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Cardiac Amyloidosis: An Update on Pathophysiology, Diagnosis, and Treatment

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Abstract

The amyloidoses are a group of systemic diseases characterized by organ deposition of misfolded protein fragments of diverse origins. The natural history of the disease, involvement of other organs, and treatment options vary significantly based on the protein of origin. In AL amyloidosis, amyloid protein is derived from immunoglobulin light chains, and most often involves the kidneys and the heart. ATTR amyloidosis is categorized as mutant or wild-type depending on the genetic sequence of the transthyretin (TTR) protein produced by the liver. Wild-type ATTR amyloidosis mainly involves the heart, although the reported occurrence of bilateral carpal tunnel syndrome, spinal stenosis and biceps tendon rupture in these patients speaks to more generalized protein deposition. Mutant TTR is marked by cardiac and/or peripheral nervous system involvement. Cardiac involvement is associated with symptoms of heart failure, and dictates the clinical course of the disease. Cardiac amyloidosis can be diagnosed noninvasively by echocardiography, cardiac MRI, or nuclear scintigraphy. Endomyocardial biopsy may be needed in the case of equivocal imaging findings or discordant data. Treatment is aimed at relieving congestive symptoms and targeting the underlying amyloidogenic process. This includes anti-plasma cell therapy in AL amyloidosis, and stabilization of the TTR tetramer or inhibition of TTR protein production in ATTR amyloidosis. Cardiac transplantation can be considered in highly selected patients in tandem with therapy aimed at suppressing the amyloidogenic process, and appears associated with durable long term survival.

Keywords

AL amyloidosis; transthyretin amyloidosis; restrictive cardiomyopathy

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Introduction and Classification

Cardiac amyloidosis is a restrictive cardiomyopathy marked by extracellular accumulation of misfolded protein fragments. The systemic amyloidoses are classified by the misfolded precursor protein and display significant heterogeneity in clinical course, prognosis and treatment considerations that depend upon the type of protein involved. While there are over 27 known proteins that can aggregate as amyloid (1), defined histologically by staining with Congo red, nearly all cases of cardiac amyloidosis result from only two protein precursors. Cardiac amyloidosis may represent one aspect of a systemic disease with multi organ involvement, as is seen with AL (light-chain) amyloidosis where amyloid protein is derived from misfolded immunoglobulin light chains in the context of a plasma cell dyscrasia. Other organ systems commonly involved in AL amyloidosis include the kidneys (manifesting commonly as nephrotic syndrome), soft tissue, the gastro-intestinal tract, and the autonomic nervous system (2). Table 1 details the extra cardiac manifestations of systemic AL amyloidosis (3). Distinct from AL amyloidosis, transthyretin (ATTR) amyloidosis results from accumulation of the protein transthyretin (formerly known as prealbumin) that is produced by the liver (4), (5). ATTR cardiac amyloidosis is further sub-divided into two disease entities depending upon the amino acid sequence of the protein. Wild-type (formerly known as senile systemic) ATTR cardiac amyloidosis (abbreviated ATTRwt) is thought to be largely cardiac restricted, although soft tissue deposition occurs, and can be clinically manifest as bilateral carpal tunnel syndrome, biceps tendon rupture and spinal stenosis. In contrast, hereditary or mutant ATTR cardiac amyloidosis (ATTRm) which results from inherited mutations in the transthyretin gene, often also involves the peripheral and autonomic nervous system, depending on the mutation. Mutations in the form of single nucleotide polymorphisms exhibit an autosomal dominant inheritance pattern, rendering a 50% chance of passage to offspring (6). Other manifestations of systemic amyloidosis may also involve the heart, including secondary (AA) amyloidosis due to chronic inflammatory conditions, apolipoprotein associated amyloidosis, or gelsolin familial amyloid polyneuropathy, but these are not common contributors to cardiac amyloidosis (7). It is imperative to accurately recognize cardiac involvement in systemic amyloidosis, as therapeutic options are constrained by reductions in cardiac function, and the degree of impairment serves as the principal determinant of prognosis and clinical course.

This review aims to describe clinical features, diagnostic tools, and therapies available for the assessment and treatment of cardiac amyloidosis.

Pathophysiology

Cardiac amyloidosis results in increased biventricular wall thickness and ventricular stiffness, which are hallmarks of this restrictive cardiomyopathy. Atrial infiltration by amyloid protein likely contributes to the high prevalence of atrial fibrillation in this disease. Electromechanical dissociation results from this atrial infiltration as well, and increases the risk of atrial thrombus formation and thromboembolism, even in sinus rhythm (8), (9), (10). In addition, in AL disease, amyloid can deposit within and/or around the small arterioles of the heart resulting in the clinical syndrome of angina, or in some cases, myocardial

infarction (11). Coronary flow reserve abnormalities by positron emission tomography (PET) have been reported in patients with microvascular amyloid infiltration (12).

In addition to interstitial infiltration, cardiac dysfunction in AL amyloidosis may also result from direct light chain toxicity (13). Amyloidogenic free light chains can promote lysosomal dysfunction which leads to the generation of reactive oxygen species and eventually cell death (14). Microvascular dysfunction may also result from arteriolar abnormalities caused by light chain proteotoxicity (15). Thus, there is ample evidence that, in addition to the restrictive physiology caused by direct extracellular protein infiltration, direct light chain toxicity contributes to the pathophysiology of AL cardiac amyloidosis.

Systemic AL amyloidosis

Amyloid fibrils in AL amyloidosis are derived from immunoglobulin light chains that are produced by a plasma cell clonal process like multiple myeloma, but usually with lower plasma cell involvement (<20%) in the bone marrow. The incidence of AL amyloidosis is approximately 1 per 100,000 or 2500-5000 new cases annually in the US (16). About 10% of patients with multiple myeloma may have AL amyloidosis, however, and a similar percentage of AL amyloidosis patients may have multiple myeloma (17). Between 50-70% of AL amyloidosis patients have some degree of heart involvement (18), depending upon definition, which is the most important determinant of survival as historically, patients with untreated AL cardiac amyloidosis and congestive heart failure evidence an overall median survival of only six months (16). Tremendous advances in survival have been made in AL amyloidosis with contemporary treatment strategies extending median survival to > 5 years or longer (19).

Transthyretin amyloidosis (ATTR)

Transthyretin (TTR) is a plasma transport protein synthesized by the liver that circulates as a stable tetramer. Formerly known as prealbumin, the function of TTR is to transport thyroid hormone and retinol (vitamin A). In the course of aging, through unclear mechanisms, or in the setting of a mutation, thermodynamic stability of the TTR protein is altered to favor dissociation into oligomers and monomers which then result in organ dysfunction through direct toxicity and/or accumulation as amyloid fibrils.

