Chapter 3

Cardiac Amyloidosis: Typing, Diagnosis, Prognosis and Management

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Additional information is available at the end of the chapter

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1. Introduction

Amyloidosis is uncommon, with age-adjusted incidences of between 6.1 and 10.5 per million person-years,[1] and an estimated 1275 to 3200 new cases occurring annually in the United States.[1, 2] The contemporary understanding of amyloidosis points to a group of complex systemic disorders involving the extracellular deposition of misfolded proteinaceous material in many organs, most commonly the kidneys, heart, liver, central and peripheral nervous systems.[2-4] The normal function of tissues is altered, and end-organ dysfunction usually ensues. Cardiac amyloidosis can be isolated to the heart, but it often coexists with disease elsewhere in the body.[4, 5] Cardiac manifestations may predominate the clinical presentation or may be subclinical and detected on routine investigation of a patient presenting with non-cardiac complaints.[5] The presence and relative prominence of cardiac involvement in the clinical picture is dependent on the type of amyloidosis and severity of amyloid infiltration in the tissue.[5]

2. Classification of amyloidosis

Amyloidosis refers to a group of unrelated diseases involving the extracellular deposition of proteinaceous material that demonstrates apple-green birefringence under polarized light on staining with Congo red.[5] In all forms of amyloidosis, abnormal and unstable protein is produced in response to a variety of stimuli and precipitates as amyloid in the extracellular matrix.[2, 3] The contemporary classification of amyloidosis is primarily based on the biochemistry of the disease process from the precursor amyloid proteins, and comprises several major subgroups. Table 1 describes the typical characteristics of each type of amyloidosis.

Type of amyloidosis	Precursor protein	Spectrum of organ involvement	Frequency of cardiac involvement	Median survival, months	Diagnostic testing	Treatment
Immunoglobulin amyloidosis (AL)	Immunoglobulin light chain	Heart, kidneys, liver, peripheral/autonomic nervous systems, soft tissue, gastrointestinal system	Up to 50% have clinical cardiac involvement	13 (4 months if heart failure present at diagnosis)	SPEP, UPEP, bone marrow biopsy tissue analysis revealing plasma cell dyscrasia, κ and λ light chain antiserum staining	Anti-plasma cell chemotherapy, autologous stem cell replacement, sequential heart and stem cell transplant
Familial amyloidosis (ATTR)	Mutant transthyretin	Peripheral/autonomic nervous systems, heart	Variable, depending on exact mutation	70	ATTR antiserum staining, serum TTR isoelectric focusing, restriction fragment length polymorphism analysis	Liver transplantation, combined liver and heart transplantation in certain cases, new pharmacological strategies to stabilize TTR
Senile systemic amyloidosis	Wild-type transthyretin	Heart (predominant, usually atrial)	Common	75	ATTR antiserum staining	Supportive, new pharmacological strategies to stabilize TTR
Reactive amyloidosis (SAA)	Serum amyloid A	Kidney, heart	Uncommon, <10%	24.5	Target organ biopsy specimen analysis, AA antiserum staining	Treat the underlying inflammatory process
Hemodialysis-associated amyloidosis	β2-microglobulin	Musculoskeletal system, rare in heart	Unknown, asymptomatic	Unclear clinical significance	Synovial and bone biopsy specimen analysis, β2-microglobulin antiserum, serum β2-microglobulin concentration	Renal transplantation
Isolated atrial amyloidosis	Atrial natriuretic peptide	Heart	Limited to heart	Unclear clinical significance	Atrial natriuretic peptide antiserum staining	None required

Table 1. Types of amyloidosis affecting the heart.

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2.1. Immunoglobulin light chain amyloidosis (AL)

AL amyloidosis is a monoclonal plasma cell disorder in which the precursor protein is an immunoglobulin light chain or light chain fragment. It may occur as a primary disease or in association with multiple myeloma or other plasma cell dyscrasias.[3, 6, 7] The median number of clonal plasma cells in AL amyloidosis is between 5% and 10%.[2] The extent of clonal plasma cell marrow infiltration is an important prognositic indicator, presumably because it reflects the degree of pathogenic light chain synthesis.[8] In primary amyloidosis, there is 2:1 preponderance for λ over κ light chain synthesis.[9] While in itself uncommon, with an incidence of 8.9 per million,[1] AL amyloidosis is the commonest type of amyloidosis, accounting for about 85% of all newly diagnosed cases.[3, 10] The clinical picture of AL amyloidosis is the most varied, since it commonly affects a large number of organ systems including the heart, kidney, liver, peripheral and autonomic nervous systems, soft tissue and gastrointestinal systems.[3, 5] The heart is affected in over 50% of cases,[11] and symptomatic cardiac involvement portends a worse prognosis.[11, 12] Conversely, involvement limited to the heart constitutes <5% of patients with AL amyloidosis.[11] Cardiac involvement with resultant heart failure or arrhythmia accounts for >50% of the mortality in patients with AL amyloidosis.[12] Furthermore, thromboembolism also contributes significantly to morbidity and mortality. Intracardiac thrombosis was found in 51% and 35% of subjects with AL amyloidosis in the Mayo amyloid autopsy study and in a group of patients undergoing follow up echocardiographic imaging respectively.[13, 14]

2.2. Familial amyloidosis (ATTR)

Familial amyloidosis is a hereditary autosomal dominant disorder involving amyloidogenic mutations in most commonly the transthyretin gene.[15] The age of onset of familial amyloidosis appears to vary with ethnicity. Interestingly, about 10% of gene carriers remain asymptomatic (although the disease manifestation can be age dependent with variable penetrance),[16-18] suggesting that the pathogenesis of these diseases may involve other genetic or environmental factors. Familial amyloidosis usually affects the peripheral and autonomic nervous systems and the heart.[5] While usually more slowly progressive than AL amyloidosis, the familial type may also cause clinically significant heart failure. Significant cardiac disease is associated with mutations at positions 30, 60 and 84 of the transthyretin gene.[17] A mutation involving isoleucine at position 122 which involves solely the heart has been described in elderly African-American persons.[19, 20] This form of amyloid is probably underdiagnosed since nearly 4% of newborn African Americans harbor this mutation.[19] The TranstHyretin Amyloidosis Outcome Survey (THAOS) registry is a global observational survey set up with the aim of furthering our understanding of hereditary amyloidosis.

2.3. Senile systemic amyloidosis

Senile systemic amyloidosis is primarily a disease of the elderly, most commonly affecting men over the age of 70. It accounts for approximately 25% of patients over 80 years with amyloidosis.[21, 22] It is caused by wild-type transthyretin.[5, 21] Cardiac, particularly at-

rial, involvement is common,[23, 24] and may be associated with clinically significant heart failure, atrial fibrillation and conduction abnormalities.[25, 26]

2.4. Reactive amyloidosis (SAA)

Reactive amyloidosis is characterized by the deposition of serum amyloid A protein (SAA), an acute phase reactant produced in response to chronic inflammatory processes such as chronic infections, rheumatologic disease and familial periodic fever syndromes.[27, 29] With efficacious treatment of chronic infections in patients in the developed world, the incidence of reactive amyloidosis has fallen.[29] The kidney is commonly involved, [5] and cardiac involvement, if present, is rarely clinically significant.[30, 31]

2.5. Hemodialysis-associated amyloidosis (Aβ2M)

Hemodialysis-associated amyloidosis occurs in chronic renal failure patients undergoing hemodialysis.[12] β2-microglobulin is the precursor protein.[32, 33] Musculoskeletal involvement is common, and the clinical effect from cardiac deposition is minimal and typically clinically insignificant.[34, 35]

