Diagnosis and Management of the Cardiac Amyloidoses

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Cardiac amyloidosis is a manifestation of one of several systemic diseases known as the amyloidoses.[1,2] This uncommon disease is probably underdiagnosed, and even when a diagnosis of amyloidosis of the heart is made, the fact that there are several types of amyloid, each with its unique features and treatment, is often unrecognized. This can lead to errors in management and in the information conveyed to the patient. The purpose of this review is to familiarize the reader with the clinical features of amyloidosis and to address the approach to the patient with this disease, focusing on the various types of amyloidosis, their prognosis and treatment.

The common feature of this group of diseases is the extracellular deposition of a proteinaceous material that, when stained with Congo red, demonstrates apple-green birefringence under polarized light and that has a distinct color when stained with sulfated Alcian blue (Figure 1). Viewed with electron microscopy, the amyloid deposits are seen to be composed of a β-sheet fibrillar material (Figure 2). These nonbranching fibrils have a diameter[3] of 7.5 to 10 nm and are the result of protein misfolding.[4,5] Cardiac involvement in amyloidosis may be the predominant feature or may be found on investigation of a patient presenting with another major organ involvement. The presence of cardiac amyloidosis and its relative predominance varies with the type of amyloidosis. Thus, senile systemic amyloidosis and some forms of transthyretin amyloidosis invariably affect the heart, whereas cardiac involvement ranges from absent to severe in amyloidosis derived from a light-chain precursor (AL amyloidosis). Secondary amyloidosis almost never affects the heart in any clinically significant manner.[6] The specific composition of the fibrils differs in the different types of amyloid[7] and are outlined in the Table. Both on the basis of common usage and for the sake of simplicity, "cardiac amyloidosis" is used here to describe involvement of the heart by amyloid deposition, whether as part of systemic amyloidosis (as is most commonly the case) or as a localized phenomenon.

Regardless of the underlying pathogenesis of amyloid production, cardiac amyloidosis is a myocardial disease characterized by extracellular amyloid infiltration throughout the heart.[8] Amyloid deposits occur in the ventricles and atria, as well as perivascularly (particularly in the small vessels) and in the valves. The conduction system may also be involved. The infiltrative process results in biventricular wall thickening with nondilated ventricles. The ensuing elevation of pressure in the thin-walled atria is associated with atrial dilation, despite thickening of the atrial walls by amyloid deposition.

Because cardiac involvement very frequently coexists with significant dysfunction of other major organs, the initial suspicion of cardiac amyloidosis is often triggered by the recognition that the heart disease is part of a multiorgan disorder. Conversely, if other organ dysfunction such as nephrotic syndrome predominates, recognition of a cardiac problem may be delayed because of the focus on these organ systems. Because the clinical manifestations and progression of the disease may vary considerably on the basis of the amyloid fibril precursor, the various types of amyloid heart disease are dealt with individually in this review.

AL Amyloidosis

The commonest form of amyloidosis is that associated with a plasma cell dyscrasia. Amyloid is produced from clonal light chains, so the disease is referred to as AL amyloidosis. The commonest plasma cell dyscrasia is multiple myeloma, and AL amyloidosis overlaps with it. However, only a minority of myeloma patients develop amyloidosis, and most patients with AL amyloidosis do not have multiple myeloma. Although AL amyloidosis is considered an uncommon disease, it has an incidence similar to better-known diseases such as Hodgkin disease or chronic myelocytic leukemia,[9] with an estimated 2000 to 2500 new cases annually in the United States. The heart in AL amyloidosis is affected in close to 50% of cases (Figure 3), and congestive heart failure is the presenting clinical manifestation in about half of these patients.[10] Even among patients in whom another organ system dysfunction predominates, the presence of cardiac amyloidosis is frequently the worst prognostic factor.[11] Once congestive heart failure occurs, the median survival is <6 months in untreated patients[10,11]; therefore, early recognition of the disease and prompt initiation of therapy is critical.

Clinical Features

The typical patient with heart failure resulting from AL amyloidosis frequently presents with rapidly progressive signs and symptoms. Progressive dyspnea is common, almost always associated with evidence of elevated right-sided filling pressure. Peripheral edema may be profound, and in
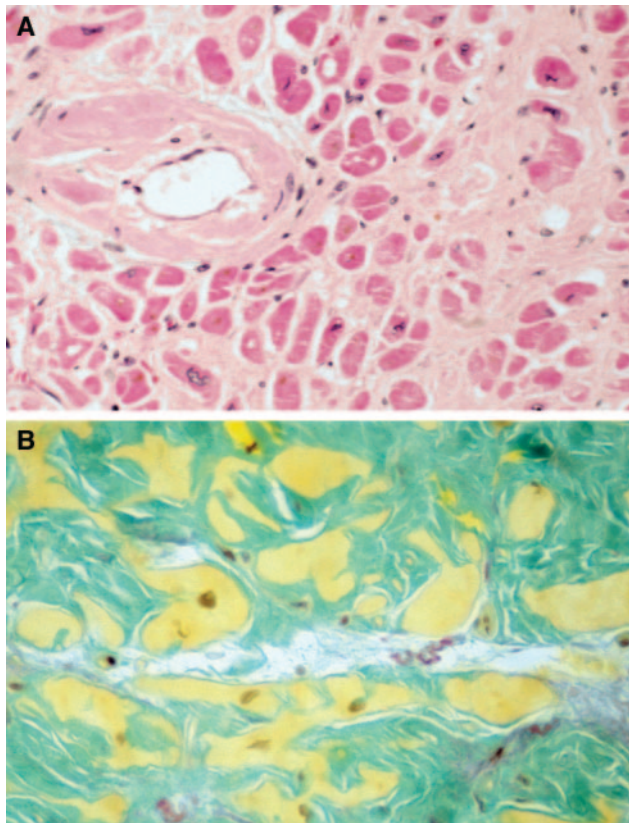
Figure 1. A, Endomyocardial biopsy specimen, stained with hematoxylin and eosin, from a patient with cardiac amyloidosis. The amyloid stains light pinkish red and is seen as an amorphous material that separates the darker staining myocytes. B, Staining of the tissue from the same patient using sulfated Alcian blue. The amyloid stains turquoise green and the myocytes stain yellow, characteristic of amyloid. Courtesy of Dr Gayle Winters, Brigham and Women's Hospital. Boston, Mass.
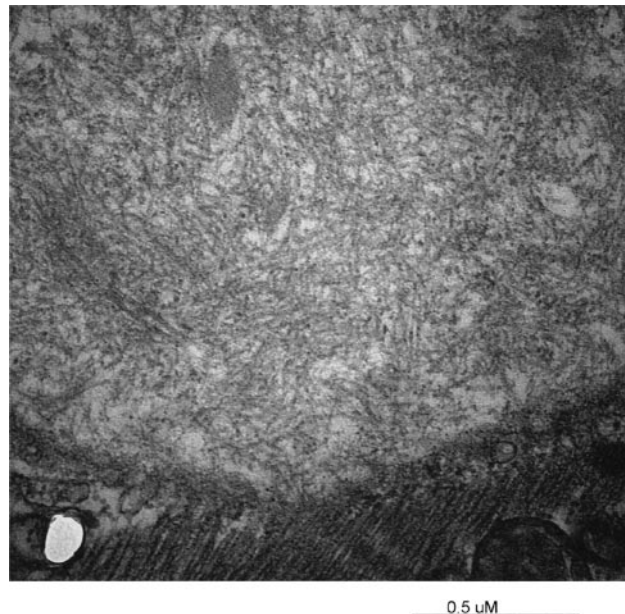

Figure 2. Myocardial biopsy in cardiac amyloidosis viewed under electron microscopy. At the lower portion of the figure is the edge of a myocyte; above it is a mass of amyloid fibrils. Original magnification ×15 000.

late-stage disease, ascites is not uncommon. Weight loss, which is common, may represent the effects of the systemic disease or may be a manifestation of cardiac cachexia. Patients with cardiac amyloidosis may present with chest discomfort. Most commonly, this is not typical of angina and is associated with congestive heart failure, but typical angina can occur because of involvement of the small vessels of the heart.[12] Imaging studies may be positive, leading to cardiac catheterization with apparently normal epicardial coronary arteries on coronary angiography. Myocardial flow reserve in such patients is impaired[13] because of the small vessel involvement, and a small but persistent elevation in serum troponin may be present, leading to a misdiagnosis of non–Q-wave infarction.[14–18] Presumably, the troponin elevation represents ongoing myocyte necrosis, and it has been shown be a negative prognostic factor.[15–17] Small vessel cardiac amyloid may occur in the absence of wall thickening on the echocardiogram, although there is often a mild elevation of left ventricular filling pressure, suggesting diastolic abnormalities of the ventricle. This presentation of amyloidosis is rare; it is seen in only 1% to 2% of patients with cardiac involvement.