Wild type (formerly referred to as senile systemic or senile cardiac) ATTR amyloidosis predominantly affects the heart with a striking male predominance (6), however, a recent cohort from two amyloid referral centers in Europe demonstrated a higher prevalence of females with ATTRwt (19%) than was previously assumed (20). Prevalence definitively increases with age and up to 25% of patients over the age of 80 have demonstrable amyloid deposition by histopathology (21). Recent studies suggest that ATTRwt may account for up to 10% of elderly patients with heart failure (22).

In contrast, ATTRm amyloidosis varies in prevalence and the pattern of organ involvement depending on the mutation. Unlike ATTRwt that almost solely affects the heart, ATTRm amyloidosis is also characterized by some combination of sensory and motor small fiber polyneuropathy. Mutations can cause familial amyloid polyneuropathy (FAP) or familial

amyloid cardiomyopathy (FAC), or both. Table 2 summarizes the key features of the most common ATTR mutations associated with cardiac amyloidosis.

Diagnosis of cardiac amyloidosis: noninvasive imaging

Electrocardiography

Low voltages on ECG in the setting of increased left ventricular wall thickness on echocardiogram is a classic feature of cardiac amyloidosis (23). Pseudo infarct patterns may occur in approximately 50% of patients with AL cardiac amyloidosis (24). In addition, atrioventricular block may be seen in up to 22% of patients with cardiac amyloidosis. Intraventricular conduction delays and bundle branch blocks are also common ECG features of cardiac amyloidosis, and are more commonly observed in ATTR (25). Finally, ECG defined left ventricular hypertrophy can also be observed in approximately 10-15% of patients with AL amyloidosis, but this likely reflects preexisting hypertensive heart disease, with superimposed amyloidosis (24).

Echocardiography

Echocardiography, standard of care testing for all patients with heart failure, is the imaging modality that most often raises suspicion for cardiac involvement. Historically, “granular sparkling” or “speckling” of the myocardium was felt to be diagnostic of cardiac amyloidosis. With advances in digital image analysis techniques (particularly harmonic imaging), myocardial speckling has a low sensitivity and specificity for diagnosis of cardiac amyloidosis (26). Cardiac amyloidosis is characterized by symmetrically increased biventricular wall thickness (LV wall thickness >12 mm, and is often ≥15 mm), in the setting of a non-dilated ventricle (27). Wall thickness is generally more prominent in patients with transthyretin cardiac amyloidosis at diagnosis, as patients with AL amyloidosis tend to become symptomatic earlier on in the disease course.

Extracellular deposition of amyloid protein leads to this increase in wall thickness, and contributes to ventricular stiffening and LV diastolic dysfunction. Advanced diastolic dysfunction (pseudonormalization or restrictive filling) is the norm. Elevated biventricular filling pressures, as well as direct atrial infiltration by amyloid protein, lead to atrial dilation. Low or even absent trans mitral A velocities are often encountered in patients with an advanced restrictive cardiomyopathy, despite sinus rhythm. A trans-mitral A velocity of less than 30 cm/sec was associated with intracardiac thrombi in AL cardiac amyloidosis patients without atrial fibrillation (10). Amyloid infiltration also leads to thickening of the interatrial septum, valvular thickening and valvular regurgitation (28). Small pericardial effusions are common, but larger effusions and tamponade are relatively rare (29).

Unlike LV diastolic dysfunction, which is impaired early in the disease process, global LV systolic function, as assessed by the ejection fraction (EF), is usually preserved until advanced stages of disease. However, impairments in ventricular deformation as measured by global longitudinal strain (GLS) are often evident early in the course of the disease (30). Various deformation metrics involving ratios of apical to mid-ventricular or basal strain have been reported to be useful for differentiation of cardiac amyloidosis from other wall-

thickening diseases. In specific, an apical to basal ratio > 2.1 conferred high discriminative capacity for cardiac amyloidosis identification (31) (32). In addition, a higher relative regional strain ratio (average apical longitudinal strain divided by the sum of the average mid and basal longitudinal strain) is associated with a worse prognosis (31). Most recently, the dissociation between LVEF preservation and GLS reduction, expressed as an EF/GLS ratio, has been reported as a reproducible and accurate means to differentiate cardiac amyloidosis from other causes of LV thickening (33). Furthermore, GLS is an independent predictor of survival in patients with AL cardiac amyloidosis (34) that provides additive information to biomarkers and other clinical characteristics (35). Finally, longitudinal strain measures followed serially can also identify early cardiac improvement following treatment for AL amyloidosis (36), prior to changes in wall thickness or EF. Figure 1 demonstrates echocardiographic features of cardiac amyloidosis.

Cardiac Magnetic Resonance (CMR) Imaging

The myocardial deposition of amyloid fibrils increases extracellular volume (ECV) and results in the accumulation of gadolinium contrast (37). For this reason, late gadolinium enhancement (LGE) imaging has proven effective in identifying cardiac amyloidosis. While cardiac amyloidosis is typified by a characteristic pattern of diffuse sub-endocardial LGE that has been associated with clinical heart failure (37) and survival (38), different non-infarct LGE patterns, from sub endocardial to transmural, may be seen (39). The modality is useful as a screening test for cardiac amyloidosis. Among patients with multiple myeloma, CMR has sensitivity and negative predictive values of 100% and specificity and positive predictive values of 80% and 81% respectively for diagnosis of AL cardiac amyloidosis (40). Additionally, LGE by CMR is an independent predictor of mortality in patients with AL cardiac amyloidosis and has prognostic value beyond the usual clinical and laboratory data (41). Figure 2 shows common LGE patterns that may be encountered in patients with cardiac amyloidosis.

Myocardial and blood pool kinetics of gadolinium contrast are also abnormal in cardiac amyloidosis resulting in a smaller difference between blood and myocardial T1, a fundamental MR parameter on which image contrast is based (42). The contemporary approach to LGE imaging in cardiac amyloidosis involves use of a phase sensitive inversion recovery (PSIR) technique that has superior accuracy compared to conventional mag-IR (inversion recovery) LGE imaging (43).

LGE is very useful for differentiating abnormal from normal myocardium, but this presupposes regions of normal are present. Amyloidosis is a diffuse disease, and in many instances, there is no “normal” myocardium to contrast. Quantitative imaging techniques including non-contrast (native) T1 mapping and direct extracellular volume fraction (ECV) determination have been recently explored in cardiomyopathic diseases including amyloidosis. Extracellular volume (ECV) measurement has shown promise for detection of cardiac amyloidosis (44). Of the two quantitative techniques, ECV appears the most reproducible (not subject to field strength or technique differences) and confers insight into the severity of amyloid deposition (43). Inherently quantifiable, ECV may be a useful parameter to follow for treatment response.