2.6. Isolated atrial amyloidosis (AANF)

Isolated atrial amyloidosis is predominantly seen in those >80 years and in females,[23] but also occurs in younger patients with valvular abnormalities or chronic atrial fibrillation. [36-38] The precursor protein is atrial natriuretic peptide.[39-41] Involvement is usually limited to the subendocardial region of the heart, and its clinical significance is unclear.[42]

3. Pathophysiology of cardiac amyloidosis

In cardiac amyloidosis, the clinical presentation is typically heart failure with initially preserved ejection fraction and restrictive diastolic physiology. This has led to its classification as a "restrictive" cardiomyopathy.[3, 5, 9, 43] This is defined by a high filling pressure that can lead classically to heart failure with preserved ejection fraction. Cardiac contractile function and electrical conduction can be impaired with amyloid infiltration.[9] At a cellular level, amyloid infiltration results in abnormal cellular metabolism, calcium transport and receptor regulation. [3] Adrenergic input is disrupted and the neurohormonal milieu is altered in cardiac amyloidosis.[44] Amyloid deposition induces oxidant stress[45] and modulates interstitial matrix composition and tissue remodeling,[46] leading to further depression of myocyte contractility. Furthermore, there is evidence of a direct toxic role of the monoclonal light chain extracted from the urine of AL patients on myocardial diastolic function in the mouse hearts; infusion of the monoclonal light chain caused a significant elevation in the LV end diastolic pressure in this animal model.[47] Involvement of the coronary microvasculature may also result in coronary flow abnormalities; this is seen in 90% of patients with AL amyloidosis.[48] This global involvement leads to diffuse ischemia and microinfarction,

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further compromising cardiac contractility.[49] The resultant perivascular amyloid infiltration commonly involves the conduction system, leading to conduction abnormalities.[50, 51]

4. Clinical presentation – When should physicians suspect amyloidosis?

Depending on the spectrum of organ involvement, a patient can present with a multitude of symptoms and signs which are often nonspecific and variable, especially in the early stages of disease.[12] This is particularly so in AL amyloidosis, in which many systems can be affected. Common constitutional complaints include weakness, fatigue, peripheral edema and weight loss.[9] Hepatomegaly is common and results from either direct hepatic infiltration or congestion secondary to cardiac failure.[52, 53] Renal involvement may cause profound proteinuria and the nephrotic syndrome.[5, 9] Easy bruising and periorbital purpura results from clotting factor deficiencies and fragile venules; the latter is virtually pathognomonic of the AL type disease.[54, 55] Soft tissue involvement may result in carpal tunnel syndrome[5, 9] and macroglossia,[56] while peripheral and/or autonomic neuropathy may be the hallmark of neurological involvement.[5, 9, 12] The presence of complaints involving multiple organ systems without any other known cause should trigger a search for multisystem disease, one of which being amyloidosis. Early diagnosis improves outcomes, given the irreversible damage caused by amyloidosis and that patients with advanced disease are often not candidates for definitive treatment options (some of which may be curative),[43] but this requires a high index of suspicion and a systematic algorithm for evaluation.[4, 9]

Cardiac findings are predominantly due to diastolic dysfunction, also known as heart failure with preserved ejection fraction.[3, 5, 9] The initial presentation is often that of progressive exertional dyspnea followed by worsening heart failure, pulmonary congestion, pleural effusions, edema, and ascites.[11] Valvular insufficiency or stenosis due to endocardial involvement may result in a murmur,[9, 43, 57] and atrial fibrillation is common, although all manner of arrhythmias have been reported.[57, 58] Coronary flow abnormalities due to microvascular involvement may present as angina chest pain;[59] rarely, this may be the only presenting complaint.[59-63] Patients may have syncope and lightheadedness, particularly postural, caused by autonomic dysfunction and arrhythmias in the face of declining cardiac functional reserve.[64] The heart should be screened in all patients with known or suspected amyloidosis even in the absence of cardiac symptoms, as involvement of the heart portends a poor prognosis and affects treatment strategies.[3]

5. Diagnosis and evaluation of cardiac amyloidosis

Histologic examination remains the definitive diagnostic modality in cardiac amyloidosis.[9, 65] While not definitive, certain non-invasive imaging and laboratory findings may guide further diagnostic testing and management and assess the severity of the disease for prognostic purposes.[9, 43] Often, the diagnosis of cardiac amyloidosis and perhaps the type of

amyloidosis can be reasonably ascertained by employing one or more non-invasive imaging and laboratory modalities.

5.1. Echocardiography

Echocardiography remains the most widely utilized noninvasive modality in the diagnosis of cardiac amyloidosis, in part because of its widespread availability and relatively low cost.[5, 66] In cases with characteristic echocardiographic findings, signs and symptoms of heart failure, and a positive biopsy of another organ, cardiac involvement is almost certain. However, echocardiography cannot determine the type of amyloidosis and in some patients with early disease the findings may be subtle.[43]

Echocardiography may show mild diastolic dysfunction [9] as the only clue in early amyloid heart disease, but this is non-specific and may often be mistaken for more common conditions such as hypertensive or hypertrophic cardiomyopathy. Recently, it has been found that tissue Doppler imaging could identify abnormalities in both early and late-stage cardiac amyloidosis, affording the possibility for early diagnosis and disease-modifying intervention.[66, 67] Tissue Doppler imaging can also be helpful in differentiating restrictive cardiomyopathy from constrictive pericarditis.[68, 69] Diastolic dysfunction is the predominant pathology in cardiac amyloidosis; the classic picture of a thick and stiff ventricle elevates diastolic filling pressures causing restrictive hemodynamics and atrial dilatation.[70, 71] Decreased ejection fraction typically occurs only in late-stage disease as a result of loss of myocardial contractile function through myocyte necrosis and local interstitial amyloid infiltration;[5, 72-75] despite preserved ejection fraction, systolic function is not normal in cardiac amyloidosis. Techniques of myocardial deformation imaging have shown that abnormal strain and strain rate imaging occur in most cases of cardiac amyloidosis.[76-79] Amyloid cardiomyopathy seems to be associated with a marked dissociation between short and long-axis systolic function; tissue Doppler or strain rate imaging may show severe impairment in long-axis contraction even when the left ventricular ejection fraction remains within the normal range.

The typical features of cardiac amyloidosis such as left ventricular wall thickening[66, 72-74, 80, 81] with myocardial hyperechogenicity,[74, 81-84] biatrial enlargement,[74, 75, 81] thickened atrial septum[81] and valve leaflets,[75, 81] as well as pericardial effusion [75, 81] are usually seen at a more advanced stage of the disease (Figure 1). A thickened left ventricular wall in the absence of high electrocardiographic voltages is suggestive of infiltrative cardiac disease. Deposition in the atria is usually extensive and may cause atrial mechanical failure and atrial standstill, i.e. atrial electro-mechanical dissociation even in patients who are in normal sinus rhythm. Atrial involvement may also result in atrial arrhythmias; in fact, atrial fibrillation can significantly affect the cardiac output from an already impaired ventricle.[85, 86] Heart failure can be further worsened by valvular insufficiency caused by subendocardial infiltration. [9] Rarely, pericardial involvement occurs in severe disease leading to pericardial effusion or constriction.[48] In some cases, pulmonary hypertension and cor pulmonale may occur in patients with amyloidosis.[87] Although usually caused by concomitant and frequently more severe cardiac amyloidosis with left ventricular failure,[88] pulmonary hypertension may be the result of advanced pulmonary amyloid infiltration.[87]

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While pulmonary involvement is a harbinger of adverse outcome, it is often difficult to determine the exact extent to which pulmonary amyloid deposition contributes to symptoms or outcome because cardiac deposition commonly coexists.[89]

