

Updates in Cardiac Amyloidosis: A Review

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Systemic amyloidosis is a relatively rare multisystem disease caused by the deposition of misfolded protein in various tissues and organs. It may present to almost any specialty, and diagnosis is frequently delayed.¹ Cardiac involvement is a leading cause of morbidity and mortality, especially in primary light chain (AL) amyloidosis and in both wild-type and hereditary transthyretin amyloidosis. The heart is also occasionally involved in acquired serum amyloid A type (AA) amyloidosis and other rare hereditary types. Clinical phenotype varies greatly between different types of amyloidosis, and even the cardiac presentation has a great spectrum. The incidence of amyloidosis is uncertain, but it is thought that the most frequently diagnosed AL amyloidosis has an annual incidence of 6 to 10 cases per million population in the United Kingdom and United States. Amyloidosis due to transthyretin deposition (ATTR) can be wild-type transthyretin amyloid deposits, which predominantly accumulate in the heart and are very common at autopsy in the elderly. Although the associated clinical syndrome known as senile systemic amyloidosis is diagnosed rarely in life,² there is increasing evidence that this disorder is much underdiagnosed and that with increasing longevity and improved diagnostic methods it may be identified as a substantial public health problem.

This review focuses on recent progress in the field: novel diagnostic and surveillance approaches using imaging (echocardiography, cardiovascular magnetic resonance), biomarkers (brain natriuretic peptide [BNP], high-sensitivity troponin), new histological typing techniques, and current and future treatments, including approaches directly targeting the amyloid deposits.³

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Pathophysiology

Amyloidosis is caused by the extracellular deposition of autologous protein in an abnormal insoluble β -pleated sheet fibrillary conformation—that is, as amyloid fibrils. More than 30 proteins are known to be able to form amyloid fibrils in vivo, which cause disease by progressively damaging the structure and function of affected tissues.⁴ Amyloid deposits also contain minor nonfibrillary constituents, including serum amyloid P component (SAP), apolipoprotein E, connective tissue components (glycosaminoglycans, collagen), and basement membrane components (fibronectin, laminin).^{3,5–8} Amyloid deposits can be massive, and cardiac or other tissues may become substantially replaced. Amyloid fibrils bind Congo red stain, yielding the pathognomonic apple-green birefringence under cross-polarized light microscopy that remains the gold standard for identifying amyloid deposits.

Clinical Features

Cardiac amyloidosis, irrespective of type, presents as a restrictive cardiomyopathy characterized by progressive diastolic and subsequently systolic biventricular dysfunction and arrhythmia.¹ Key “red flags” to possible systemic amyloidosis include nephrotic syndrome, autonomic neuropathy (eg, postural hypotension, diarrhea), soft-tissue infiltrations (eg, macroglossia, carpal tunnel syndrome, respiratory disease), bleeding (eg, cutaneous, such as periorbital, gastrointestinal), malnutrition/cachexia and genetic predisposition (eg, family history, ethnicity). Initial presentations may be cardiac, with progressive exercise intolerance and heart failure. Other organ involvement, particularly in AL amyloidosis, may cloud the cardiac presentation (eg, nephrotic syndrome, autonomic neuropathy, pulmonary or bronchial involvement). Pulmonary edema is not common early in the disease process,⁹ but pleural and pericardial effusions and atrial arrhythmias are often seen.^{10,11} Syncope is common and a poor prognostic sign.¹² It is typically exertional or postprandial as part of restrictive cardiomyopathy, sensitivity to intravascular fluid depletion from loop diuretics combined with autonomic neuropathy, or conduction tissue involvement (atrioventricular or sinoatrial nodes) or ventricular arrhythmia.^{13–15} The latter may rarely cause recurrent syncope. Disproportionate septal amyloid accumulation mimicking hypertrophic cardiomyopathy with

Table. Summary of Pathology, Presentation, and Management of Different Amyloid Types