Nuclear Scintigraphy

Bone-avid, phosphate-based isotopes, including ^{99m}Tc-PYP (pyrophosphate) and ^{99m}Tc-DPD (3,3-diphosphono-1,2-propanodiacarboxylic acid), have a specific avidity for ATTR amyloid deposits. An international consensus document has confirmed the utility of the bone-avid compounds for the accurate identification of ATTR amyloidosis (45), and differentiation from AL amyloidosis or other wall thickening diseases. The methodology has been demonstrated in a multi-center study as reproducible and accurate (46). ^{99m}Tc-PYP is now starting to be used clinically in the US and is highly useful for the detection of ATTR cardiac amyloidosis, but it is not useful for identification of AL. A ^{99m}Tc-PYP scan that does not show uptake, or shows mild uptake (Perugini grade 1), is completely consistent with AL amyloidosis (Figure 3). Conversely, a bone scintigraphy scan (^{99m}Tc-PYP or ^{99m}Tc-DPD) with abnormal uptake (grade 2 or 3), in combination with a negative plasma cell dyscrasia evaluation has a specificity and positive predictive value of 100% for diagnosis of ATTR cardiac amyloidosis (45). However, TTR genotyping must still be performed to differentiate wild-type from mutant ATTR cardiac amyloidosis. Finally, there is increasing evidence that amyloid specific positron emission tomography (PET) tracers, including 18-F florbetapir (47), and the 11-C Pittsburgh B compound (PiB) (48), can identify cardiac amyloidosis, specifically the AL type.

Diagnosis of cardiac amyloidosis: pathology

Cardiac Biopsy/Histology

Tissue biopsy remains the gold standard for diagnosis of amyloidosis, despite advances in noninvasive imaging. Since therapy for different kinds of amyloidosis varies widely and may be associated with significant toxicity, it is imperative to diagnose amyloidosis by Congo Red (or other amyloid specific) stain, and to ascertain the identity of the precursor protein. Monoclonal gammopathies (MGUS) are relatively common in ATTR amyloidosis, occurring in up to 10% of patients (49). As such, AL and ATTR can be confused if the proper diagnostic algorithm is not followed.

Abdominal fat aspirate can be safely performed in the outpatient setting and, in experienced hands, Congo red staining has a sensitivity of 70-90% for diagnosis of systemic AL amyloidosis (50), (51). However, abdominal fat aspirate is only 45% and 15% sensitive for diagnosis of ATTRm and ATTRwt amyloidosis, respectively (52). It is essential to identify the precursor protein by tissue biopsy in the case of AL amyloidosis, though the biopsy need not be cardiac. Cardiac involvement can be inferred in the setting of consistent non-invasive cardiac testing results and a positive extra-cardiac biopsy.

In patients with a plasma cell dyscrasia and equivocal cardiac imaging findings, or when AL cardiac amyloidosis needs to be differentiated from ATTR cardiac amyloidosis in the setting of a MGUS, an endomyocardial biopsy should be performed. Precursor protein identification can be accomplished by immunohistochemistry, electron microscopy, or mass spectrometry, depending upon institutional expertise.

Prognosis: AL cardiac amyloidosis

The prognosis of patients with AL amyloidosis has dramatically improved over time, with a four-year overall survival of approximately 90% for successfully treated patients with stem cell transplantation in the contemporary era (53). For patients with cardiac involvement successfully treated with stem cell transplantation, median overall survival can exceed 10 years (19), The Mayo Biomarker Stage is a risk score using pre-treatment serum cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) to stratify patients. Using threshold values of cTnT < 0.035 ng/mL and NT-proBNP < 332 pg/mL, patients were classified in stages I, II or III, if both biomarkers were negative, if one was positive, or if both were positive respectively. Median survivals were 26.4 months, 10.5 months, and 3.5 months (54). This score was subsequently enhanced with the addition of a fourth metric, the absolute difference in serum free light chains. Patients were assigned one point each for free light chain difference ≥ 18 mg/dL, cTnT ≥ 0.025 ng/mL and NT-proBNP ≥ 1800 pg/mL, resulting in stages I through IV with a total of 0 to 3 points respectively. This modified staging system resulted in improved risk stratification with mean overall survival ranging from 94.1 months for stage 1 to 5.8 months for stage IV (55). These staging systems have proven indispensable in selection of chemotherapeutic treatment regimen.

Prognosis: ATTR cardiac amyloidosis

The clinical course of ATTR cardiac amyloidosis varies significantly depending on the type of transthyretin fibrils involved (wild type vs mutant), as well as the specific mutations and the age of onset (6). In general, untreated ATTR cardiac amyloidosis is slowly progressive and has a better prognosis than AL cardiac amyloidosis. This is especially true of ATTRwt in which the median age of symptom onset is in the early 70's (compared to the early 60's in AL cardiac amyloidosis) and median survival ranges from three and a half to six years (20), (49), (56), (57).

Of the transthyretin mutations that lead to ATTR cardiac amyloidosis, the Val122Ile (valine to isoleucine at position 122; Ile122) mutation is the most common in the United States, being present in about 4% of African Americans (58). The four-year survival is 16% (59), owing in part to delayed recognition, with median survival of around 26 months (60) for this disease that is felt to be largely cardiac restricted. In contrast, the Thr60Ala (threonine to alanine at position 60; Ala 60) is also strongly associated with cardiac involvement, but peripheral neuropathy is also common, affecting about 60% of patients. Overall survival is similar to that of patients with Val122Ile, with an estimated four-year survival of 40% (61), (59). The Val30Met (valine to methionine at position 30; Met30) mutation is the most common worldwide and is strongly associated with peripheral neuropathy, with cardiomyopathy being present in a minority of patients. Val30Met patients have the best four-year survival at 79% (59).