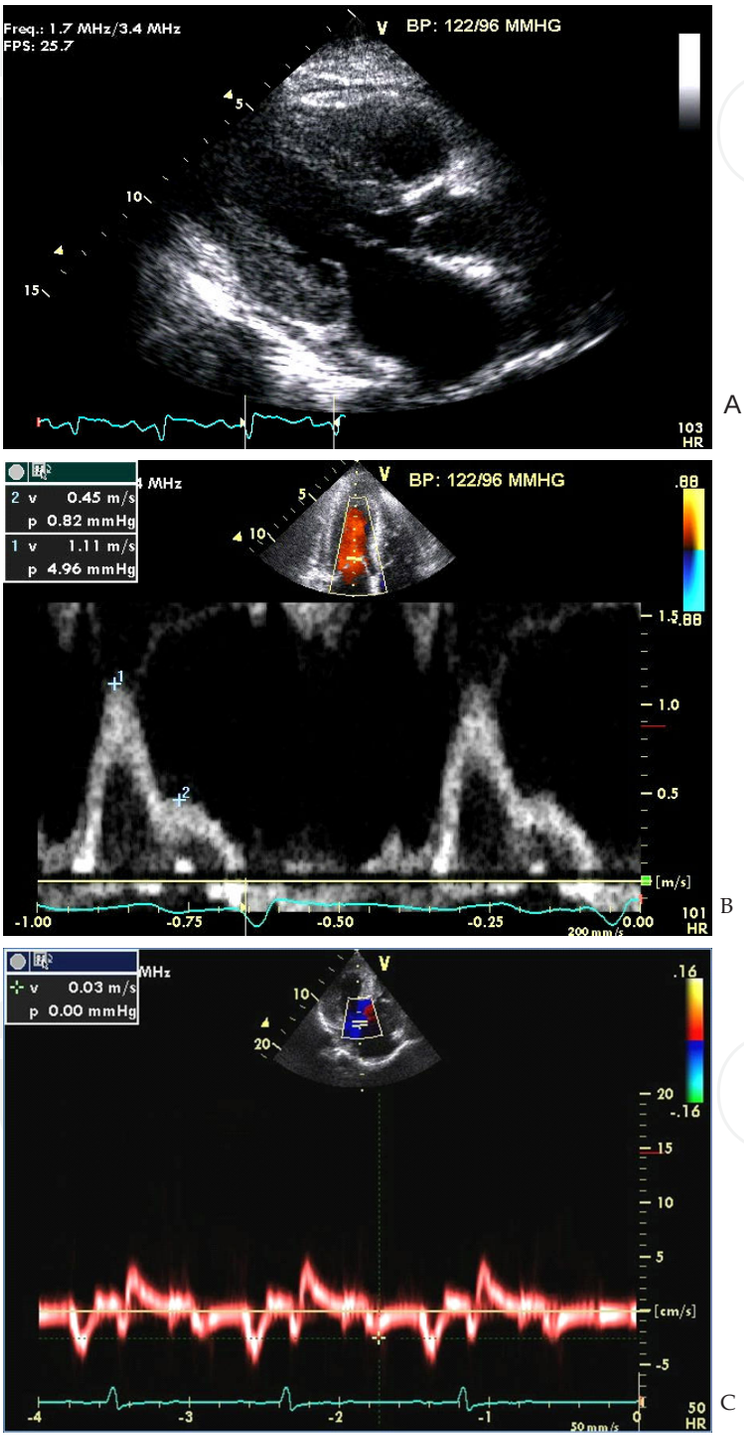

Figure 1. (A) Two-dimensional echocardiographic, (B) transmitral Doppler and (C) tissue Doppler images classical of AL amyloidosis.

Several other findings on echocardiography may have prognostic significance in cardiac amyloidosis, such as left ventricular ejection time,[90] wall motion abnormalities,[91, 92] dyssynchrony,[93] as well as increased right ventricular Tei index (which reflects right ventricular dysfunction).[94] Myocardial contrast echocardiography can reveal microvascular dysfunction, and may be a useful adjunct in echocardiographic assessment for the early diagnosis of cardiac amyloidosis, although it is not typically utilized in day to day practice.[95] Transesophageal echocardiography (TEE) may be useful in characterizing atrial thrombi and assessing left atrial appendage dysfunction,[96] a common finding in cardiac amyloidosis even in the absence of atrial fibrillation (Figure 2).[96, 97] Risk factors for intracardiac thrombosis include: AL type amyloidosis, atrial fibrillation, and diastolic dysfunction. Increased right ventricular wall thickness is a marker of increased risk in intracardiac thrombosis, probably due to the presence of advanced infiltrative cardiomyopathy.[14] Timely assessment for intracardiac thrombosis in high-risk patients is important for anticoagulation considerations.[13, 14, 98] Patients with amyloidosis should not be cardioverted without adequate anticoagulation and in some institutions, TEE imaging is routinely performed prior to cardioversion even in the presence of adequate anticoagulation.

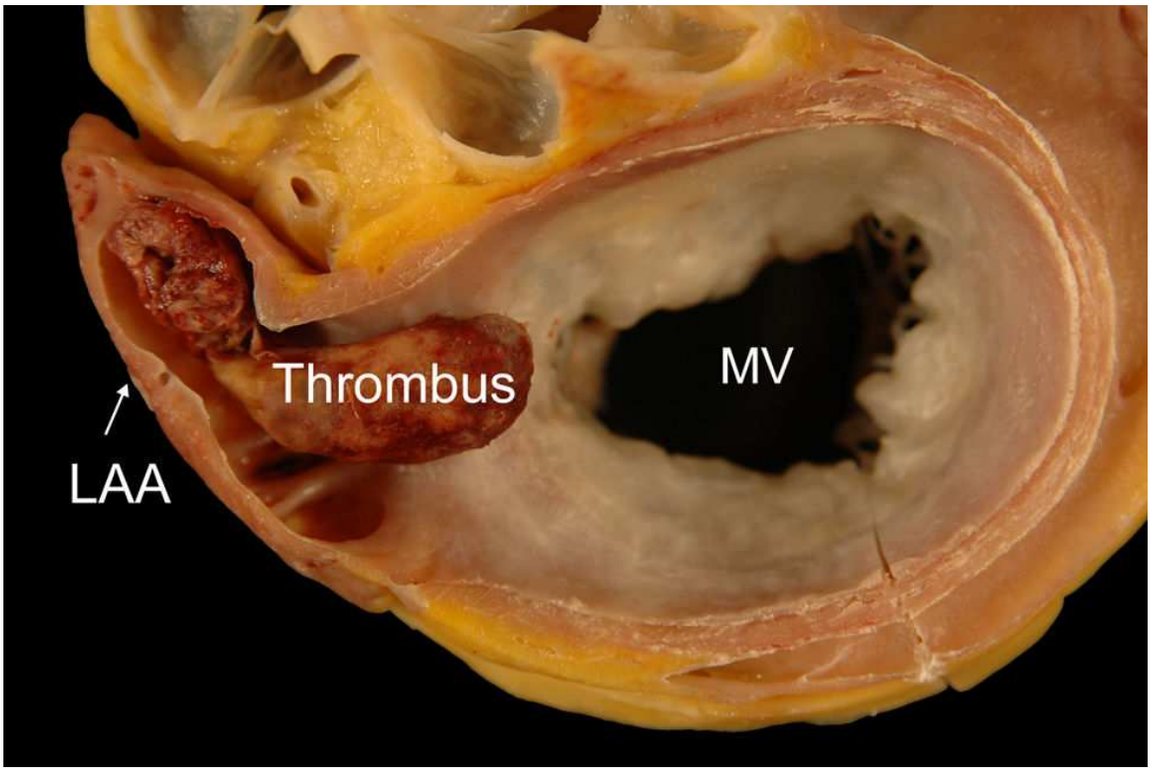

Figure 2. Left atrial appendage (LAA) thrombus in a patient with cardiac amyloidosis; the patient was known to be in sinus rhythm. (With permission from Feng et al. *Circulation.* Nov 20 2007;116(21):2420-2426.)