Although sudden death is common in AL amyloidosis, ventricular arrhythmias are an uncommon presenting fea-

ture.[19] Monitored sudden death in severe cardiac amyloid is often found to have been due to electromechanical dissociation rather than ventricular arrhythmia; in this, amyloidosis is similar to other forms of very severe heart disease.[20] The management of syncope is discussed below, but a careful history may help distinguish arrhythmia-induced syncope from other sources such as autonomic neuropathy. Sustained ventricular tachycardia or resuscitation from ventricular fibrillation is a rare presenting manifestation that occurs in patients with less severe heart failure, presumably because patients with more advanced disease do not survive an initial episode.

Fewer than 5% of patients with AL amyloidosis involving the heart have clinically isolated cardiac disease.[10] Complaints of noncardiac symptoms should be sought because their presence is a clue to the systemic nature of the disease. The patient should be carefully questioned about dizziness and syncope with emphasis on the positional nature of any such symptoms because there are several potential mechanisms of syncope in amyloidosis.[20] Dermatological manifestations such as easy bruising and periorbital purpura may occur[21,22]; the latter is virtually pathognomonic of the disease. Macroglossia, characterized by a stiffening and enlargement of the tongue, often with tooth indentation, is seen in 10% to 20% of patients and sometimes produces dysphonia or dysgeusia. It may occasionally be profound enough to interfere with eating, swallowing, or breathing. A subtle change in the voice (particularly hoarseness toward the end of the day), a quite common complaint, probably represents vocal cord involvement.[23] Neurological symptoms include carpal tunnel syndrome and peripheral and autonomic neuropathy. Right upper quadrant discomfort may be due to hepatic congestion or with amyloid hepatic infiltration.[24] Carpal tunnel syndrome often precedes other organ involvement by a few

Summary of the Main Forms of Amyloidosis That Affect the Heart

Nomenclature	Precursor of Amyloid Fibril	Organ Involvement	Treatment	Comment
AL	Immunoglobulin light chain	Heart Kidney Liver	Chemotherapy	Plasma cell dyscrasia related to (but usually not associated with) multiple myeloma
		Peripheral/autonomic nerves Soft tissue Gastrointestinal system		Heart disease occurs in 1/3 to 1/2 of AL patients; heart failure tends to progress rapidly and has a very poor prognosis
ATTR (familial)	Mutant transthyretin	Peripheral/autonomic nerve Heart	Liver transplantation ? New pharmacological strategies to stabilize the TTR	Autosomal dominant; amyloid derived from a mixture of mutant and wild-type TTR; if present before, cardiac amyloid may progress despite liver transplantation
AApoA1	Mutant apolipoprotein	Kidney Heart	? Liver transplantation	Kidney disease is the commonest presentation; heart involvement rare
Senile systemic amyloid	Wild-type transthyretin	Heart	Supportive ? New pharmacological strategies to stabilize the TTR.	Almost exclusively found in elderly men; slowly progressive symptoms
AA	Serum amyloid A	Kidney Heart (rarely)	Treat underlying inflammatory process	Heart disease rare and, if present, rarely clinically significant
AANP	Atrial natriuretic peptide	Localized to the atrium	None required	Very common; may increase risk of atrial fibrillation and/or be deposited in greater amounts in the fibrillating atrium

years, and a history of surgical carpal tunnel release is not uncommon. Although widespread lymphadenopathy is present in only a small minority of patients, submandibular swelling caused by lymph node and salivary gland infiltration is not uncommon and often is accompanied by macroglossia. Nail dystrophy (brittle and slow-growing nails) is sometimes seen, particular in the hands, and when present is a clue to the systemic nature of the cardiac disease.[25]

The cardiovascular physical examination in a patient with heart failure resulting from amyloidosis usually reveals sinus rhythm with a normal to low radial pulse volume, although atrial arrhythmias (most commonly atrial fibrillation) occur in 10% to 15% of patients. When present, atrial fibrillation is associated with a very high incidence of thromboembolism. The jugular venous pressure is often markedly elevated, and the waveform is generally unrevealing, but occasionally, a prominent X and Y descent is noted.[26,27] In contrast to constrictive pericarditis, with which it may be confused, Kussmaul's sign is very rarely present. The apex beat is frequently impalpable and, when it can be felt, is generally not displaced. The first and second heart sounds are usually normal in character. A left ventricular third heart sound is rarely heard, but in advanced cases, a right ventricular S3, which often is associated with right ventricular dilation and dysfunction on the echocardiogram, may be heard best at the left parasternal edge. Despite the increased stiffness of the left ventricle, a fourth heart sound is almost never present, possibly because of atrial dysfunction resulting from amyloid infiltration.[28,29] Blood pressure is often low, even in the absence of postural hypotension; this may represent decreased cardiac output in conjunction with early autonomic dysfunction. Blood pressure may fall further on standing, particularly if autonomic neuropathy is present,[30] and should be measured in the supine, seated, and standing positions both

immediately after standing and after at least 2 minutes because the systolic pressure may continue to drift down in the presence of autonomic dysfunction. Hypertension is unusual, and in patients with a history of hypertension, "spontaneous" resolution of hypertension over the preceding few months is common. Examination of the chest may reveal bilateral pleural effusions, but rales are rarely present, even in association with advanced heart failure. The pleural effusions in a patient with AL amyloidosis may simply represent heart failure, but patients with cardiac amyloid may also have pleural infiltration with amyloid, resulting in disproportionately large effusions that are diuretic resistant and rapidly recur after a pleural tap.[31]

Splenomegaly is rare, whereas hepatomegaly is common and is due either to congestion from right heart failure or to amyloid infiltration.[32,33] When extensive amyloid infiltration of the liver is present, the organ is rock-hard and not tender, often extending several centimeters below the costal margin and crossing the midline. This contrasts with the firm, sometimes tender, liver of heart failure. Peripheral edema may be profound, and if it appears disproportionate to the degree of heart failure, the possibility of associated nephrotic syndrome should be considered. In addition to autonomic dysfunction, amyloidosis may cause a sensory neuropathy, and the patient may complain of numbness or painful extremities.[11] A history of weight loss is common, and proteinuria, frequently reaching nephrotic range ($\geq$3 g/24 h), coexists with cardiac disease in 30% to 50% of cases.