Amyloid Type	Precursor Protein	Typical Decade of Presentation	Cardiac Involvement	Other Organ Involvement	Treatment	Prognosis (Median Survival)
Primary (AL) amyloidosis	Monoclonal light chain	6th or 7th decade (but can be any)	40% to 50%	Renal, liver, soft tissue, neuropathy	Chemotherapy or peripheral blood stem cell transplantation	48 mo but 8 mo for advanced-stage disease
Transthyretin amyloidosis						
ATTR (V30M)	Variant transthyretin	3rd or 4th decade (but geographical variation)	Uncommon (but can occur in older patients)	Peripheral and autonomic neuropathy	Liver transplantation (younger cases) not proven in others	Good with liver transplantation for V30M progressive disease
ATTR (T60 A)	Variant transthyretin	6th decade	Up to 90% by diagnosis	Peripheral and autonomic neuropathy	Liver transplantation possible in selected patients	Variable with liver transplantation
Wild-type ATTR	Wild-type transthyretin	70 y (but remains a consideration after 50 y)	Almost all cases	Carpal tunnel syndrome	Supportive	7 to 8 y
ATTR Ile 122	Variant transthyretin	6th decade or older	Almost all cases	Carpal tunnel syndrome	Supportive	7 to 8 y
Apolipoprotein A1 (ApoA1)	Variant apolipoprotein	6th decade or older	Rare	Predominantly renal	Renal (±liver) transplantation	Usually slowly progressive (y)
Secondary (AA) amyloidosis	Serum amyloid A (SAA)	Any	Rare	Renal, liver	Treat underlying inflammatory condition	Good
Atrial natriuretic peptide (ANP)	ANP	70 y or older	All cases but significance uncertain	None reported	Not needed	-

dynamic left ventricular (LV) outflow tract obstruction^{16–19} is rare but well documented. Myocardial ischemia can result from amyloid deposits within the microvasculature.^{20,21} Atrial thrombus is common, particularly in AL amyloidosis, sometimes before atrial fibrillation occurs.²² Intracardiac thrombus can embolize, causing transient ischemic attacks or strokes, and may be an early or even presenting feature.²³ Anticoagulation is therefore important in the appropriate clinical situation, but careful consideration must be given to patients with extensive systemic AL amyloidosis who may have an elevated bleeding risk due to factor X deficiency or in some cases with gastrointestinal involvement.²⁴ The Table gives an outline of the clinical phenotypes of the common amyloid subtypes.

AL Amyloidosis

AL amyloidosis is caused by deposition of fibrils composed of monoclonal immunoglobulin light chains and is associated with clonal plasma cell or other B-cell dyscrasias. The spectrum and pattern of organ involvement is very wide, but cardiac involvement occurs in half of cases and is sometimes the only presenting feature.²⁵ Cardiac AL amyloidosis may be rapidly progressive. Low QRS voltages, particularly in the limb leads,

are common. Thickening of the LV wall is typically mild to moderate and is rarely > 18 mm even in advanced disease. Cardiac AL amyloid deposition is accompanied by marked elevation of the biomarkers BNP and cardiac troponin, even at an early stage. Involvement of the heart is the commonest cause of death in AL amyloidosis and is a major determinant of prognosis; without cardiac involvement, patients with AL amyloidosis have a median survival of around 4 years,²⁶ but the prognosis among affected patients with markedly elevated BNP and cardiac troponin (Mayo stage III disease)²⁷ is on the order of 8 months.

Hereditary Amyloidoses

Mutations in several genes, such as transthyretin, fibrinogen, apolipoprotein A1, and apolipoprotein A2 can be responsible for hereditary amyloidosis, but by far the most common cause is variant ATTR amyloidosis (variant ATTR) caused by mutations in the transthyretin gene causing neuropathy and, often, cardiac involvement.

The TTR gene is synthesized in the liver, and several point mutations are described (see the Table), but the most common is the Val122Ile mutation.^{28,29} In a large autopsy study

that included individuals with cardiac amyloidosis, the TTR Val122Ile allele was present in 3.9% of all African Americans and 23% of African Americans with cardiac amyloidosis. Penetration of the mutation is not truly known and is associated with a late-onset cardiomyopathy that is indistinguishable from senile cardiac amyloidosis. Although the prevalence of disease caused by this mutation is unknown, it is almost certainly underdiagnosed, because the wall thickening is often incorrectly attributed to hypertensive heart disease. Neuropathy is not generally a feature of this ATTR due to Val122Ile.