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Besides its diagnostic value, echocardiography is a useful adjunct during the endomyocardial biopsy procedure. It complements, and in some institutions has replaced, fluoroscopy as a method of bioptome guidance because of its superior resolution of the tricuspid valve anatomy, endocardial surface, and thin right ventricular free wall and apex.[99]

5.2. Electrocardiography

Electrocardiography (ECG) provides useful and complementary information in patients with cardiac amyloidosis. The classic findings of low voltages and pseudoinfarct patterns (Figure 3) are common occurrences,[11, 58, 100] and both findings may occur in 25% to 50% of patients.[43] Poor R wave progression is also often seen.[3, 101] Low voltage correlated with the presence of a pericardial effusion but not with decreased ejection fraction.[43] The combination of low voltage and an interventricular septum thickness >1.98 cm is very specific for cardiac amyloidosis.[74] The finding of low voltage in a patient with echocardiographic evidence of increased wall thickness should raise the clinical suspicion of infiltrative cardiomyopathy, but the reverse is not necessarily true – normal voltage does not exclude amyloidosis.[58] ECG criteria for left ventricular hypertrophy, especially limb lead ECG left ventricular hypertrophy, however, is rarely present in patients with cardiac biopsy proven amyloidosis.[58]

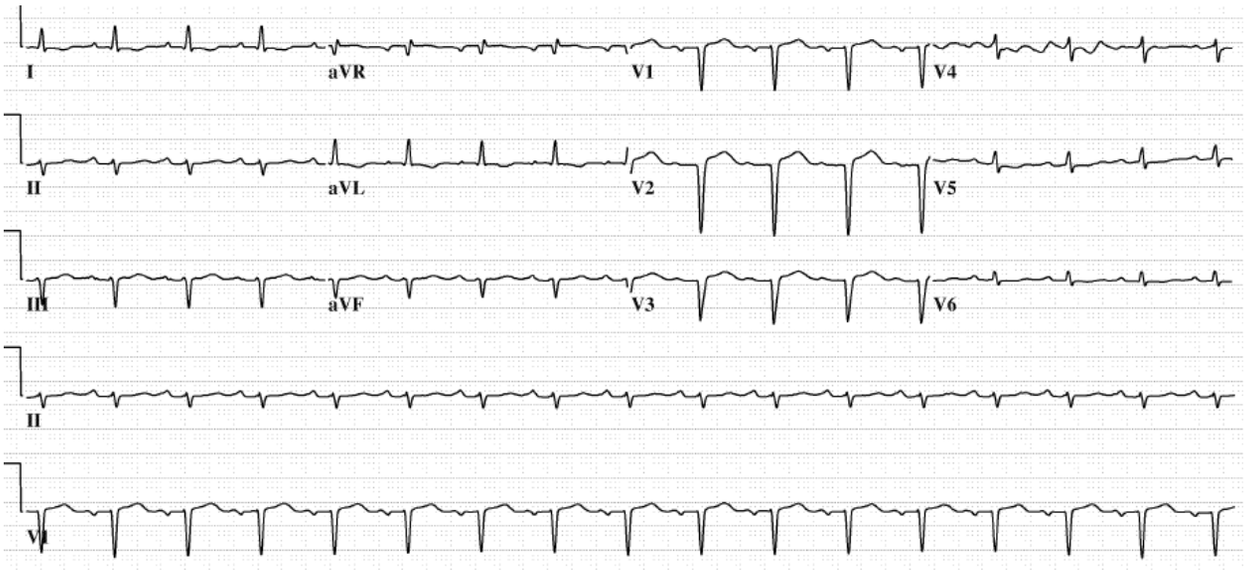

Figure 3. ECG changes classical of cardiac amyloidosis with sinus tachycardia, low voltage and pseudoinfarct patterns.

The conduction system can often be affected in cardiac amyloidosis.[11] Atrial fibrillation and flutter are the commonest arrhythmias seen,[58] but atrioventricular and bundle branch blocks may occur.[65] Sinus tachycardia seen in advanced cardiac amyloidosis is probably

due to the restrictive filling leading to cardiac output adjustments based solely on heart rate; in one study this was a marker of increased risk for intracardiac thrombosis.[14] Prolonged QT intervals and junctional rhythms may be present. [9] Advanced ventricular arrhythmias such as sustained ventricular tachycardia are rarely seen (although frequent PVCs, couplets or triplets are common), which is likely due to poorly tolerance of the arrhythmia in the advanced cardiac amyloid patients who would die suddenly from sustain VT.[58, 102] Sudden death in severe cardiac amyloidosis is commonly attributed to electromechanical dissociation; a pattern similar to severe cardiac diseases of other etiologies.[64]

The largest reported ECG series consists of 127 patients with AL amyloidosis and biopsy proven cardiac involvement seen at the Mayo Clinic. The two most common abnormalities were low voltage and a pseudoinfarct pattern, which were seen in 46 and 47 percent of cases. Other findings included first degree AV block in 21 percent, nonspecific intraventricular conduction delay in 16 percent, second or third degree AV block in 3 percent, atrial fibrillation or flutter in 20 percent, and ventricular tachycardia in 5 percent. ECG criteria for left ventricular hypertrophy were present in 16 percent, but some of these patients had a history of hypertension. The left ventricular hypertrophy criteria were limited almost exclusively to precordial leads, sometimes with low-voltage limb leads.[58] In patients with AL amyloidosis, signal-averaged ECG may demonstrate delayed myocardial activation or "late potentials"; this is an independent predictor of sudden death.[43, 100] Reduced heart rate variability predicts mortality in the short-term in both AL and familial amyloidosis, and probably represents autonomic dysfunction.[103, 104]

Many of the ECG findings in cardiac amyloidosis are nonspecific, and other causes of such should be ruled out.[65] On the other hand, ECGs, especially if done serially, allows for early diagnosis and intervention in cardiac amyloidosis. Physicians should understand the characteristics and symptoms of amyloidosis, and be aware of subtle changes in the ECG, especially abnormalities that suggest disorders in the conduction system (such as prolonged PR interval, widened QRS, atrioventricular blocks, and bundle branch blocks) or decreased electromotive force (such as progressive R wave decrease).[105]

5.3. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) is emerging as a useful tool in the diagnosis of cardiac amyloidosis. Its strength lies in its high three-dimensional spatial resolution and signal-to-noise ratio, permitting reproducible measurements of cardiac chamber volumes and mass, as well as left ventricular and atrial septal wall thickness.[106] Additionally, it can characterize pericardial and pleural fluid.[106] Late gadolinium enhancement (LGE) is the cornerstone of detecting myocardial amyloid infiltrates and is seen in almost all cases.[107] Compared with normal myocardium which has no LGE because of little gadolinium accumulation on delayed imaging, contrast accumulates in the extracellular space in cardiac amyloidosis which is expanded by amyloid infiltration, resulting in LGE. [108] The predominant pattern of LGE seen in cardiac amyloidosis is global transmural (Figure 4) or subendocardial; [108, 109] other patterns including focal patchy LGE and difficulty nulling can also be seen.