Low voltage on the ECG (defined as all limb leads <5 mm in height) is found in a high proportion of patients and is often associated with extreme left- or right-axis deviation (Figure 4). Although voltage criteria for left ventricular hypertrophy have been described in the precordial leads of some patients with AL amyloidosis, increased limb lead voltage is ex-
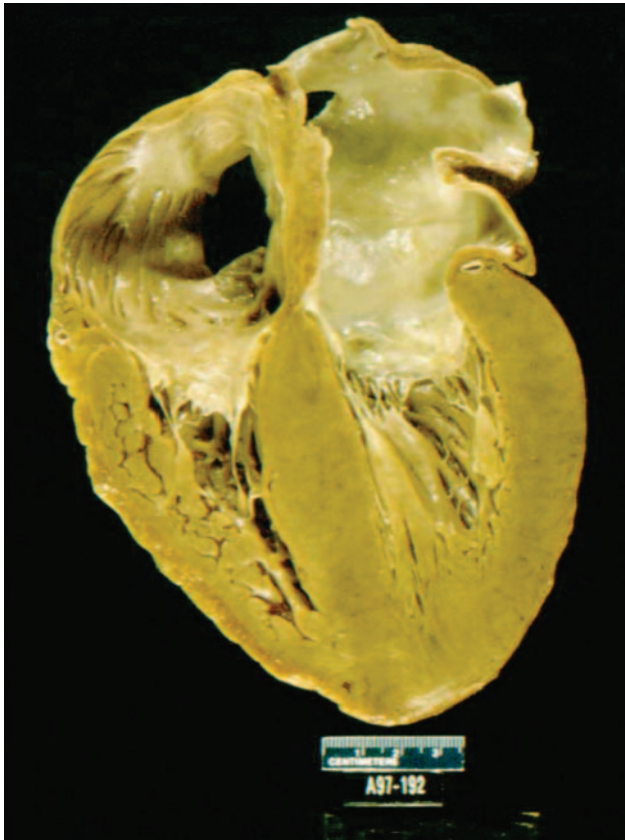
Figure 3. Autopsy specimen of a heart with extensive amyloid infiltration. Note the nondilated ventricles with biventricular thickening and the biatrial enlargement with thickening of the atrial septum. Atrial infiltration leads to atrial failure and can be associated with atrial thrombi.

tremely uncommon.[34] When increased limb or precordial lead voltage is present, it is frequently a result of an unrelated coexistent condition such as hypertension. Interestingly, right bundle-branch block is uncommon, and left bundle-branch block is very unusual unless it is a preexisting condition.[10] The reason for the virtual absence of left bundle-branch block in patients with AL amyloidosis is unclear. However, because amyloid deposition affects the heart uniformly, the more vulnerable right bundle is anticipated to be involved before the left bundle, so sparing of the right bundle with complete left bundle-branch block would be very unlikely.

The echocardiographic features of advanced cardiac AL amyloidosis are distinctive. The initial descriptions concentrated on patients with severe cardiac disease and depicted nondilated ventricles with concentric left ventricular thickening, right ventricular thickening, prominent valves, and infiltration of the atrial septum. The myocardial texture was abnormal and described as "granular sparkling."[26,35–37] Subsequent changes in image processing produced a myocardial appearance that is less "granular" in appearance, but advanced amyloid heart disease still demonstrates an increased echogenicity of the myocardium and often of the valves (Figure 5). The classic appearance of a restrictive pattern by Doppler echocardiography and associated increased echogenicity, biventricular thickening, and valvular infiltration is limited to patients in the end stage of the disease. More commonly, the ventricle appears thickened to a degree that is disproportionate to the degree of current or prior hypertension, and the Doppler features depend on the stage of the disease, with serial studies demonstrating a progression of diastolic dysfunction as myocardial infiltration progresses.[36] The left ventricular ejection fraction is normal or nearly normal until late in the disease, and because the left ventricle does not dilate, a reduced ejection fraction is associated with a substantially reduced stroke volume. Because the thickening of the ventricle in amyloidosis is due to myocardial infiltration rather than hypertrophy, the ECG limb lead voltage tends to decrease as the ventricle thickens. This results in a decreased ratio of voltage to left ventricular mass, a finding that strongly suggests an infiltrative cardiomyopathy, of which amyloidosis is the commonest cause.[38] In $\approx 5\%$ of patients with cardiac amyloidosis, left ventricular infiltration may mimic hypertrophic cardiomyopathy on the echocardiogram.[10,39,40] These patients often have normal or even mildly hyperdynamic left ventricular function with normal voltage on the ECG. Associated postural hypotension is common in these patients, and low afterload may in part account for the normal to increased ejection fraction. Unlike true hypertrophic cardiomyopathy, ventricular hypertrophy on the ECG limb leads is almost never seen and systolic anterior motion of the mitral valve is uncommon, although chordal anterior motion may be present with an associated outflow tract murmur.

Doppler echocardiography is also useful in cardiac amyloidosis. In advanced disease, there is a restrictive transmitral flow pattern characterized by a short deceleration time of the E wave and a low-velocity A wave, with associated abnormalities in pulmonary venous flow.[26,41,42] The decreased transmitral A wave in AL amyloidosis is related not only to late-stage restrictive pathophysiology but also to atrial amyloid infiltration, which results in intrinsic atrial dysfunction[28,29,43–46]; thus, a normal deceleration time can be seen in association with a diminutive A wave. Further insights into cardiac function in AL amyloidosis can be gained by pulsed tissue Doppler imaging, which can demonstrate the presence of diastolic dysfunction more accurately than transmitral and pulmonary flow and can provide evidence of longitudinal systolic impairment before the ejection fraction becomes abnormal.[47,48] Strain and strain rate imaging are even more sensitive than tissue Doppler, demonstrating long-axis dysfunction in early cardiac amyloidosis and often showing disproportionate impairment of longitudinal contraction despite apparently preserved fractional shortening (Figure 6). In addition to giving sensitive information about myocardial function, tissue Doppler and strain and strain rate imaging may have potential for evaluating the prognosis in AL amyloidosis.[47–49]

Other imaging modalities such as cardiac magnetic resonance show promise for diagnosing cardiac amyloidosis if echocardiographic features are suspicious.[50] Recent descriptions of cardiac MRI in advanced cardiac amyloidosis show an unusual pattern characterized by global subendocardial late gadolinium enhancement and associated abnormal myocardial and blood-pool gadolinium kinetics.[50] However the
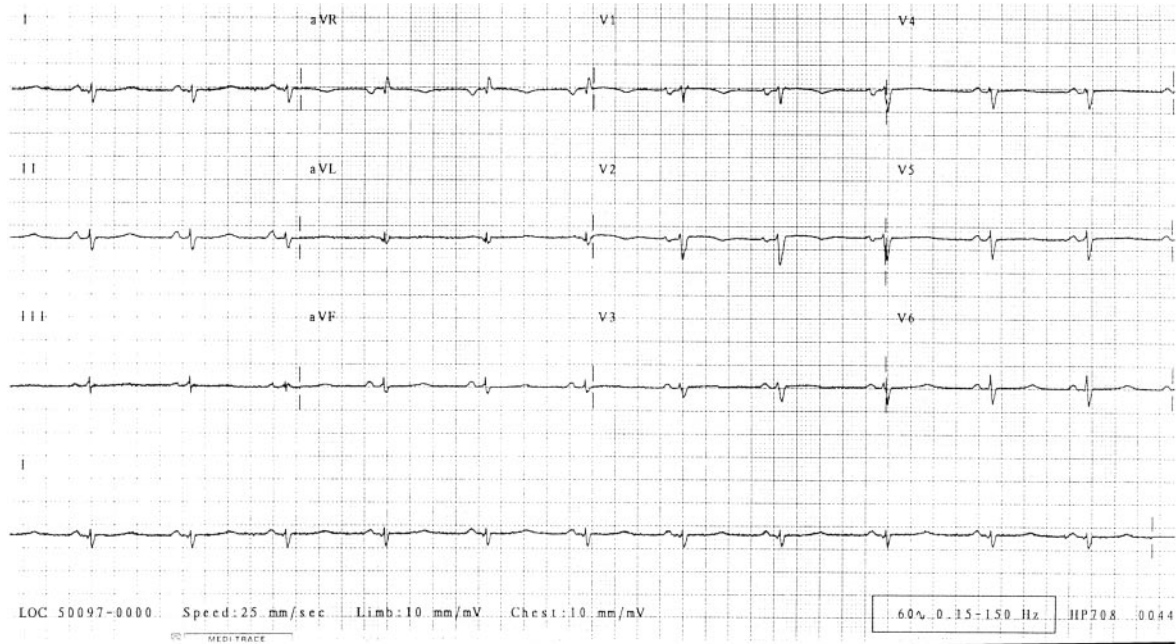
Figure 4. Typical appearance of the ECG in AL amyloidosis of the heart. There is low voltage with an abnormal axis and poor R-wave progression in the precordial leads. The association of low voltage of this degree with thickening of the left ventricle on echocardiogram is highly suggestive of an infiltrative cardiomyopathy.