More than 100 genetic variants of TTR are associated with amyloidosis. Most present as the clinical syndrome of progressive peripheral and autonomic neuropathy. Unlike wild-type ATTR or variant ATTR Val122Ile, the features of other variant ATTR include vitreous amyloid deposits or, rarely, deposits in other organs. Cardiac involvement in variant ATTR varies by mutations and can be the presenting or indeed the only clinical feature.³⁰ For example, cardiac involvement is rare in variant ATTR associated with Val30Met (a common variant in Portugal or Sweden), but it is almost universal and develops early in individuals with variant ATTR due to Thr60Ala mutation (a mutation common in Ireland).

Mutations in apolipoprotein A1 gene can cause systemic amyloidosis, typically causing renal and hepatic involvement—although cardiac involvement is well recognized.³¹

Senile Systemic Amyloidosis (Wild-Type ATTR)

Wild-type TTR amyloid deposits are found at autopsy in about 25% of individuals >80 years of age, but their clinical significance has not been clear.^{32–34} The prevalence of wild-type TTR deposits leading to the clinical syndrome of wild-type ATTR cardiac amyloidosis remains to be ascertained, but the syndrome is distinct and clearly far rarer. Wild-type ATTR is a predominantly cardiac disease, and the only other significant extracardiac feature is a history of carpal tunnel syndrome, often preceding heart failure by 3 to 5 years.³⁵ Extracardiac involvement is most unusual.

Both wild-type ATTR and ATTR due to Val122Ile are diseases of the >60-year age group and are often misdiagnosed as hypertensive heart disease.⁹ Wild-type ATTR has a strong male predominance, and the natural history remains poorly understood, but studies suggest a median survival of about 7 years from presentation.^{32,33} The true incidence of wild-type ATTR is probably underestimated, and recent developments in cardiac magnetic resonance (CMR), which have greatly improved detection of cardiac amyloid during life, suggest that wild-type ATTR is more common than previously thought: It accounted for 0.5% of all patients seen at the UK amyloidosis center until 2001 but now accounts for 7% of 1 100 cases with amyloidosis seen since the end of 2009 (unpublished data). There appears to be an association between wild-type ATTR and history of my-

ocardial infarctions, G/G (Val/Val) exon 24 polymorphism in the alpha2-macroglobulin (alpha2M), and the H2 haplotype of the tau gene³⁶; the association of tau with Alzheimer's disease raises interesting questions as both are amyloid-associated diseases of aging. Although the echocardiographic manifestations of cardiac ATTR may be indistinguishable from advanced AL amyloidosis, patients with the former typically have fewer symptoms and better survival.³⁷

Other Types of Cardiac Amyloidosis

Localized atrial amyloid deposits derived from atrial natriuretic peptide are associated with atrial fibrillation, notably postoperatively,^{9,38} and become ubiquitous with age, being present at autopsy in 80% of people >70 years of age.^{39,40} The significance and causality of atrial natriuretic peptide amyloid deposits remain unknown. Amyloid of as yet unknown fibril type is also common in explanted cardiac valves.^{41,42} Systemic AA amyloidosis complicating chronic inflammatory diseases, in which the amyloid fibrils are derived from the acute-phase reactant serum amyloid A protein, involves the heart in about 2% of cases with systemic AA amyloidosis. Incidence of AA amyloidosis is generally in decline, likely reflecting better treatment for rheumatological disorders with biological agents.