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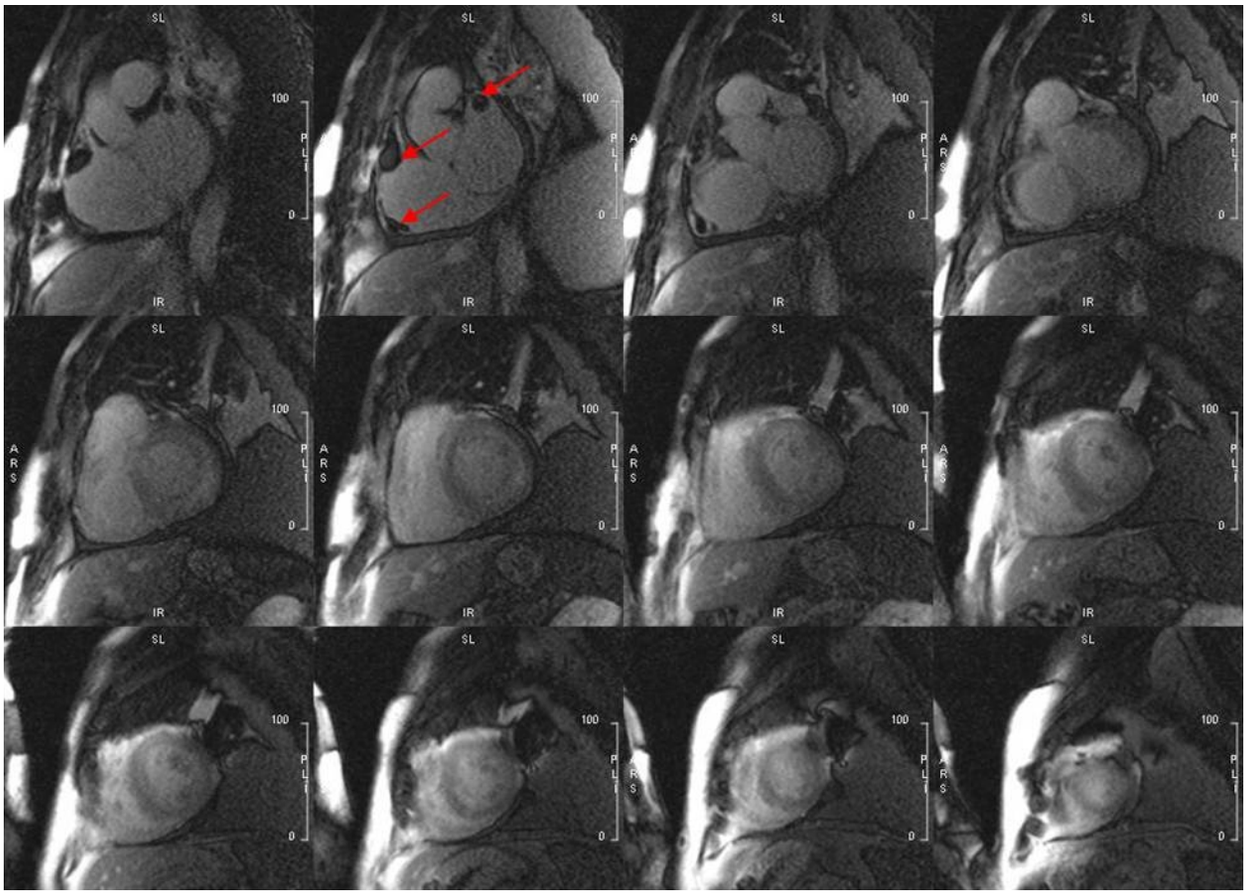

Figure 4. CMR findings of global transmural LGE classical of cardiac amyloidosis; this patient had histologically proven AL amyloidosis. Furthermore, three intracardiac thrombi (red arrows) were detected in the left atrial appendage, right atrial appendage and at the right atrial free wall close to tricuspid annulus.

Maceira et al [108] first studied LGE in CMR in 29 patients with cardiac amyloidosis. They found that CMR shows a characteristic pattern of global subendocardial LGE coupled with abnormal myocardial and blood-pool gadolinium kinetics. In 22 of these, myocardial gadolinium kinetics with T1 mapping was compared with that in 16 hypertensive controls. Subendocardial T1 in amyloid patients was shorter than in controls (at 4 minutes: 427±73 vs. 579±75 ms; $p<0.01$), and was correlated with markers of increased myocardial amyloid load such as left ventricular mass, wall thickness, interatrial septal thickness and diastolic function. Global subendocardial LGE was found in 20 amyloid patients (69%); these patients had greater left ventricular mass than unenhanced patients. Histological quantification showed substantial interstitial expansion with amyloid (30.5%) but only minor fibrosis (1.3%). Amyloid deposition was predominantly subendocardial (42%), compared with midwall (29%) and subepicardial (18%). The LGE findings agree with the transmural histological distribution of amyloid protein and the cardiac amyloid load. Using the difference between the T1 of subendomyocardium and blood, a cutoff value of 191 ms at 4 minutes had 90% sensitivity, 87% specificity and 88% of accuracy for the correct diagnosis of cardiac

amyloidosis. There was 97% concordance in diagnosis of cardiac amyloidosis by combining the presence of late gadolinium enhancement and an optimized T1 threshold between myocardium and blood.

Mayo investigators further evaluated the mechanism of LGE in CMR in identifying cardiac involvement in a population of known amyloidosis patients and to investigate associations between LGE and clinical, morphological, functional, and biochemical features.[107] Gadolinium-enhanced CMR was performed in 120 patients with amyloidosis of which 100 had AL amyloidosis, 11 had familial amyloidosis and 9 had senile amyloidosis. Cardiac autopsy and/or histology was available in 35 patients. The remaining 85 patients were divided into those with and without echocardiographic evidence of cardiac amyloidosis. Abnormal LGE was present in 34 (97%) patients with histologically proven cardiac amyloidosis. Global transmural or subendocardial LGE (83%) was most common while suboptimal myocardial nulling (8%) and patchy focal LGE (6%) were also observed (Figure 5). Global LGE was associated with a higher burden of interstitial amyloid quantified from histology. LGE distribution matched the deposition pattern of interstitial amyloid at autopsy. Importantly, the study found that LGE was present in 47% of patients without evidence of cardiac amyloidosis by echocardiography. LGE presence and pattern was associated with New York Heart Association class, ECG voltages, left ventricular mass index and thickness, right ventricular thickness, troponin-T, and B-type natriuretic peptide levels. The global LGE patterns were associated with the worst clinical, ECG, echocardiographic and biomarker abnormalities compared to other types of LGE (focal or suboptimal nulling).

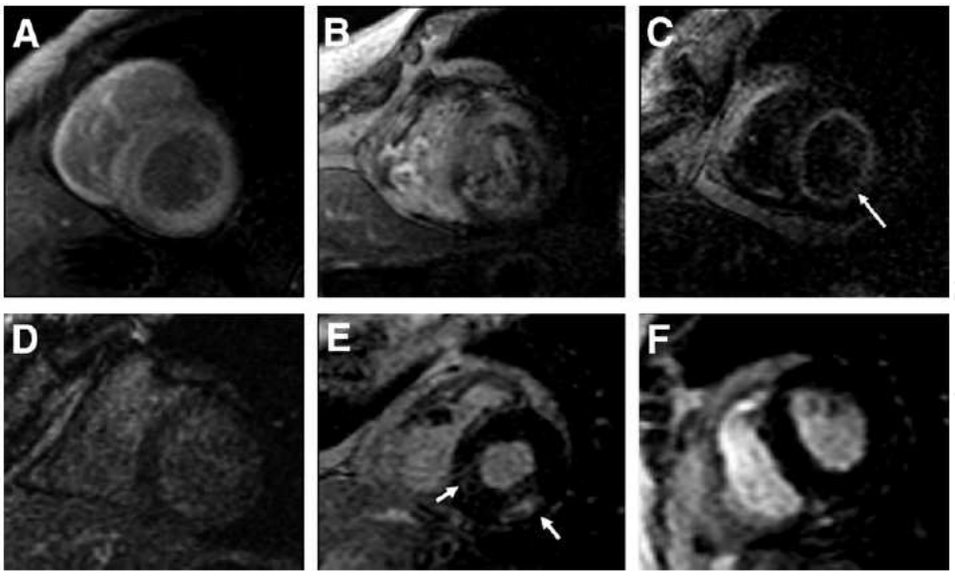

Figure 5. The different patterns of LGE on CMR in patients with cardiac amyloidosis. (With permission from Syed et al. *JACC Cardiovasc Imaging.* 2010;3:155-164.)