sensitivity of this technique for detecting early disease is not known, and the specificity of the described abnormalities is likely to be low in an unselected population of patients.[51]

Cardiac Catheterization

The noninvasive imaging features of amyloidosis described above are usually sufficient to strongly suspect the correct diagnosis. Thus, cardiac catheterization, other than to obtain an endomyocardial biopsy, to better assess hemodynamics, or to evaluate coronary anatomy, currently is of limited value in the routine evaluation of a patient with suspected amyloidosis. Nevertheless, many patients with an eventual diagnosis of cardiac amyloidosis undergo cardiac catheterization during the workup, and if a full hemodynamic study is done, careful examination of the pressure tracing may provide clues to the diagnosis. Impaired ventricular filling in advanced cardiac amyloidosis is associated with an elevated left ventricular end-diastolic pressure, and the pressure tracings may reveal a dip-and-plateau waveform[52] (Figure 7). It has been suggested that, unlike constrictive pericarditis, amyloidosis is associated with a left ventricular end-diastolic pressure that exceeds right ventricular end-diastolic pressure by at least 7 mm Hg.[52] However, this is not always the case, and both disorders may manifest a dip-and-plateau diastolic pressure tracing with pressure equalization.[53,54] A pulmonary artery systolic pressure >50 mm Hg is rarely seen in "uncomplicated" constrictive pericarditis but may occur in cardiac amyloidosis,[55] and the finding of an inspiratory rise in right ventricular pressure with an associated fall in left ventricular pressure, representing ventricular interdependence, has been proposed as a specific sign of constrictive pericarditis that distinguishes it from restrictive cardiomyopathy.[56] However, although certain hemodynamic clues suggest one diagnosis or the other,

overlap remains, and the diagnosis should not be made on hemodynamic data alone. In suspected cases of amyloidosis, clinical examination and review of the echocardiogram are generally extremely valuable in favoring a diagnosis of cardiac amyloidosis if present and should never be omitted.

Tissue Diagnosis

The diagnosis of amyloidosis requires a tissue biopsy that demonstrates apple-green birefringence when stained with Congo red and viewed under a polarizing microscope. Sulfated Alcian blue is an alternative stain with a high specificity for amyloid[57] (Figure 1). It is not necessary to biopsy the heart if the echocardiographic appearances are typical for cardiac amyloidosis, providing that a histological diagnosis has been made from another tissue. Fine-needle aspiration of the abdominal fat is a simple procedure that is positive for amyloid deposits in >70% of patients with AL amyloidosis.[58,59] If the diagnosis is not confirmed by biopsy of another tissue, endomyocardial biopsy is a safe and relatively simple procedure in skilled hands; it is virtually 100% sensitive because the amyloid is widely deposited throughout the heart.[60,61] In patients with known amyloid deposits in other organs and a history of poorly controlled hypertension, there may be uncertainty as to whether ventricular thickening represents amyloid infiltration or hypertensive heart disease. In such cases, endomyocardial biopsy may be helpful to determine whether the heart is infiltrated with amyloid.

Once a tissue diagnosis of amyloid has been established, the confirmation that this is AL amyloid requires a search for the presence of a plasma cell dyscrasia. Serum and urine immunofixation should be performed rather than serum and urine electrophoresis because the amount of serum or urine paraprotein may be small and immunofixation is a much
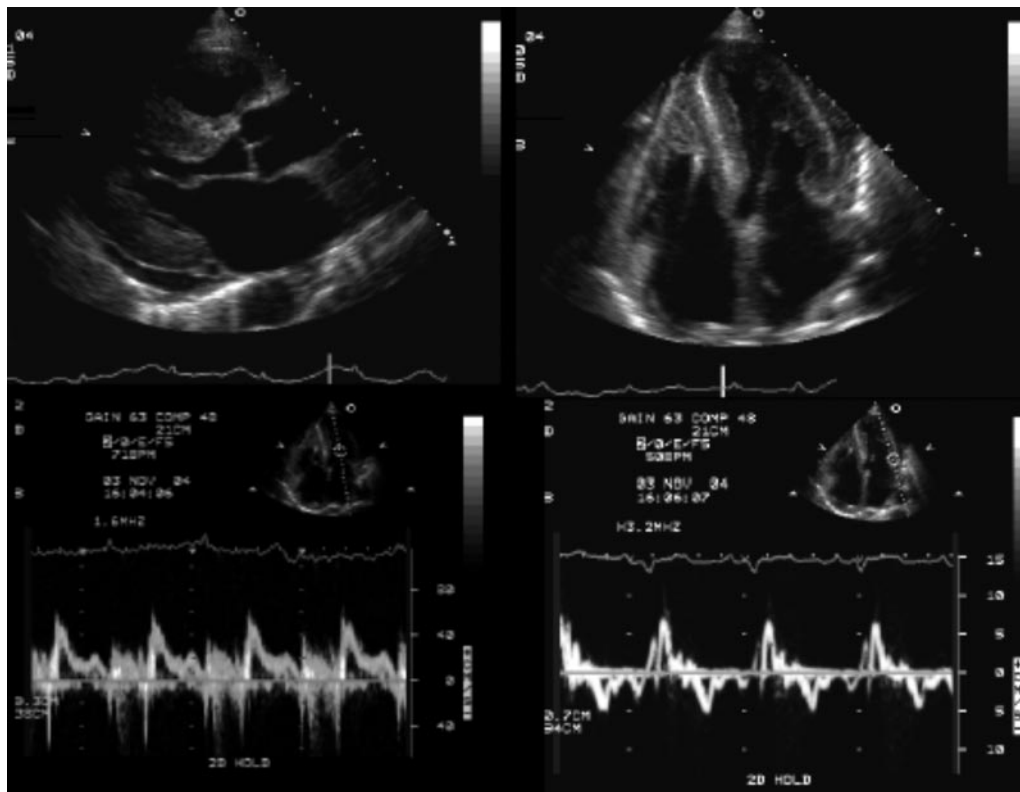
Figure 5. Selection of echocardiographic images from a patient with severe AL cardiac amyloidosis. Top left, Parasternal long-axis view showing concentric left ventricular thickening with a pericardial effusion. The echogenicity of the myocardium is increased, and the valves are seen unusually clearly suggestive of infiltration. Top right, Apical 4-chamber view showing normal biventricular dimensions and biatrial enlargement. The atrial septum is thickened, and a pacemaker/ICD lead is seen in the right ventricle. Bottom left, Transmitral Doppler flow showing a restrictive pattern with a short deceleration time and reduced A-wave velocity. Bottom right, Tissue Doppler recorded from the lateral mitral annulus. There is reduced myocardial velocity throughout systole and both phases of diastole, compatible with a restrictive pathophysiology.