Therapy

Medical therapy for heart failure in cardiac amyloidosis aims to relieve congestive symptoms of the infiltrative cardiomyopathy. Unlike other therapeutic interventions in heart failure, there are no randomized trials on which to base treatment decisions, thus

recommendations are made based on experience or data from small cohort studies. Diuretics are the mainstay and often a loop diuretic is used in combination with a mineralocorticoid receptor antagonist (such as spironolactone). Orthostatic hypotension is frequently observed in AL amyloidosis owing to involvement of the autonomic nervous system or toxicity from specific chemotherapy agents, and may significantly limit diuresis. Peripheral vasoconstrictors such as midodrine may be used for blood pressure support to support diuresis. Standard cardiomyopathy therapy with beta blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers often leads to hypotension and fatigue in patients with cardiac amyloidosis, thus limiting its tolerability in this population. A common scenario that should heighten clinical suspicion of cardiac amyloidosis is the development of profound hypotension and fatigue after initiation of beta blockers. Cardiac amyloidosis patients depend greatly on heart rate and contractility to maintain cardiac output, and beta blockade interferes with this adaptation. That stated, beta blocking medications at low dosage can be tolerated in some patients and may be used with caution for rate control in the context of atrial arrhythmias. Tolerance of high dose beta blockade suggests that cardiac amyloidosis is not present or not clinically important. ACE inhibitors and angiotensin receptor blockers compound the orthostatic hypotension that often occurs in amyloidosis due to autonomic dysfunction.

Atrial arrhythmias are common in cardiac amyloidosis, and rate control can prove to be challenging. In addition to beta blockers, calcium channel blockers are in general poorly tolerated in patients with cardiac amyloidosis. These drugs complex with amyloid fibrils, leading to unacceptable toxicities and may precipitate worsening heart failure (62). Pharmacologic rhythm control options are limited, although amiodarone is most commonly administered and relatively well tolerated. Catheter ablation may be attempted, however, in the case of typical atrial flutter, but for AF the recurrence rate is high (63), and the continued high risk of thromboembolic events warrants continued treatment with therapeutic anticoagulation. No clear guidelines exist for placement of implanted cardio-defibrillators (ICDs) and the rates of appropriate ICD therapies are high in patients with AL cardiac amyloidosis (64). However, overall mortality remains high following implantation, with pulseless electrical activity (PEA) being the dominant cause of death. Studies to date have not shown a survival benefit with ICD implantation for primary or secondary prevention (65). Therefore, ICDs are likely not associated with a significant mortality benefit and their routine use in AL cardiac amyloidosis is not recommended. Our general practice is to place devices for true secondary prevention episodes including aborted sudden death and/or documented sustained VT/VF.

ATTR cardiac amyloidosis

Organ transplantation

The majority of transthyretin is produced by the liver and thus orthotopic liver transplantation (OLT) is an attractive option for halting production of TTR in patients with ATTRm amyloidosis. Most of the experience with OLT has been in Val30Met patients, where early OLT can prevent the development of a peripheral neuropathy in at risk patients and halt the progression of organ deposition (66). Overall survival after OLT is 75% at five

years for patients with Val30Met amyloidosis (67). However, the widespread adoption of this treatment has been limited by reports of progressive amyloid cardiomyopathy and polyneuropathy after OLT, which is thought to be due to wild type TTR complexing with already deposited mutant ATTR in the heart and peripheral nervous system (68), in a process known as templating. In patients with a severe familial amyloid cardiomyopathy but no other disease manifestation, an orthotopic heart transplant (OHT) combined with an OLT can be performed, however outcomes after OHT for amyloid cardiomyopathy are worse than after OHT for other indications, so this therapy is not routinely employed (69). OLT is thus not offered to patients with the V122I mutation and those with wild-type ATTR as these patients often have isolated heart involvement and tend not to respond to organ transplantation. Additionally, most patients with severe cardiac amyloidosis are not OHT candidates due to age and other comorbidities. Nevertheless, in patients without other comorbidities who are transplant candidates, combined OHT and OLT may provide a good chance of extended survival.

TTR stabilization

One approach to treat ATTR amyloidosis involves the development of small molecule TTR stabilizers. Diflunisal is a generic non-steroidal anti-inflammatory drug (NSAID) that binds to the thyroxine binding sites on TTR, preventing dissociation of the TTR tetramer and amyloid fibril formation. As an NSAID, diflunisal is not tolerated by many ATTR amyloidosis patients owing to worsening volume overload and renal dysfunction, but data does suggest that some patients tolerate therapy (70), and importantly, a randomized, placebo-controlled trial of diflunisal in patients with FAP showed a reduction in progression of neuropathy in the diflunisal arm, with preservation of quality of life, after two years of treatment (71).

Tafamidis (Pfizer) is a novel, small-molecule TTR stabilizer that has been approved by the European Medicines Agency (EMA) for amyloid polyneuropathy, but not by the US FDA. Tafamidis has been shown to stabilize cardiac and neurologic function in ATTRm amyloidosis in a phase 2 trial (72), and a large phase 3 clinical trial for amyloid cardiomyopathy is fully enrolled, with results expected in 2018 (ATTR-ACT, NCT01994889). Another agent, AG10 (Eidos Therapeutics), has been shown to stabilize wild-type and mutant ATTR *in vitro* (73), but has yet to be tested in a human clinical trial.

TTR suppression

A second approach being currently pursued is suppression of TTR expression. Small interfering RNA (siRNA) are agents that bind to conserved sequences on TTR messenger RNA (mRNA), leading to degradation of the mRNA and reducing TTR gene expression. The siRNA patisiran (ALN-TTR02; Alnylam, Cambridge, MA) has been associated with significant reductions in serum TTR levels in a phase 2 study of patients with familial amyloid polyneuropathy, without serious adverse events (74). A phase 3 trial of patisiran in patients with FAP (APOLLO trial; NCT01960348) is currently underway. However, in a major setback, a phase 3 trial of the siRNA (ENDEAVOUR trial; NCT02319005) for cardiac amyloidosis was terminated prematurely due to increased mortality in the treatment arm. No increased risk has been reported with patisiran, however.

Anti-sense oligonucleotides (ASO) provide another strategy for reduction of TTR translation through suppression of gene expression. These are synthetic nucleotide sequences that bind to and promote degradation of mRNA (75). IONIS-TTRx (Ionis Pharmaceuticals, Carlsbad, CA) is an ASO which has proven to be safe in healthy volunteers during the course of a phase 1 trial, with a sharp decline in TTR production (76). A phase 2/3 trial of IONIS-TTRx in patients with familial amyloid polyneuropathy is ongoing (NCT01737398). Like the RNAi experience, clinical testing of a specific ASO agent for cardiomyopathy was also terminated owing to safety concerns (NCT02627820).

TTR disruption

Animal studies have demonstrated the ability of doxycycline to disrupt amyloid fibrils (77), while tauro-ursodeoxycholic acid (TUDCA) can reduce amyloid fibril aggregation (78). Acting synergistically, these drugs can reduce amyloid fibril concentrations (79). Natural polyphenols such as epigallocatechin-3-gallate (EGCG), the predominant polyphenol in green tea, and curcumin, the principle ingredient of turmeric also disrupt mature amyloid TTR fibrils *in vitro* (80). Larger trials are needed to explore the efficacy of these treatments.