CMR relaxometry is a novel approach in the diagnosis of cardiac amyloidosis, showing elevated relaxation times in patients with the disease. A T1 relaxation time cutoff value of

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≥1273 milliseconds was found to be both sensitive and specific for the diagnosis of cardiac amyloidosis.[110]

Based on these studies, it is apparent that gadolinium-enhanced CMR is the most accurate imaging modality to diagnose cardiac amyloidosis. LGE is common in cardiac amyloidosis and it is due to interstitial expansion from amyloid deposition and kinetic change of gadolinium in the blood pool and myocardium/interstitia. This modality may potentially detect early cardiac involvement in patients with amyloidosis and normal left ventricular wall thickness.[43, 107] It also affords global assessment of the heart, eliminating the sampling error that endomyocardial biopsy may potentially carry.[111] Furthermore, it may be useful in detecting subclinical early cardiac involvement;[43] indeed studies have shown that even early cardiac involvement carried a significant mortality risk, in particular cardiac mortality.[112, 113] Serial CMR studies may have the potential to chart the progression or regression of the disease over time after the initiation of treatment.[114] However, despite the high sensitivity and specificity of CMR in the diagnosis of cardiac amyloidosis, similar patterns, while uncommon, have been occasionally reported in systemic sclerosis and post-heart transplant patients. The autopsy study by Syed et al suggests that rarely, gadolinium-enhanced CMR may be falsely negative because the amyloid infiltrate is mild.[107]

CMR may be a reasonable adjuvant or even an alternative to endomyocardial biopsy, especially in patients with a tissue diagnosis from a remote site and who are high-risk for invasive investigation. However, it is important to notice that the diagnosis of cardiac amyloidosis is confirmed by demonstrating amyloid deposits on endomyocardial biopsy. Cardiac amyloidosis may be presumably, but not conclusively, established in patients with appropriate cardiac imaging findings with demonstration of amyloid deposits on histological examination of a biopsy from other tissues (e.g., abdominal fat pad, rectum, or kidney).

There are several limitations in the use of this modality. Firstly, it is incompatible with patients with implanted devices such as pacemakers or implantable cardioverter-defibrillators. Nevertheless, pacemakers compatible with magnetic resonance imaging were recently approved by the United States Food and Drug Administration for clinical use in the 1.5 tesla magnetic resonance imaging scanner. Secondly, gadolinium contrast administration is contraindicated in patients whose creatinine clearance is less than 30 mL/minute given the risk of nephrogenic systemic fibrosis.[115] Many patients with cardiac amyloidosis have indications for heart failure device therapy (e.g. pacemakers, implantable cardioverter-defibrillators) as well as renal impairment as a result of amyloid deposition in the kidneys, both of which may preclude them from undergoing CMR.

5.4. Nuclear scintigraphy

Several single-photon emission computed tomography tracers have been evaluated in the diagnosis of cardiac amyloidosis.[116] There is evidence that [123]I-metaiodobenzylguanidine may be an indirect measure of cardiac amyloid deposition. The finding of intense uptake in the heart on [99]mTc-pyrophosphate scintigraphy, which was indicative of cardiac amyloidosis, was insufficiently sensitive to warrant routine use in the diagnosis of the disease. While not routinely performed for diagnosing cardiac amyloidosis given its variable

sensitivity, a new technique, [99]mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, may be able to differentiate familial transthyretin-associated amyloidosis from AL amyloidosis, a clinically-relevant distinction; however, further study into this new technique is needed.[117]

5.5. Fat aspirate and endomyocardial biopsy for tissue diagnosis

Even with current imaging technology, amyloidosis remains a histological diagnosis (Figure 6). The presence of serum or urine monoclonal paraprotein is suggestive of AL amyloidosis, but on its own does not firmly establish the diagnosis because low serum concentrations of a monoclonal protein (possibly from an unrelated monoclonal gammopathy of undetermined significance) can incorrectly suggest AL amyloid in some familial cardiac amyloidosis confirmed later by cardiac biopsy.[118] For the diagnosis of systemic disease, less invasive tissue sampling methods are available.[9] Biopsies may be taken from the abdominal subcutaneous fat, with sensitivities of >80% for the latter in AL.[119-121]. Abdominal subcutaneous fat aspiration is easily obtained with minimal risk and is now preferred over rectal biopsy. Endomyocardial biopsy should be considered if the diagnosis of amyloidosis cannot be made with noninvasive techniques and the suspicion of cardiac amyloidosis remains high, or in cases of isolated cardiac amyloidosis, for example in the isoleucine 122 form of familial amyloidosis and senile systemic amyloidosis.[9] The sensitivity of four endomyocardial biopsy samples for the disease is nearly 100%.[111] Mass spectrometry of the tissue biopsy is used to determine the type of amyloidosis.

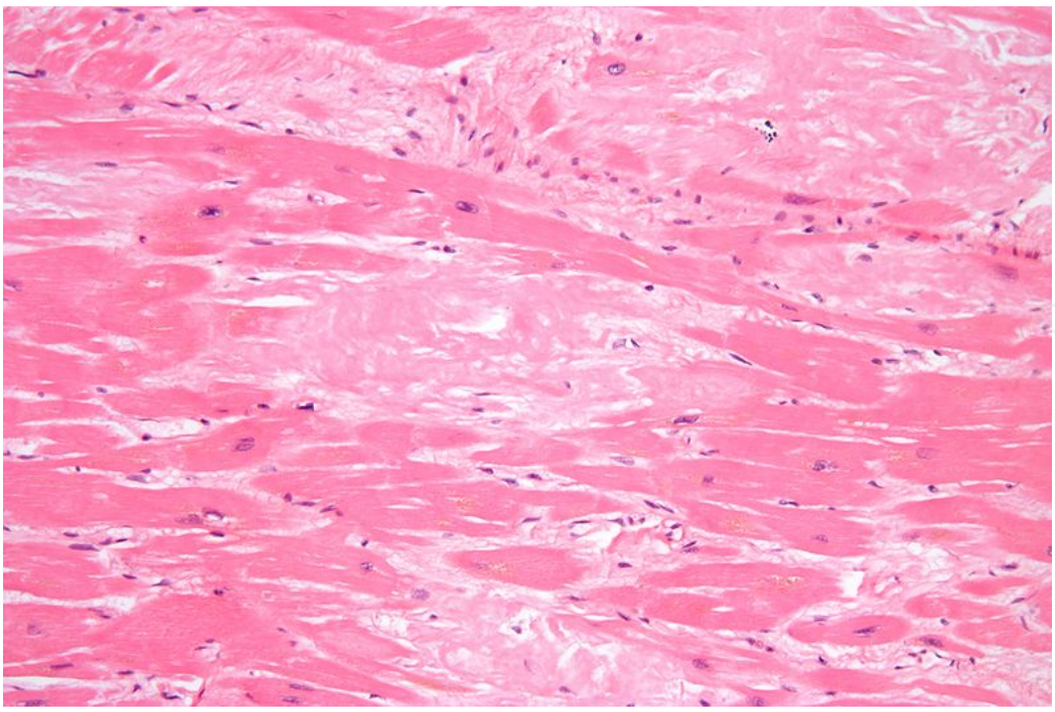

Figure 6. Histologic findings classical of cardiac amyloidosis. Hematoxylin and eosin staining of an amyloid-infiltrated left ventricular myocardium is shown here. The amyloid protein stained an amorphic light pink color (arrows).