Diagnosis and Evaluation of Cardiac Amyloidosis

Electrocardiography

Low QRS voltages (all limb leads <5 mm in height) with poor R-wave progression in the chest leads (pseudoinfarction pattern) occur in up to 50% of patients with cardiac AL amyloidosis.⁴³ The combination of low ECG voltage with concentrically increased wall thickness is highly suspicious for cardiac amyloidosis (see Figure 1), but voltage criteria for LV hypertrophy can nevertheless sometimes occur.⁴⁴ Other findings include first-degree atrioventricular block (21%), nonspecific intraventricular conduction delay (16%), second- or third-degree atrioventricular block (3%), atrial fibrillation/flutter (20%), and ventricular tachycardia (5%).⁴⁴ Left and right bundle branch block can also occur.¹⁸ ECG patterns can provide clues to differentiate between AL and TTR amyloidosis: Left bundle branch block is seen in 40% of patients with wild-type ATTR but is rare in AL (4%), whereas typical low QRS voltages are seen in 40% wild-type ATTR versus 60% AL.⁴⁵ There has been little recent study of ECG correlation with cardiac biomarkers, treatment toxicity, and mortality. Progressive ECG changes may be useful in assessing silent cardiac progression.⁴⁶ Changes in ECG abnormalities after treatment in AL amyloidosis remain poorly studied but can occur—more often little improvement is seen. Holter ECG monitoring identifies asymptomatic

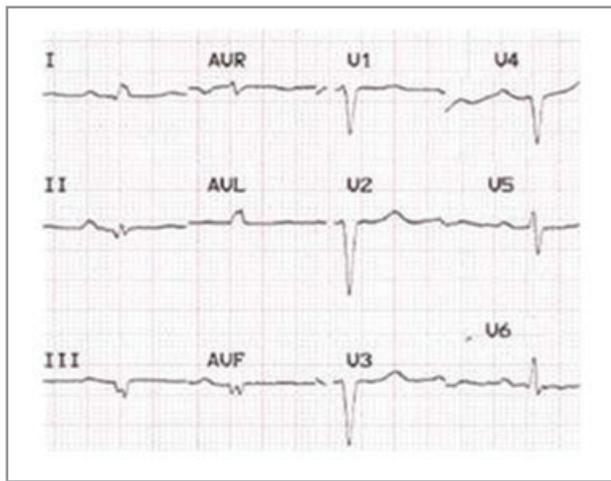


Figure 1. ECG of a patient with cardiac AL amyloidosis showing small QRS voltages (defined as ≤ 6 mm height), predominantly in the limb leads and pseudoinfarction pattern in the anterior leads.

arrhythmias in $>75\%$ of cardiac AL patients (mainly supraventricular tachyarrhythmias and some nonsustained ventricular tachycardia).⁴⁷

Echocardiography

All patients with suspected amyloidosis should undergo echocardiography. Findings are characteristic in advanced disease but are harder to elicit earlier on and have prognostic as well as diagnostic significance.^{48–50} Typical findings include concentric ventricular thickening with right ventricular involvement, poor biventricular long-axis function with normal/near-normal ejection fraction,^{51,52} and valvular thickening (particularly in wild-type or variant ATTR).⁴⁵ Diastolic dysfunction is the earliest echocardiographic abnormality and may occur before cardiac symptoms develop.^{53,54} As with all investigations, echocardiography must be interpreted within the clinical context; a speckled or granular myocardial appearance, although characteristic of amyloid, is an inexact finding, which is dependent on machine gain settings. Biatrial dilatation in presence of biventricular, valvular, and interatrial septal thickening⁵³ is a useful clue to the diagnosis.

Advanced echocardiographic techniques are beginning to reveal more about the underlying pathology and functional abnormalities, such as the twisting and untwisting cardiac motion that may be augmented through compensatory mechanisms before reversing to impairment later in the course of the disease.^{55,56} Strain and strain rate imaging, derived from speckle tracking (see Figure 2), may help differentiate cardiac amyloidosis from hypertrophic cardiomyopathy.^{57,58} Typically, there is much greater restriction of basal compared to apical movement. Mean LV basal strain is an independent predictor of both cardiac and overall deaths. Contrast echocardiography

using transpulmonary bubble contrast can show microvascular dysfunction in AL amyloidosis.⁵⁹ Although transesophageal echo may help detect atrial appendage thrombus in a third of cases of AL amyloid, translation of this into routine clinical practice for this frail and unwell patient population needs further study.^{53,60}

