocardial involvement is accepted as a constant feature in Fabry's disease (37), and the presence of glycolipid deposits in the myocardium has the potential to cause a decrease in compliance with restriction. The most common cardiovascular manifestations include systemic hypertension with renal failure, valvular involvement with mitral regurgitation (38), coronary artery narrowing with myocardial ischemia and infarction, and cerebrovascular insufficiency with cerebral infarctions (39).

Endomyocardial fibrosis is a progressive restrictive endomyocardial disease of uncertain etiology seen in Africa (40) and in tropical regions, but isolated cases have occurred in temperate zones (41). In some cases the prognosis can be altered by surgical excision of some of the fibrotic endocardium and valve replacement (41), while heart transplantation could be an alternative in selected cases.

Fig 5—Gross specimen of a typical example of cardiac amyloidosis. Same patient as in Fig 2.