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5.6. Biochemical markers and prognostication

Cardiac biomarkers may be elevated in cardiac amyloidosis, often disproportionate to the clinical presentation.[122] Amyloid-induced myonecrosis and small vessel ischemia causes raised cardiac troponins,[123] while diastolic dysfunction and upregulation of natriuretic peptide genes in diseased ventricles result in elevated B-type natriuretic peptide levels.[124]

Cardiac troponins and N-terminal-pro-B-type natriuretic peptide are important prognostic indicators in cardiac amyloidosis, and also allow for monitoring progression of disease or efficacy of therapy.[43, 77, 125-127] One study showed a significantly decreased median survival in patients with troponin elevation; this may even predict survival better than symptomatic congestive heart failure and two-dimensional echocardiographic findings.[128] A 30% decrease in N-terminal-pro-B-type natriuretic peptide after effective chemotherapy correlates with increased event-free survival even without objective echocardiographic findings.[129] A combination of high-sensitivity cardiac troponin T at presentation and N-terminal-pro-B-type natriuretic peptide changes after chemotherapy had superior predictive value for survival.[130] Serum uric acid is a novel independent prognostic factor in AL amyloidosis. The median overall survival was lower in patients with uric acid levels ≥8 mg/dL.[131] A combination of uric acid, troponin T and N-terminal-pro-B-type natriuretic peptide provides a strong predictive model for early mortality.[132]

The serum immunoglobulin free light chain assay enables quantification of aberrant circulating amyloidogenic fibril protein precursors.[129] It enables serial monitoring of amyloidogenic light chain production during chemotherapy.[133] A fall in aberrant free light chain production by half following chemotherapy was associated with reductions in N-terminal-pro-B-type natriuretic peptide but not in left ventricular wall thickness, and was associated with clinical improvement.[129] Further highly reproducible and quantifiable imaging studies such as CMR may assist in defining associations between cardiac function and alterations in light chain load.[43]

6. Management of cardiac amyloidosis

Although the management of cardiac amyloidosis is challenging, evolution of treatment options have improved prognosis. It is essential to determine the type of amyloidosis to guide treatment.[43] In general, the management aims can be broadly divided into the general supportive care of cardiac and extracardiac manifestations of the disease, as well as type-specific targeted therapy.[5, 43] Table 2 shows a general algorithm for the investigation and management of cardiac amyloidosis.

Step 1 – Identification of clinical scenarios suspicious for cardiac amyloidosis

Any one of the features below could trigger clinical suspicion – NOT all are required

•Dyspnea with exertion or heart failure of unknown etiology, often with thickening of the LV and/or RV walls, especially if associated with low voltages on ECG

•Unexplained fatigue and weight loss

•Associated hepatomegaly, nephrotic-range proteinuria, peripheral or autonomic neuropathy, carpal tunnel syndrome, family history of amyloidosis

•Periorbital purpura (rare but almost pathognomonic) and macroglossia

Step 2 – Cardiac diagnostic assessment

•Detailed echocardiographic examination including diastolic function analysis, tissue Doppler, strain imaging, assessment of RV wall thickness

•Cardiac MRI with late gadolinium enhancement

•Cardiac biomarkers: troponin T and NT-proBNP

Step 3 – Further evaluation for the diagnosis of amyloidosis

•Screening biopsy of abdominal subcutaneous fat aspirate or rectal mucosa with Congo red staining

•Screen serum and urine for monoclonal protein, serum free light chain assay

•If clinical suspicion remains high despite the above being negative, consider endomyocardial biopsy (or other involved organ) with Congo red staining

Step 4 – Determination of the amyloid fibril type (if the diagnosis of amyloidosis is made)

Tissue diagnosis and correct typing of amyloid is critical

•Mass spectrometry based proteomic analysis of tissue containing amyloid to determine specific type of amyloid protein

Step 5 – Do specific testing based on type of amyloidosis

•Bone marrow aspirate and biopsy if diagnosis is AL amyloidosis or myeloma with associated amyloidosis

•For TTR-related amyloidosis, genetic testing to distinguish between age-related and hereditary variant TTR types

•For other hereditary amyloidoses, appropriate genetic testing for family counseling

Step 6 – Type-specific treatment

•AL amyloidosis: quantify light chains (as baseline for follow-up), exclude concomitant myeloma, troponin and NT-proBNP measurements for staging (if not done), supportive therapy, and determine which chemotherapy (including possible autologous stem cell transplant) and/or whether, sequential cardiac and autologous stem cell transplant is appropriate

•Familial amyloidosis: supportive therapy; assess for liver transplant with or without heart transplant

•Reactive amyloidosis: treating the underlying chronic inflammatory state and anti-cytokines therapy (IL-6, TNFα)

•Senile systemic amyloidosis: supportive therapy and possibly tafamidis in the future

AL, immunoglobulin light chain; ECG, electrocardiogram; LV, left ventricular; NT-proBNP, N-terminal prohormone brain natriuretic peptide; RV, right ventricular; TTR, transthyretin

Table 2. Evaluating a patient with suspected cardiac amyloidosis.

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6.1. General supportive care

The traditional teaching that amyloidosis with cardiac involvement is universally fatal has dramatically changed in the last decade, largely due to chemotherapy and stem cell transplant therapies. However, important supportive care measures are necessary to achieve these outcomes.

Cardiac manifestations of amyloidosis primarily include heart failure and cardiac arrhythmias. The mainstay of heart failure treatment in cardiac amyloidosis is diuresis; patients with hypoalbuminemia due to concomitant nephrotic syndrome require high doses. It is essential to monitor fluid balance meticulously with daily weighing and diuretic dose adjustment.[5, 43] For a variety of reasons, beta-blockers, [9] renin-angiotensin system inhibitors,[5, 43] digoxin [134, 135] and calcium channel blockers[136]-[138] should be avoided where possible. In markedly impaired diastolic filling and reduced stroke volume, tachycardia is a compensatory mechanism that maintains cardiac output. Consequently, high doses of beta-adrenergic receptor blocking agents are often poorly tolerated. Calcium channel blockers and digitalis are considered contraindicated in cardiac amyloid disease due to potential binding of amyloid fibrils and potentiation of drug toxicity. Evidence for the use of vasodilator or inotropic agents in cardiac amyloidosis is lacking, but renal-dose dopamine may be helpful in the treatment of anasarca if renal function is unimpaired.[5] Recurrent large pleural effusions may represent pleural amyloid and may require thoracentesis and occasionally, pleurodesis.[139] Placement of a pleural catheter can helpful for palliation of recurrent pleural effusions. Anticoagulation should be administered for standard indications such as intracardiac thrombus and atrial fibrillation, and an embolic event even in the absence of atrial fibrillation should trigger a search for intracardiac thrombosis.[14, 43, 97, 140] Appropriate selection of patients suitable for thromboembolic prophylaxis is difficult given the high anticoagulation-associated bleeding risk due to vascular fragility and coagulopathy in amyloidosis.