Cardiac Biomarkers

Measurements of BNP, its more stable N-terminal fragment (NT-proBNP), and cardiac troponins are extremely informative in AL amyloidosis, which is the only type in which they have been systematically studied to date. Their value in TTR amyloidosis is yet to be determined. BNP/NT-proBNP is cleared by the kidneys (BNP also partially cleared by the liver), confounding evaluation of patients with kidney involvement. Elevated NT-proBNP levels in systemic AL amyloidosis are a sensitive marker of cardiac involvement, with a cutoff >152 pmol/L being associated with higher mortality rate (72% vs 7.6% per year).⁶¹ Abnormal NT-proBNP is predictive of clinically significant cardiac involvement developing in the future.⁶² BNP/NT-proBNP in general reflects high filling pressures, but amyloid deposits may have a local effect—BNP granules are found in higher quantities in myocytes adjacent to amyloid deposits.⁶³ Increased troponin concentrations are a marker of poor prognosis,⁶⁴ but the mechanism remains unclear. High-sensitivity troponin is abnormal in $>90\%$ of cardiac AL patients,⁶⁵ and the combination of BNP/NT-proBNP plus troponin measurements is used to stage and risk-stratify patients with AL amyloidosis at diagnosis.^{27,66} Very interestingly, the concentration of BNP/NT-proBNP in AL amyloidosis may fall dramatically within weeks after chemotherapy that substantially reduces the production of amyloidogenic light chains.⁶⁷ The basis for this very rapid phenomenon, which is not mirrored by changes on echocardiography or CMR, remains uncertain, but a substantial fall is associated with improved outcomes. An early transient increase in BNP/NT-proBNP may occur after treatment with the immunomodulatory drugs thalidomide and lenalidomide, which are frequently used in the management of AL amyloidosis (see later), but the significance and cause are unclear.^{68,69}

Cardiac Magnetic Resonance

CMR provides functional and morphological information on cardiac amyloid in a similar way to echocardiography, though the latter is superior for evaluating and quantifying diastolic abnormalities. An advantage of CMR is in myocardial tissue characterization. Amyloidotic myocardium reveals subtle pre-contrast abnormalities (T1, T2),^{70,71} but extravascular contrast agents based on chelated gadolinium provide the key information. The appearance (see Figure 3) of global, subendocardial late gadolinium enhancement is highly characteristic of