AL cardiac amyloidosis

Chemotherapy/stem cell transplant

Treatment in AL amyloidosis is intended to normalize free light chain concentrations and eradicate the monoclonal paraprotein in blood and urine. A complete hematologic response (CR) is defined as normalization of the affected light chain in blood and urine, with normalization of bone marrow. An organ-specific response is associated with a reduction in markers of amyloid toxicity, marked by a reduction in serum nT-proBNP levels and LV wall thickness in the case of cardiac amyloid (19). The alkylating agent melphalan and the proteasome inhibitor bortezomib are most commonly used as first line chemotherapy, the latter is often used in combination with cyclophosphamide and dexamethasone as part of the CyBorD regimen (81). Treatment with such a bortezomib containing regimen may be associated with increased survival in patients presenting with symptomatic heart failure (82). Another approach involves administration of high doses of melphalan (HDM) followed by autologous stem cell transplantation (SCT) that is associated with extended survival (83). It is important to note that these favorable outcomes with HDM/SCT are achieved in a highly selected patient population deemed eligible for SCT with an estimated risk of peri-transplant mortality < 5%. For this reason, a randomized trial of oral melphalan and prednisone vs. HDM/SCT reported a high transplant-related mortality that significantly reduced any survival benefit that was seen from this therapy (84).

Emerging therapies

New anti-plasma cell therapies include the second-generation oral proteasome inhibitor ixazomib, and multiple myeloma drugs such as the proteasome inhibitor carfilzomib, the anti-plasma cell antibody daratumumab, and the antibody elotuzumab. Another exciting area of development involves administration of antibodies that specifically target the misfolded amyloidogenic light chain or deposited fibrils. The monoclonal antibody NEOD001 (Prothena Pharmaceuticals) targets amyloid fibrils and a phase I/II trial in AL amyloidosis

patients demonstrated a cardiac response rate of 50% (85), while another antibody based agent, 11-1F4 (Caelum Biosciences) is in earlier stages of clinical trial (86). An antibody directed against serum amyloid P (SAP) administered in conjunction with a SAP binding agent resulted in removal of amyloid deposits in a small phase I study (87), with larger studies planned.

Orthotopic heart transplantation (OHT)

OHT in patients with cardiac, and particularly AL, amyloidosis has been associated with a high risk of disease progression in the transplanted heart, as well as with a five-year survival of only 30% (88). While it seems reasonable to perform an OHT after CR has been achieved through treatment of the plasma cell dyscrasia, this strategy is not practical as most patients with AL cardiac amyloidosis are not candidates for aggressive chemotherapy owing to advanced myocardial dysfunction. Instead, a more feasible approach involves OHT followed closely by HDM/SCT. This approach yields a 5-year survival rate of 60% that is similar to non-amyloid cardiomyopathy treated with OHT (89), (90), with a median survival of 9.7 year (91). With these data in mind, cardiac amyloidosis is now an acceptable indication for OHT in the 2016 Listing Criteria of the International Society for Heart and Lung Transplantation (92).

Conclusions

Cardiac amyloidosis is a group of diverse diseases caused by extracellular deposition of misfolded protein derived most commonly from monoclonal light chains in the setting of a plasma cell dyscrasia (AL amyloidosis), or from accumulation of wild type or mutant transthyretin produced from the liver (ATTR amyloidosis). Heart involvement in the setting of systemic amyloidosis is important to diagnose as it is associated with significant morbidity and mortality. The flowchart in figure 4 details a diagnostic algorithm for identification of cardiac amyloidosis. While treatment has historically focused on symptomatic management of heart failure and dysrhythmias, advances in chemotherapy, immune therapy, stem cell transplantation, and modulation of gene expression are creating credible opportunities for durable remission and even cure, for what is rapidly becoming a treatable chronic disease.

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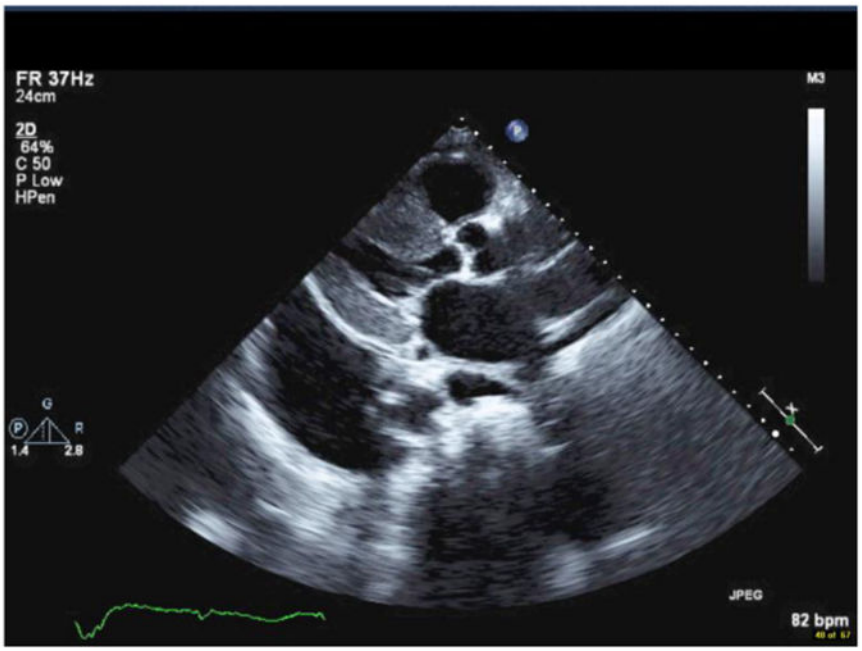