more sensitive test. Even more sensitive is the recently introduced serum free-light-chain assay, which can detect circulating free light chains with >10-fold sensitivity than immunofixation[62,63] This is a quantitative test. In AL amyloidosis, free lambda or (less commonly) free kappa levels are elevated. The normal serum range of kappa free light chains is 3.3 to 19.4 mg/dL; for lambda, 5.7 to 26.3 mg/dL with a kappa-to-lambda ratio of 0.26 to 1.65.[62,63] It is important to assess the ratio of kappa to lambda free light chains because they are renally excreted and renal impairment elevates kappa and lambda levels without changing the ratio. In AL amyloidosis with renal impairment, elevated levels of both free lambda and free kappa will be seen because renal impairment reduces light-chain excretion. However, the kappa-to-lambda ratio remains abnormal and should always be calculated in addition to the absolute values. A kappa-to-lambda ratio <0.26 strongly suggests the presence of a population of plasma cells producing clonal lambda free light chains, whereas a ratio >1.65 suggests production of clonal kappa free light chains. In 110 patients with AL amyloidosis, serum immunofixation was positive in 69%, urine immunofixation was positive in 83%, and the kappa-to-lambda ratio was abnormal in 91%. The combination of an abnormal kappa lambda ratio and a positive serum immunofixation identified 99% of patients with AL amyloidosis.[64] A bone marrow

biopsy is mandatory to assess the percentage of plasma cells, and immunoperoxidase staining will determine whether the abnormal plasma cells are producing kappa or lambda light chains.[65] Bone marrow biopsy is also required to exclude myeloma and other less common disorders that can be associated with AL amyloidosis such as Waldenstrom's macroglobulinemia. It is important to recognize that a monoclonal band present on serum immunofixation may be seen as an apparently incidental finding in 5% to 10% of patients >70 years of age ("monoclonal gammopathy of uncertain significance").[66] The serum free-light-chain assay is often normal in such cases,[67] but if any doubt exists about the clinical picture, further testing must be done to exclude familial or senile forms of amyloid. Such testing includes either special staining techniques of the amyloid such as immunogold electron microscopy[68–70] or genetic testing to rule out familial forms of amyloid.[71]

Management
Management of cardiac amyloidosis requires a 2-fold approach: management of the cardiac-related symptoms and treatment of the underlying disease. The mainstay of the treatment of heart failure in AL amyloidosis is the use of diuretics; higher doses than anticipated may be required if the albumin level is low as a result of concomitant nephrotic syndrome. In a patient with anasarca, intravenous diuresis is
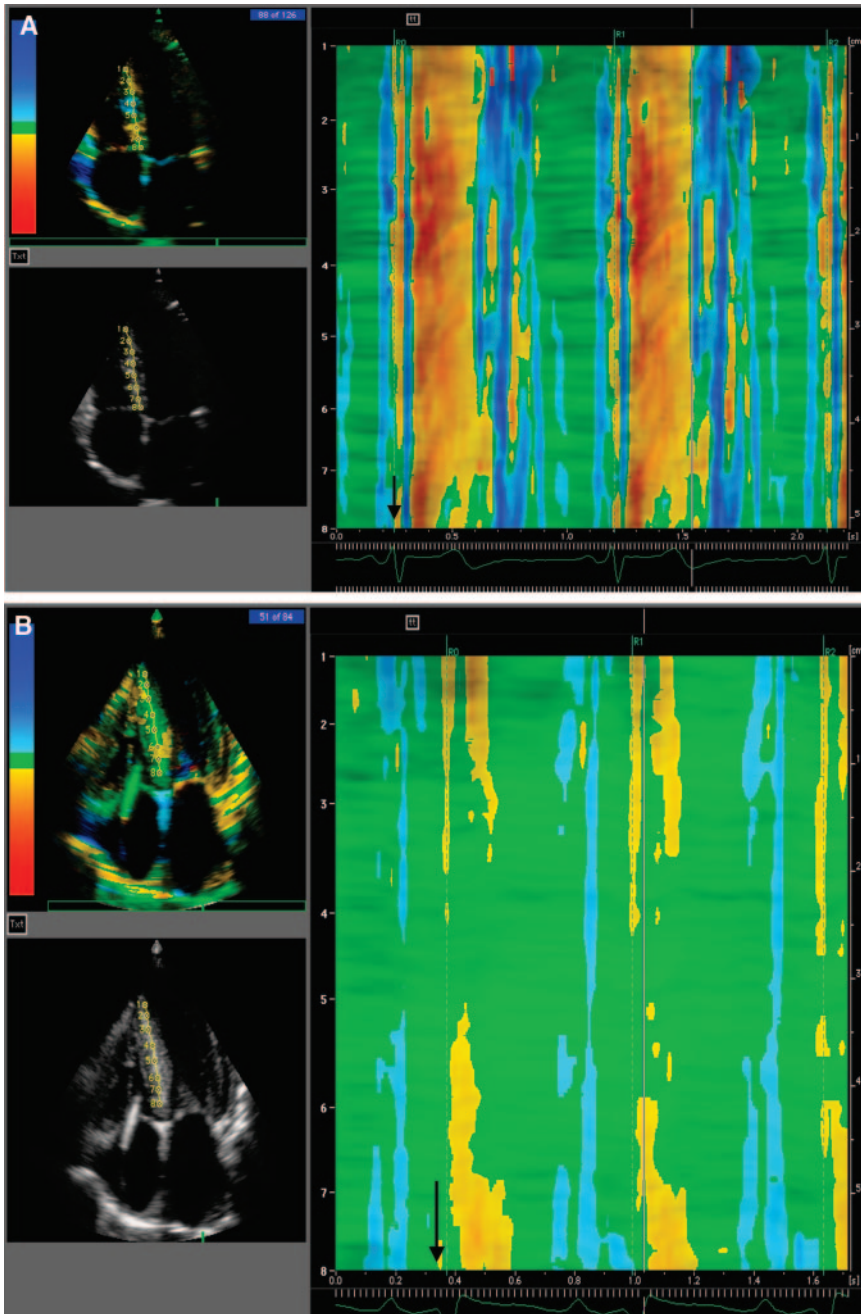
Figure 6. Color-coded map of myocardial long-axis strain (percentage change in length) recorded from the ventricular septum. Note the top left image recorded in the apical 4-chamber view, with a bar representing a key to the color coding. The numbers on the ventricular septum correspond to the numbers on the map; the apical septal strain is represented on the top part of the map, and the base is represented at the bottom. A, Recording from a normal subject. Immediately after the onset of systole (arrow indicates R wave), there is a brief light blue vertical line, representing isovolumic systole, followed by a broad, uniform orange/red-coded band representing ventricular contraction. This is followed by early relaxation in blue, diastasis in green, and a late diastolic relaxation represented in a second brief blue area. B, Strain map from a patient with cardiac amyloid, heart failure, and a mildly reduced ejection fraction. The arrow again represents the onset of the QRS complex. There is almost no longitudinal motion in any portion of the septum, with the large area of green representing absent motion and the brief patches of color representing slight elongation in late diastole (light blue). Systolic strain is almost absent except for some severely reduced longitudinal motion at the base and a brief, reduced contraction in midsystole near the apical septum (yellowish orange.)

often needed because absorption of diuretics may be impaired. Resistant, large, pleural effusions may indicate the presence of pleural amyloid.[31] They may necessitate recurrent pleural taps and occasionally require pleurodesis. ACE inhibitors and angiotensin II inhibitors are very poorly tolerated in subjects with AL amyloidosis; even small doses may result in profound hypotension. If an attempt is made to introduce them, it should be done with extreme caution, ideally in a monitored setting and starting with a very low dose of captopril, chosen because of its relatively short duration of action. The extreme hypotensive response seen in some patients is probably a function of autonomic neuropathy because angiotensin receptors play a role in the maintenance of blood pressure and, in the setting of autonomic nervous system dysfunction, their role may be much greater than

normal. There are no data on the effectiveness of β-blockade on survival in amyloidosis, but the use of β-blockers may be limited because of refractory heart failure or disease-related severe hypotension. Calcium channel blockers are contraindicated because they often produce a significant negative inotropic effect.[72,73] On occasion, I have been able to maintain patients on oral nitrates for preload reduction, but they often have only a minor benefit and require cautious introduction and gradual dose escalation. There are no published data on the use of intravenous inotropic or vasodilator drugs in patients with severe heart failure resulting from amyloidosis. However, I have found renal-dose dopamine (1 to 3 μg · kg^{-1} · min^{-1}) to be a helpful adjunct for the treatment of anasarca, provided that renal function is unimpaired. Digoxin, used for its inotropic properties, is of little value in amyloid-