Patient with cardiac amyloidosis are predisposed to many different types of arrhythmias, [57, 58] most commonly atrial fibrillation.[58] Given the atrial dilation from increased ventricular end-diastolic pressures as well as atrial amyloid infiltration, restoration of sinus rhythm is challenging and frequently unsuccessful in the long term.[14] It is reasonable, however, to attempt sinus rhythm restoration with DC cardioversion in highly symptomatic and medication refractory cases, provided no atrial thrombus is present by TEE. Atrial fibrillation recurs in most patients, and as such a rate-control and anticoagulation strategy is warranted in most circumstances. Patients with AL amyloidosis with concomitant AF are at an extremely high risk of thromboembolism, and the thromboembolic risk in transthyretin-related amyloidosis is also elevated above that of non-amyloid AF patients. Proper anticoagulation therapy reduces thromboembolic risk.[14] Amiodarone can be useful as both a rate controlling and rhythm maintaining agent. Amiodarone is presumed safe in cardiac amyloidosis although systemic study is lacking. Patients must be monitored for the known toxicities, and the drug should be avoided in the presence of significant conduction disease (e.g., left bundle branch block) without pacemaker placement. Dronedarone as well as many other antiarrhythmic medications (typically of classes IA, IC and III) have not been well studied

in cardiac amyloidosis. However, based on studies in patients with structural heart disease and heart failure, they should be considered as contraindicated in advanced amyloid patients at this time. Sudden death is often due to electromechanical dissociation; however, ventricular tachyarrhythmias are not infrequent.[102] The role of implantable cardioverter-defibrillator for primary prevention of sudden cardiac death in cardiac amyloid remains unclear and controversial. Strategies to reduce the elevated defibrillation thresholds in cardiac amyloidosis such as a subcutaneous array lead system may improve the efficacy of implantable cardioverter-defibrillator therapy.[141] The standard indications for pacing generally apply to cardiac amyloidosis,[142] but the threshold to introduce pacing is often lower in view of the propensity for the concomitant autonomic neuropathy and hypoalbuminemia to worsen any preexisting amyloidosis-related hemodynamic compromise.[43] Dual-chamber pacing may be particularly useful for optimizing the atrial filling component in this restrictive cardiomyopathy.[43] However, there is no evidence that the symptomatic improvement from pacing translates into increased survival.[143] The generally accepted indications for cardiac resynchronization therapy apply in cardiac amyloidosis.[144] There are currently no prospective randomized controlled trials evaluating the use of continuous intra-axial cardiac flow pumps and left ventricular assist devices, but one patient received the former in a feasibility study with subsequent symptom relief.[145]

6.2. Targeting the underlying amyloid pathology

This is an area of management that is specific to the type of amyloidosis, but the general aim is to decrease the formation new amyloid proteins and possibly facilitate the regression of existing deposits.[5, 43] Recent advancements in both our ability to diagnose the type of amyloidosis and the treatment options for the various types have greatly improved outcome.[43]

AL amyloidosis. The mainstay of treatment in this type of amyloidosis is targeting the pathogenic light chain-producing clonal plasma cells with chemotherapy.[146-152] This minimizes amyloid production (potentially reversing the disease process), preserves organ function and enhances survival.[153, 154] Indeed, immunoassays for free light chains are useful in monitoring the disease process and responses to treatment, and halving the aberrant monoclonal light chain on a sustained basis improves survival.[154] Reducing the circulating amyloidogenic precursor may result in some improvement in cardiac function even as the cardiac amyloid load found on echocardiography remains fairly constant.[129] These findings supports the direct toxic role of the aberrant monoclonal light chain on myocardial function that was shown in an animal model.[47] Moreover, similar findings were observed in other organs. For example, serial kidney biopsies in patients with AL amyloidosis before and after clinically successful treatments reveal unchanging amyloid burden despite significant improvement in proteinuria.[155, 156]

For patients who are fit for chemotherapy, several treatment regimens exist. The historic regimen of melphalan and prednisolone had responses that were few and much delayed; [157] more rapid responses are seen with intermediate-intensity regimens like melphalan and dexamethasone.[43] High-dose chemotherapy with autologous stem cell replacement

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has been attempted, but significant cardiac involvement precludes it given the high peri-treatment mortality.[5, 153] Many patients are diagnosed at a stage at which such an aggressive therapeutic modality is too toxic; early studies in which patients were not carefully selected for high-dose chemotherapy with autologous stem cell transplant had transplant-related mortality of nearly 50%.[5, 158] The presence of symptomatic and structural features of cardiac amyloidosis strongly predicts poor outcomes from autologous stem cell replacement,[159, 160] and the presence of clinical findings consistent with advanced disease, multiorgan involvement and poor functional status should preclude autologous stem cell therapy.[160, 161] Newer and investigational approaches include thalidomide or lenolidamide mono- or combination therapy,[151, 162, 163] rituximab to target CD20-positive plasma cell clones,[164] and the proteasome inhibitor bortezomib.[165-167] Heart transplantation is infrequently performed due to concerns about extracardiac disease progression as well as amyloid deposition in the transplant heart. Indeed heart transplant survival rates were lower in cardiac amyloidosis compared with other indications.[168, 169] Sequential heart and stem cell transplant is promising in young patients with cardiac failure and preserved extracardiac organ function, with a 1-year survival of between 75% and 83%.[170-173] While there are several predictors of prognosis, it is at present difficult to select patients for the appropriate treatment regimen.[5, 43] In some patients high-intensity regimens may be excessive, but in others the disease remains refractory even to the most intense of regimens.[43] Therefore highly-individualized management of cardiac amyloidosis is essential.[43]

Familial amyloidosis. Because plasma transthyretin is mainly synthesized in the liver, definitive treatment for familial amyloidosis requires liver transplantation to arrest the synthesis of amyloidogenic proteins, as well as transplantation of failed organs.[174] Outcomes are generally favorable in young and fit patients with the methionine 30 mutation. However, in older patients of the non-methionine 30 variants, paradoxical acceleration of disease progression has been reported, necessitating combined heart and liver transplants.[175-177] There is some evidence that transthyretin can be stabilized by certain nonsteroidal agents like diflunisal; clinical trials are necessary to investigate their efficacy in preventing disease progression.[178] These agents, however, may precipitate or aggravate congestive heart failure by fluid retention, and other agents are actively being sought.[179] One promising therapeutic candidate is tafamidis, a small-molecule transthyretin stabilizer which prevents transthyretin from forming amyloid fibrils. Tafamidis has demonstrated efficacy for the treatment of ATTR polyneuropathy, and has therefore been granted orphan drug status in the United States. Tafamidis is currently undergoing Phase II trials for the treatment of ATTR cardiomyopathy.[180]

Reactive amyloidosis. Definitive treatment involves treating the underlying inflammatory process and decreasing the serum amyloid A concentration, improving survival.[181] Inflammatory syndromes such as rheumatoid arthritis, Crohn's disease, seronegative spondyloarthropathies, and several periodic fever syndromes can be effectively treated with tumor necrosis factor and interleukin-1 inhibitors.[182] Familial Mediterranean fever can be treated with colchicine,[183] while excision of interleukin-6-secreting masses is an effective treat-

ment for Castleman's disease.[184] A randomized controlled trial showed that eprodisate slows the decline of renal function in reactive amyloidosis, [185] and may have possible applicability to other types of amyloidosis.[186]

Currently, there is no known treatment that specifically targets senile amyloid, but research into this field is quickly evolving. Investigational approaches undergoing intensive research include targeted therapies that stabilize the soluble form of amyloidogenic proteins and reverse preexisting deposits. A new therapy based on epigallocatechin gallate, a compound that binds to denatured protein thereby inhibiting the formation of insoluble amyloid, has been proposed.[65] These potential new therapies offer exciting prospects for improvements in treatment.[43, 65]

7. Conclusion

Amyloidosis describes a heterogeneous group of several uncommon diseases by aberrant protein deposition in tissues throughout the body. Cardiac amyloidosis refers to clinically significant cardiac involvement, causing restrictive cardiomyopathy and its resultant effects, the most severe being congestive heart failure and arrhythmias. It is often underdiagnosed. However, recent advances in imaging have allowed us to accurately diagnose the condition and better characterize the degree of cardiac involvement. Cardiac biomarkers are useful in monitoring disease progression and response to therapy. The treatment of cardiac amyloidosis is rapidly evolving, and encompasses general supportive care of cardiac and extracardiac manifestations of the disease, and in addition, the management of the underlying amyloid disease process. Importance must be attached to early diagnosis of the disease, particularly in AL amyloidosis, because patients diagnosed late are often too ill to undergo disease-modifying chemotherapy. Novel therapies are actively being investigated and may present exciting new frontiers in the treatment of the disease.

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