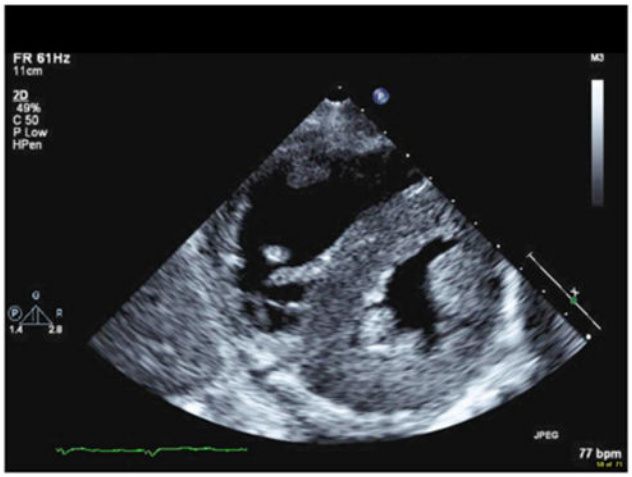

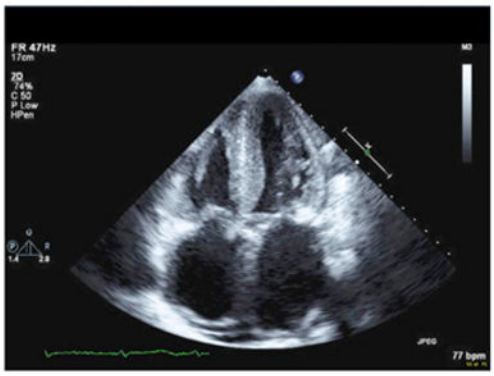

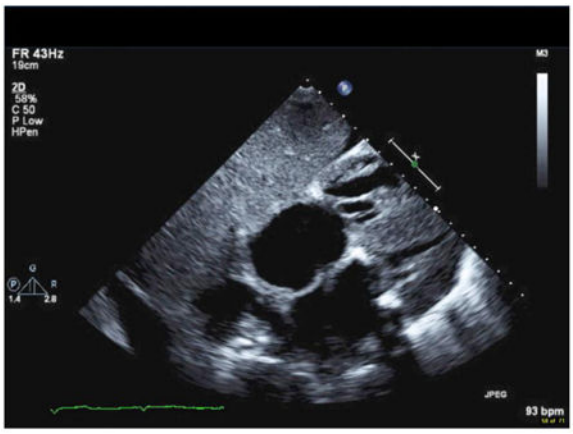

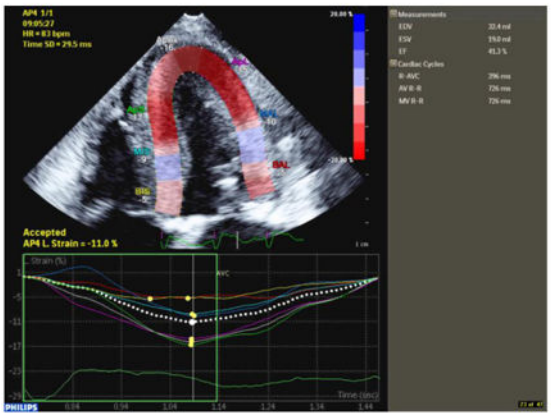

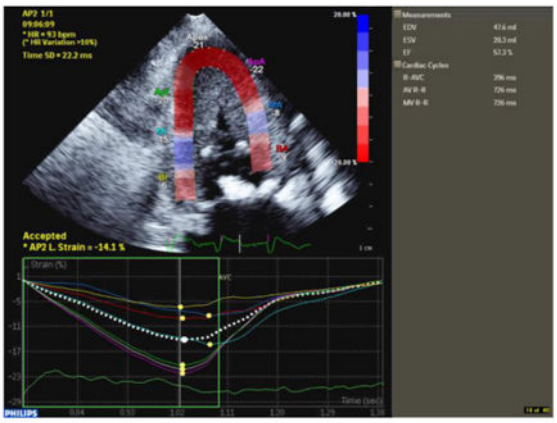

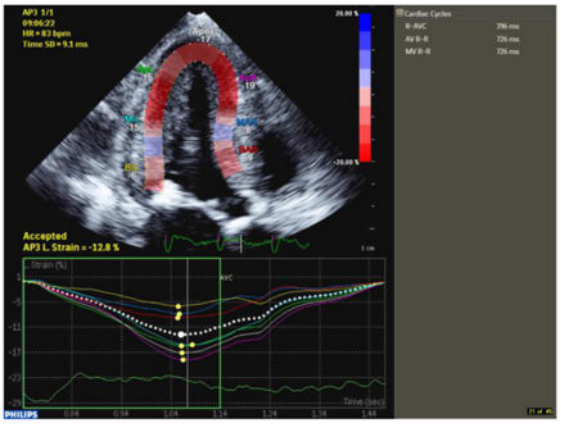

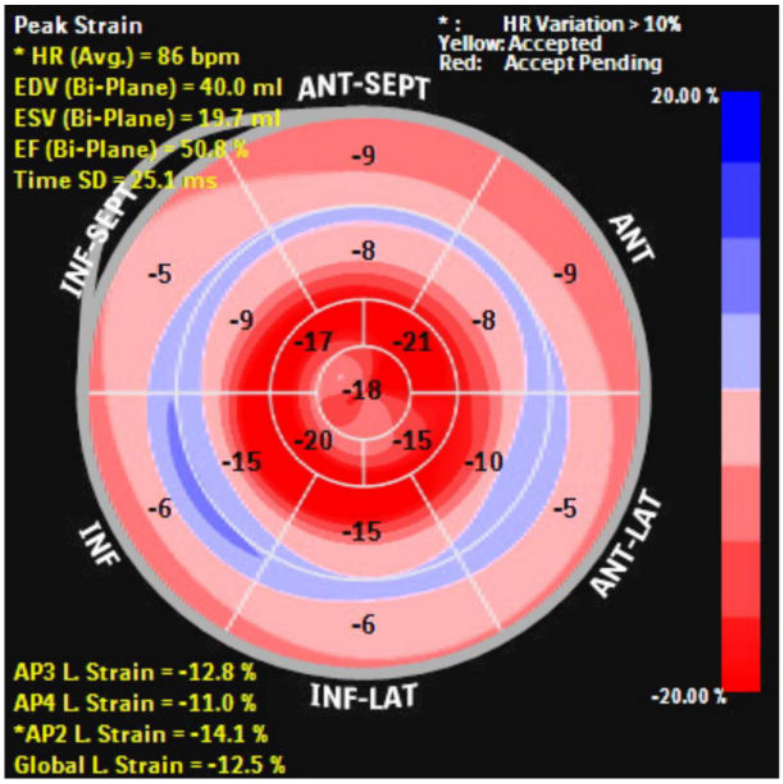

Figure 1.

a-h. Echocardiography characteristics of cardiac amyloidosis. Parasternal long- and short-axis views demonstrating severely increased LV wall thickness, with granular sparkling, which may be seen in cardiac amyloidosis. Pericardial effusions are common **(1a-b).** Atrial dilation reflects elevated filling pressures, as well as atrial infiltration of amyloid protein **(1c).** Elevated RV wall thickness (> 5mm) is often seen as well **(1d)**. Longitudinal strain in apical 4-, 2- and 3-chamber views showing severely reduced global longitudinal strain (GLS) of -12.5% with an apical to basal strain ratio of 2.7 **(1e-h)**.