Figure 7. Simultaneous right and left ventricular pressure tracings in a patient with AL amyloidosis and atrial fibrillation. After a longer R-R interval, several beats show a dip and plateau morphology of the diastolic wave form with equalization of right and left ventricular pressures, mimicking constrictive pericarditis.

osis, and these patients may be at increased risk of digoxin toxicity because the drug binds avidly to amyloid fibrils.[74] As a result of the binding to myocardial amyloid, cardiac digoxin levels may be elevated, and digoxin toxicity can exist even in the setting of "therapeutic" serum digoxin levels. Nevertheless, when atrial fibrillation with a rapid ventricular response is present, digoxin (administered cautiously) can be usually safely and successfully used.

The value of routine anticoagulation in patients with severe heart failure of any cause is uncertain. However, unless major contraindications exist, the presence of atrial fibrillation in AL amyloidosis is a very strong indication for warfarin anticoagulation because of a very high rate of thromboembolic events. In severe cardiac amyloidosis, the atrium is infiltrated, and dysfunctional[29] and atrial thrombi may be present even during sinus rhythm.[43,45] It is therefore prudent to anticoagulate patients with AL amyloidosis even if they are in sinus rhythm if there is a small transmitral A wave seen on transthoracic echocardiography ($\leq$20 cm/s). Transesophageal echocardiography may be helpful in selected patients with apparently poor atrial function[45] and, even when the patient in sinus rhythm, may reveal a left atrial appendage thrombus, left atrial appendage spontaneous echo contrast, or markedly decreased atrial appendage Doppler velocities (<40 cm/s).

The definitive treatment of AL amyloidosis is antiplasma cell therapy aimed at stopping the production of the paraprotein responsible for the formation of amyloid.[75–81] A number of chemotherapeutic regimens exist, but the highest success rate appears to be with the use of intravenous melphalan, with a complete hematologic response in $\approx$40% of patients who survive 1 year after chemotherapy.[79] Unfortunately, the advanced nature of the cardiac disease in many patients at the

time of diagnosis either renders them unfit for high-dose chemotherapy with autologous stem cell replacement or places them at a risk of peritreatment mortality as high as 30%.[82] Precise criteria to define a subgroup of patients with AL amyloidosis who have an acceptably low treatment-related mortality in patients with AL cardiac amyloid have been difficult to define, but the absence of heart failure and normal ejection fraction and the absence of pleural effusions appear to augur a better prognosis. In contrast, marked wall thickening and markedly elevated brain natriuretic peptide or elevated troponin augur a poorer outcome.[15–17] Younger patients and those without significant involvement of other organ systems are also more likely to survive chemotherapy, but unexpected arrhythmias, episodes of electromechanical dissociation, or worsening of congestive heart failure occur even in this group.[82] An ejection fraction <40% is generally considered an absolute contraindication to high-dose chemotherapy in a patient with cardiac amyloid, particularly because most of these patients have class III congestive heart failure and minimal cardiac reserve.

Nevertheless, despite the significant risk of death associated with the use of vigorous chemotherapy in patients with AL amyloidosis involving the heart, it should be considered in selected patients because survivors often have a clinical improvement in congestive heart failure despite an unchanged echocardiographic appearance.[83] The improvement in heart failure may be due to abolition of the production of freshly produced light chains, which have been shown to be toxic to myocardial cells, suggesting that AL amyloidosis is not simply an infiltrative cardiomyopathy but rather a toxic infiltrative disorder.[84,85]

For patients who cannot tolerate high-dose intravenous melphalan, preliminary data from the UK amyloid group suggest that a modified intravenous regimen of melphalan, given monthly, may be better tolerated with a similar response rate, but no direct comparative study has been performed.[86] The "standard regimen" of melphalan and prednisone given as a "pulsed" dose for 3 to 5 days every 6 weeks seems to have little benefit in patients with cardiac amyloidosis, probably because several months are required to see an effect.[87] In addition, the steroid regimen may worsen congestive heart failure. Recently, we have used a low-dose "continuous" melphalan regimen in patients with severe cardiac amyloid with evidence of hematologic response in 7 of 13 patients.[81] Unfortunately, the cardiac disease was often too severe at the start of treatment to determine whether such a regimen has any impact on long-term survival. Regimens that include the use of high-dose dexamethasone such as vincristine, adriamycin, and dexamethasone[88] are generally not tolerated in cardiac amyloidosis because adriamycin, although used in relatively small doses, can produce cardiac toxicity and dexamethasone may aggravate heart failure.

In highly selected cases, cardiac transplantation may be considered. Early experience with cardiac transplantation in AL amyloidosis suggested that short- and medium-term mortality did not differ from that in other disorders,[89] but a later report of a small series of patients treated at multiple transplantation centers demonstrated an apparently greater long-term mortality than expected, usually because of disease progression in the heart or noncardiac organs.[90,91] As a result of these observations, many transplantation centers consider AL amyloidosis a contraindication to transplantation. However, with the advent of high-dose chemotherapy and stem cell transplantation, it is possible to transplant the heart and to perform chemotherapy 6 to 12 months later to abolish amyloid production. Potential candidates for this combined procedure are uncommon because noncardiac organ involvement is a contraindication and cardiac disease is limited clinically to the heart in <5% of cases. Nevertheless, a number of patients have been treated successfully with this combined approach; several have obtained a long-term remission from the disease without evidence of recurrence after 3 to 5 years of follow-up.

Light-Chain Cardiomyopathy

Renal light-chain deposition disease is a well-recognized entity in which renal failure may occur as a result of the deposition of light chains either related to multiple myeloma or as a manifestation of a plasma cell dyscrasia.[92] Less well known, and probably less common, is the cardiac manifestation of light-chain deposition disease. Although not actually a form of amyloidosis, the rare condition of light-chain cardiomyopathy deserves mention because it may mimic AL amyloidosis. In this condition, nonfibrillar deposits of light chains are found in the myocardium in association with either multiple myeloma or plasma cell dyscrasia.[93] The echocardiographic appearance is similar to cardiac amyloidosis, and heart failure and arrhythmias may occur, but Congo red staining of the myocardium is negative.[94] Kappa light-chain deposition tends to be more common than lambda. The

importance of recognition of this entity relates to the occasional patient with evidence of a plasma cell dyscrasia and an echocardiogram suspicious of amyloidosis in whom no amyloid is seen on endomyocardial biopsy. In such cases, electron microscopy with antikappa or antilambda immunogold labeling may reveal granular deposits typical of light-chain deposition, thereby confirming the diagnosis.[93] Chemotherapy targeted to the underlying plasma cell dyscrasia may lead to reversal of the cardiomyopathy.[95]

Hereditary Amyloidosis

Hereditary amyloidosis exists in a number of forms, but most cases are due to the production of amyloid from a mutant transthyretin protein.[5] Transthyretin contains 125 pairs of amino acids, and >70 mutations have been described, most of which are amyloidogenic. The specific site of an amino acid substitution determines the phenotype of the disease, which is transmitted as an autosomal dominant with high penetrance. The onset occurs from the third decade on, most commonly after the age of 40. In some forms, peripheral neuropathy may predominate, with cardiac amyloid being either absent or limited to the conduction system, most frequently manifesting as sinus node dysfunction. Other mutations such as Thr-60-Ala (the substitution of alanine for threonine at position 60) present with a predominant cardiomyopathy characterized by heart failure and conduction system disturbances with minimal neuropathy. Renal involvement is generally not a feature of transthyretin-associated cardiac amyloidosis, and myocardial infiltration may be quite severe before the onset of heart failure. This results in an echocardiographic appearance that is very similar to advanced AL cardiac amyloidosis but is associated with less heart failure and a much better long-term survival.[96] Although strain and strain rate imaging demonstrate subtle differences in ventricular long-axis function between AL and familial amyloidosis,[97] the difference in survival between these 2 diseases is probably related to the toxic effect of light-chain deposition on the myocardium in AL amyloidosis,[84,85] which is absent in transthyretin-related amyloidosis.

Among the familial TTR amyloidoses, the mutation characterized by a substitution of isoleucine for valine at position 122 of the transthyretin molecule deserves special mention.[98,99] Approximately 4% of the black population in the United States is heterozygous for this mutation,[100] which may result in a late-onset cardiomyopathy in either sex, manifesting as progressive congestive heart failure. In our initial experience of 12 cases[101] and subsequent personal experience of a similar number of cases, the disease is found to have features that are remarkably consistent among patients. The echocardiogram is similar to that seen in other variants of TTR amyloidosis, with features of an infiltrative/restrictive cardiomyopathy. Signs of right-sided heart failure predominate, and peripheral edema and ascites may be profound. Involvement of the cardiac valves may result in tricuspid regurgitation, which can further aggravate the right heart failure. Because of the high prevalence of hypertensive heart disease in blacks, left ventricular thickening seen on the echocardiogram may be mistakenly attributed to hypertension-induced hypertrophy, and the diagnosis of an

infiltrative cardiomyopathy can be overlooked. The presence of right ventricular thickening, the absence of left ventricular hypertrophy on the ECG, and the clinical finding of right heart failure in a black patient (particularly if a history of carpal tunnel syndrome is elicited) should strongly suggest the diagnosis. Unlike AL amyloidosis, the abdominal fat aspirate frequently stains negative for amyloid, and endomyocardial biopsy may be necessary unless tissue is available for staining from prior carpal tunnel syndrome surgery. The penetrance of this disorder is unknown, but many other TTR mutations have a high penetrance, suggesting that the Ile 122 variant is probably frequently overlooked. Regardless of the penetrance, the high prevalence of the mutation probably makes it the commonest familial amyloid cardiomyopathy and possibly the commonest type of amyloid heart disease. Unfortunately, the late age of onset and the universal manifestation of heart failure preclude liver transplantation as a therapy (see below) in the vast majority of patients with this disorder, although we have treated 1 patient by cardiac transplantation who had excellent results over the succeeding several years.

Treatments for ATTR Amyloidosis
Although transthyretin is produced by the liver, it has little effect on the liver function as liver deposition of amyloid is minimal or absent.[102] Currently, the definitive treatment of ATTR is liver transplantation, which removes the source of transthyretin and hence the precursor of amyloid deposition.[103] Optimally, liver transplantation should be performed in a patient with a known mutant transthyretin as soon as there is clinical evidence of the disease documented by either deposition of amyloid in fat pad aspirate or clinical evidence of disease activity.[104] Despite significant myocardial infiltration in some patients, the clinical experience has been that they tolerate the surgical aspect of liver transplantation well. Because the liver is functionally normal, it has, on occasion, been removed from an amyloid patient and transplanted into another patient who requires an urgent liver transplant (domino transplantation).[105] To date, only a small number of domino operations have been done, and it is not known if, or when, the recipient will develop amyloidosis.

Initial enthusiasm for transplantation as a technique for arresting progressive cardiomyopathy has been tempered by the observation that wall thickening progresses in some patients who have amyloid cardiomyopathy at the time of liver transplantation.[106,107] This is most probably due to the continued deposition of wild-type transthyretin in the myocardium, a process akin to senile cardiac amyloidosis (SCA). Occasionally, combined liver and heart transplantation or heart transplantation alone has been performed for ATTR amyloid with significant cardiomyopathy.[90,108]

There is ongoing investigation into the development of drugs that will stabilize transthyretin and prevent the formation of amyloid.[109] In vitro evidence suggests that certain nonsteroidal agents such as diflunisal can stabilize transthyretin.[110] Although currently there is no clinical evidence that these agents can prevent the progression of TTR amyloidosis, clinical trials are in the planning stage. However, even if nonsteroidal agents have some effect on disease progression,

a significant limitation in patients with cardiomyopathy is the potential for precipitation or aggravation of congestive heart failure. Thus, other agents without the potential for fluid retention are actively being sought.[5,111]

There are other, very rare, causes of familial nontransthyretin amyloid cardiomyopathy. Mutations of the genes encoding apolipoprotein A may be amyloidogenic and can result an isolated cardiomyopathy that has been successfully treated with cardiac transplantation.[112] Mutations of fibrinogen A α-chain and lysozyme can also cause amyloidosis, but deposition is predominantly in organs other than the heart.[71]

SCA
SCA is the predominant clinical manifestation of senile systemic amyloidosis. It results from the cardiac deposition of amyloid derived from wild-type transthyretin (ie, transthyretin with a normal amino acid constitution)[113] and invariably presents as congestive heart failure. The diagnosis requires the finding of amyloid deposits in the myocardium, in conjunction with evidence of an infiltrative cardiomyopathy on echocardiogram. The echocardiographic appearance is indistinguishable from that found in patients with AL amyloidosis, although the degree of wall thickening may be very marked despite relatively mild, or easily controllable, heart failure.[114] Once the diagnosis is suspected, confirmation usually requires an endomyocardial biopsy because noncardiac involvement is rare. However, caution should be exercised in labeling an elderly patient as having senile amyloidosis on the basis of an endomyocardial biopsy if the amyloid deposits are sparse and the echocardiographic appearance is not consistent with amyloidosis because small amounts of amyloid derived from wild-type transthyretin are not uncommon in the very elderly.[115,116] Exclusion of a plasma cell dyscrasia is mandatory, and screening should be performed to exclude a mutant transthyretin. Although evaluation for a plasma cell dyscrasia is usually negative, an unrelated benign monoclonal gammopathy of unknown significance will be expected to be present by chance in 3% to 5% of patients of this age when sought by serum protein electrophoresis[66,117] and even more commonly if the more sensitive immunofixation is used. If immunofixation is positive, but the clinical picture is most consistent with SCA other tests to exclude AL amyloidosis are mandatory. Immunochemistry or immunogold electron microscopy of biopsy tissue staining unequivocally positive for TTR and negative for kappa and lambda are confirmatory of the transthyretin origin of the amyloid.[70]