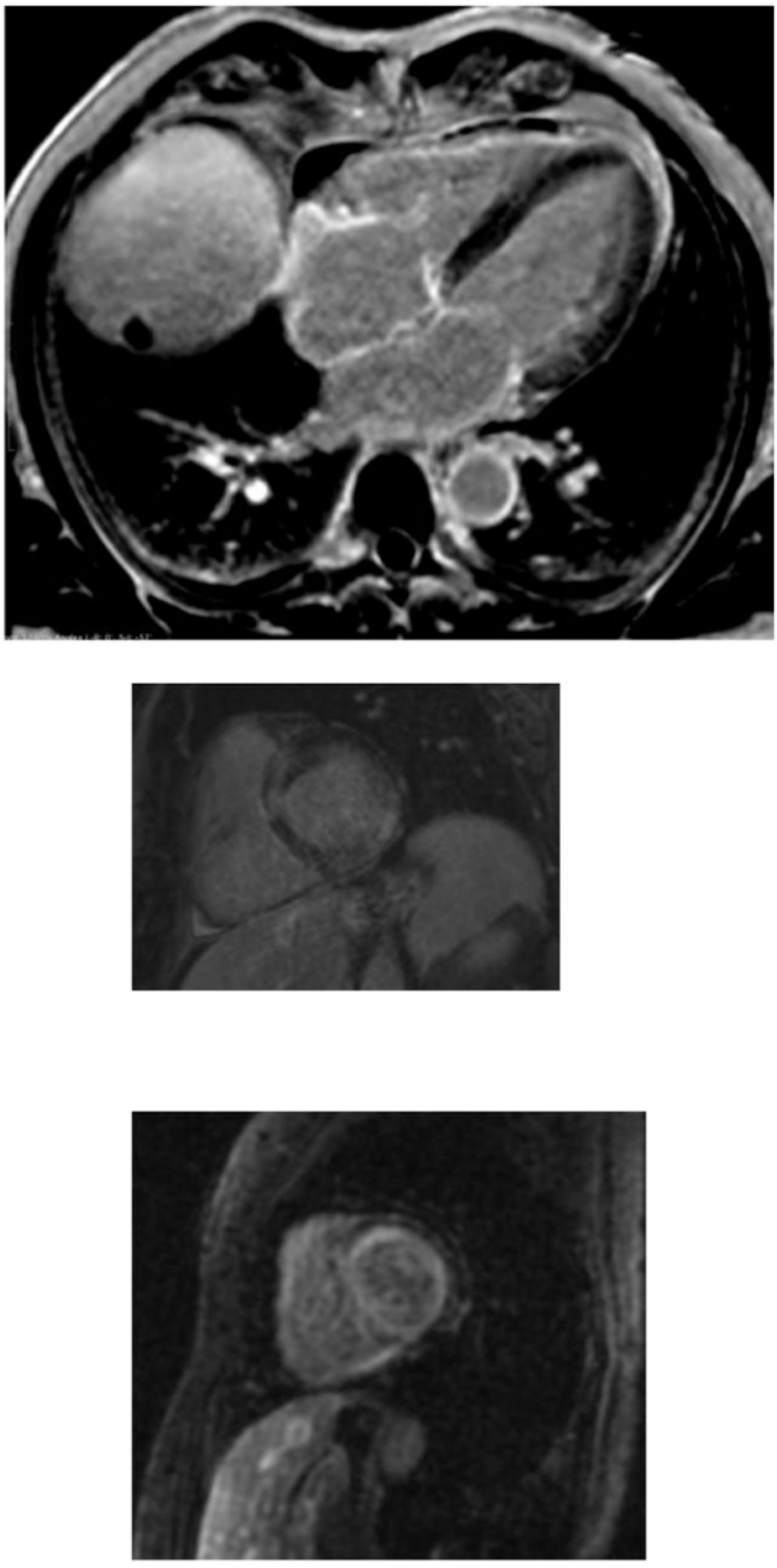

Figure 2.

a-c. Cardiac MRI demonstrating characteristic late gadolinium enhancement (LGE) patterns in cardiac amyloidosis. Phase sensitive, inversion recovery (PSIR) LGE images are illustrated in the 4-chamber **(2a)** and short axis **(2b and 2c)** views, in different patients with light chain (AL) amyloidosis.