For unclear reasons, SCA is almost exclusively a disorder of men.[114] The disease is rare individuals <70 years of age, and the median survival from the onset of heart failure is 7.5 years compared with 15 months in patients with AL amyloidosis and a similar degree of LV thickening.[114] The clinical manifestations of senile cardiac amyloidosis are quite similar among patients.[114,118] Progression of heart failure in senile amyloidosis is insidious but inexorable, and the diagnosis should be suspected in an elderly man with unexplained right-sided or biventricular failure and an echocardiogram showing left ventricular thickening with normal ventricular cavity size. The disease is not associated with any other major clinical organ involvement, although carpal tunnel syndrome,
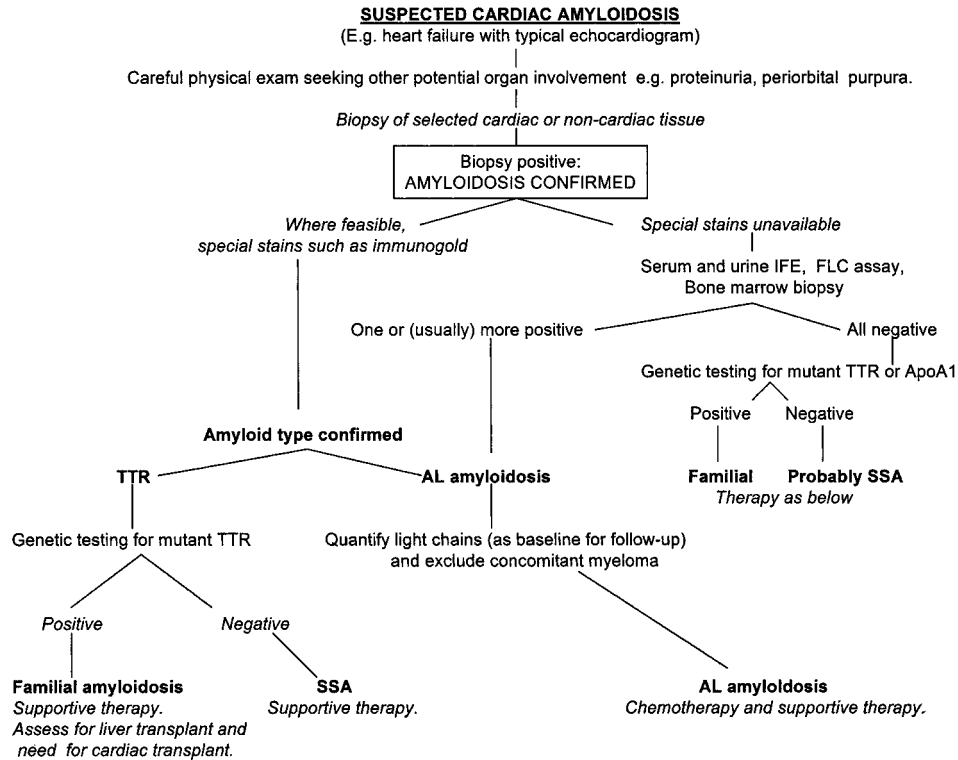
SUSPECTED CARDIAC AMYLOIDOSIS
(E.g. heart failure with typical echocardiogram)

Careful physical exam seeking other potential organ involvement e.g. proteinuria, periorbital purpura.

Biopsy of selected cardiac or non-cardiac tissue

Biopsy positive:
AMYLOIDOSIS CONFIRMED

*Where feasible,
special stains such as immunogold*   *Special stains unavailable*

Serum and urine IFE, FLC assay,
Bone marrow biopsy

One or (usually) more positive   All negative

Genetic testing for mutant TTR or ApoA1

Positive   Negative

Amyloid type confirmed

TTR   **AL amyloidosis**   **Familial   Probably SSA**
Therapy as below

Genetic testing for mutant TTR   Quantify light chains (as baseline for follow-up)
and exclude concomitant myeloma

Positive   *Negative*

Familial amyloidosis   **SSA**   **AL amyloidosis**
Supportive therapy.   *Supportive therapy.*   *Chemotherapy and supportive therapy.*
*Assess for liver transplant and
need for cardiac transplant.*

Figure 8. Flow diagram outlining the evaluation of a patient with suspected cardiac amyloidosis. Clinical evaluation may reveal clues that strengthen the likelihood of amyloidosis, but a tissue diagnosis is mandatory. Although special staining of the biopsy may confirm the type of amyloid, further workup of AL amyloid is required to exclude myeloma and to quantify free light chains. If the biopsy stains positive for transthyretin, further testing is needed to determine whether this is a wild-type or mutant transthyretin. ApoA1 indicates apolipoprotein A1; IFE, immunofixation electrophoresis; FLC, free-light-chain assay; SSA, senile systemic amyloidosis; and TTR, transthyretin.

often preceding the cardiac disease by a few years, is common. Bifascicular block on the ECG is common, and progression to complete AV block occurs not infrequently, necessitating permanent pacemaker implantation. Implantation of a permanent pacemaker for conduction system disease may be followed by a worsening of heart failure; this may be due to the dysynergy produced by right ventricular pacing in the nondilated, infiltrated ventricle with its small cavity and reduced ejection fraction. Thus, if conduction system disease warrants a pacemaker, strong consideration should be given to biventricular pacing to maximize ventricular stroke volume. Atrial fibrillation is a common arrhythmia in SCA, presumably because of the combination of atrial infiltration with amyloid, increased left atrial pressure, and the advanced age of the patient. Once atrial fibrillation occurs, thromboembolism is common, and warfarin anticoagulation should be prescribed unless a major contraindication exists. Restoration and maintenance of sinus rhythm by cardioversion and antiarrhythmic drugs such as amiodarone may provide some benefit, but atrial function is usually impaired as a result of amyloid infiltration. In addition, widespread conduction system disease may worsen in the presence of antiarrhythmic drugs. Unlike AL amyloidosis, patients with SCA often tolerate ACE inhibitors, although the mainstay of therapy is still the judicious use of diuretics. There is no specific treatment for SCA, but as in familial amyloidosis, drugs that stabilize the transthyretin molecule hold some promise[109] and are on the verge of clinical trials.

Secondary Amyloidosis

Secondary amyloidosis is increasingly uncommon in the developed world owing to the eradication of chronic infections. However, it is still seen occasionally in association with juvenile or adult rheumatoid arthritis and other rheumatic disorders such as ankylosing spondylitis, as well as with inflammatory bowel disease. Hepatic and renal amyloid deposition dominates the clinical picture, and clinical heart disease related to cardiac amyloid is very rare.[6] In the few cases in which there is echocardiographic evidence of cardiac amyloidosis resulting from secondary amyloidosis, cardiac symptoms are usually absent, although we have seen very occasional cases of mild heart failure with extensive left ventricular thickening, which was associated with sudden death in 1 case.

Isolated Atrial Amyloidosis

Atrial amyloid deposition is a common finding at autopsy, particularly in elderly patients.[115,119] Immunohistochemical evaluation demonstrates its origin from atrial natriuretic peptide.[120] Unlike the other forms of amyloid discussed, atrial amyloid is a nonsystemic deposition, limited to the atrium. Until recently, it was believed to be a clinically insignificant finding that increased in prevalence with increasing age and with the presence of organic heart disease. Recent data based on atrial biopsies taken at the time of cardiac surgery suggest that isolated atrial amyloidosis may be commoner in women and is more likely to occur in the presence of atrial fibrilla-

tion.[121,122] Interestingly, an inverse relationship with the presence of atrial fibrosis has been suggested.[121,123] The role of isolated atrial amyloid in the pathogenesis and maintenance of atrial fibrillation remains to be fully elucidated, but it may be a precipitating factor of atrial fibrillation in some patients and may be produced as part of the remodeling associated with this arrhythmia.[121]

Conclusions

In summary, cardiac amyloidosis, although uncommon, is characterized by a typical appearance on echocardiography, the recognition of which should alert the astute clinician to the probable diagnosis. It is critical to recognize that several forms of amyloidosis may cause cardiomyopathy and that treatment and prognosis of these individual cardiomyopathies differ greatly from each other. A flow diagram to aid in the diagnosis of the type of amyloid is illustrated in Figure 8. In AL amyloidosis, chemotherapy may arrest or possibly reverse the disease, with resultant stabilization or improvement of symptoms. Thus, early diagnosis is critical because patients with advanced disease are usually too ill for intensive chemotherapy. Recognition of non-AL cardiac amyloidosis is important to avoid unnecessary chemotherapy, to screen family members, and in the near future, to provide new medications that will stabilize the amyloidogenic substance in the blood and prevent the onset of progression of this important and underdiagnosed condition.

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