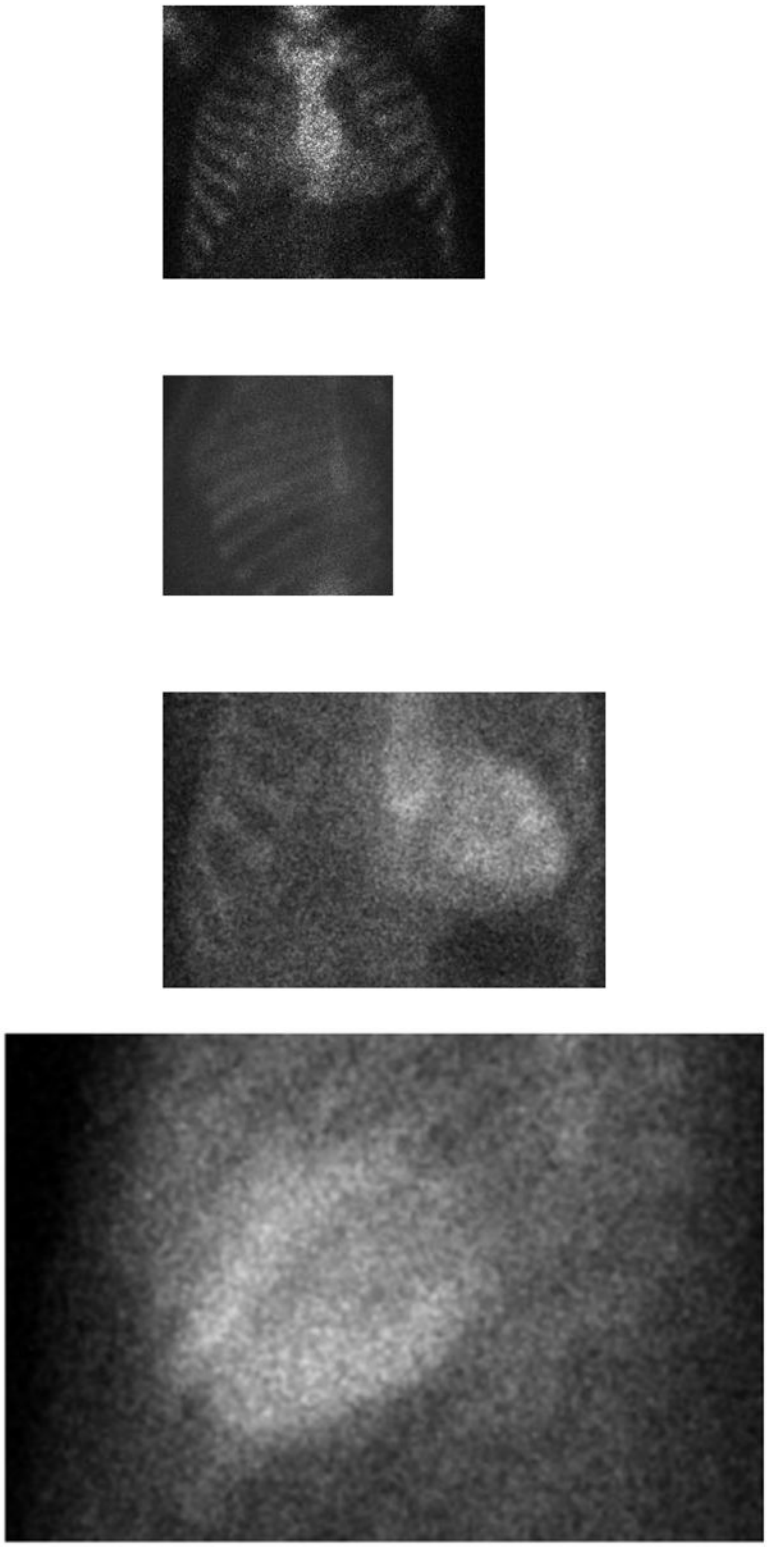

Figure 3.

a-d. Tc99m pyrophosphate (PYP) scans in AP and lateral projections revealing equivocal (Grade 1) uptake **(3a and 3b)** in a patient with AL amyloidosis, and strongly positive (Grade

3) uptake **(3c and 3d)** by the heart when compared to the surrounding ribs in a patient with ATTR wild-type amyloidosis.

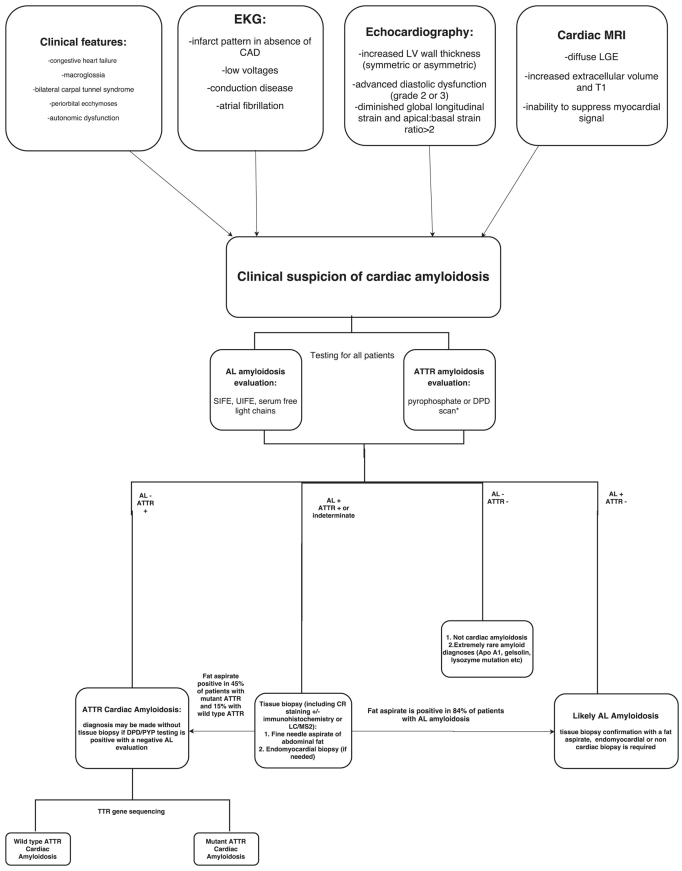

Figure 4.

Suggested algorithm for the diagnosis of cardiac amyloidosis, and for differentiating between ATTRwt, ATTRm, and AL cardiac amyloidosis. Adapted from *Siddiqi OK, Ruberg FL. Challenging the Myths of Cardiac Amyloidosis. European Heart Journal 2017* (64).

Table 1

Extramedullary and extra cardiac features of systemic AL amyloidosis (3). Specific criteria for diagnosis of proteinuria and hepatomegaly are used mostly for research purposes and are subject to refinement and updates.

Organ system	Clinical Manifestations	Diagnostic Criteria
Kidney	Albuminuria; may progress to nephrotic syndrome	1. Proteinuria > 0.5g/24 hours 2. Biopsy
Liver	Hepatomegaly/Splenomegaly	1. Liver edge > 4 cm below the costal margin 2. Serum alkaline phosphatase > 1.5 times upper limit of normal 3. Biopsy
Gastrointestinal tract	Diarrhea Constipation Early satiety Weight loss	1. Biopsy
Nervous system	Ascending, symmetric sensorimotor polyneuropathy Autonomic dysfunction: orthostatic hypotension and gastroparesis	1. Neurological exam 2. Positional BP monitoring 3. Sural nerve biopsy
Pulmonary	Diffuse alveolar infiltrates due to alveolar-septal involvement in systemic AL amyloidosis Nodules and tracheobronchial involvement in localized AL amyloidosis Pleural effusions	1. Biopsy 2. Suggestive chest CT findings in the appropriate clinical setting
Soft tissue	Macroglossia Subcutaneous nodules Rash Bilateral Carpal Tunnel Syndrome Muscle pseudohypertrophy Vascular amyloid: jaw claudication Amyloid lymphadenopathy	1. Physical exam in the appropriate clinical setting 2. Biopsy (rarely required)
Heme: coagulation	Periorbital ecchymosis Bleeding diathesis	1. Abnormal coagulation parameters 2. Factor X levels (most often involved)

Table 2

Major clinical features and geographic locations associated with the common ATTR mutations responsible for cardiac amyloidosis

ATTR Mutation	Clinical Manifestations	Geographic Location/Ethnicity
Val30Met (Met30)	Peripheral neuropathy ≫ cardiac involvement	Portugal Sweden Japan
Thr60Ala (Ala60)	Peripheral neuropathy = cardiac involvement	England Northern Island
Val122Ile (Ile122)	Cardiac involvement ≫ peripheral neuropathy	African African American Afro Caribbean