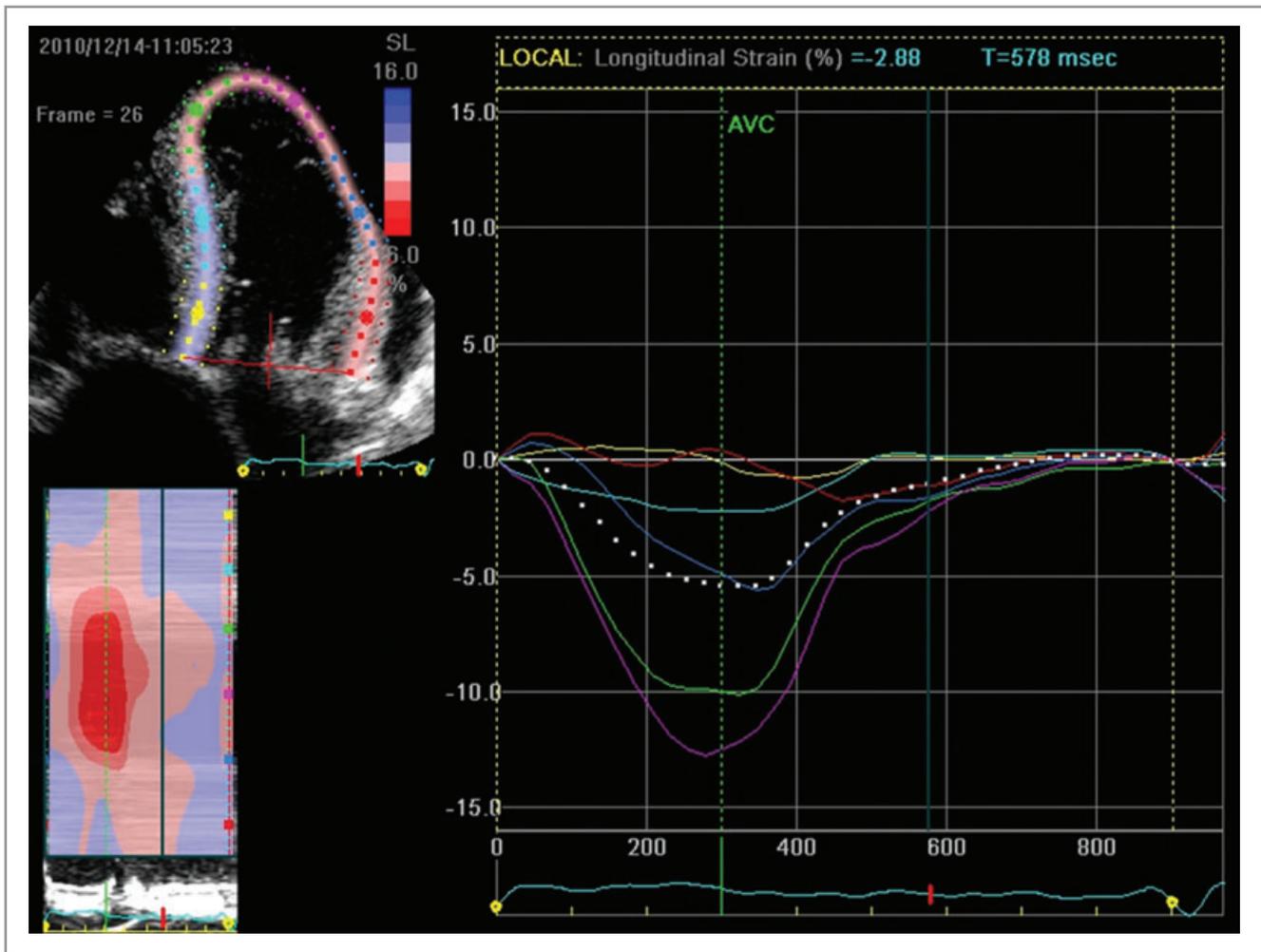


Figure 2. Transthoracic echocardiogram with speckle tracking. The red and yellow lines represent longitudinal motion in the basal segments, whereas the purple and green lines represent apical motion. This shows loss of longitudinal ventricular contraction at the base compared to apex.

cardiac amyloid^{72,73} and correlates with prognosis.^{74,75} CMR is especially useful in patients with other causes of LV thickening/hypertrophy because it can differentiate amyloidosis from hypertension, which may not be possible by routine echocardiography.

Difficulties are often encountered, however. For example, arrhythmias, particularly atrial fibrillation and ectopic beats, degrade image quality during CMR, and increasing experience of the technique in clinical practice has shown that the pattern of late gadolinium enhancement can be atypical and patchy, especially in early disease.⁷⁶ Late gadolinium enhancement imaging in amyloidosis is inherently challenging because amyloid infiltration within the interstitium of the heart reduces the differences in contrast signal between blood and myocardium such that the two compartments may null together or even be reversed and effusions may cause considerable ghosting artifact, although these both can be a strong clue to the underlying diagnosis (see Figure 4).^{73,77,78} Recently, the technique of equilibrium contrast CMR has demonstrated much higher

extracellular myocardial volume in cardiac amyloid than any other measured disease.^{79,80} It is anticipated that accurate measurements of the expanded interstitium in amyloidosis will prove useful in serial quantification of cardiac amyloid burden.

Radionuclide Imaging

SAP component scintigraphy enables visceral amyloid deposits, including those in the liver, kidneys, spleen, adrenal glands, and bones, to be imaged serially in a specific and quantitative manner,⁸¹ but it does not adequately image the moving heart. Numerous case reports over the past 30 years have indicated that various commonly used diphosphonate bone-seeking radionuclide tracers occasionally localize to cardiac amyloid, and this approach has lately been investigated systematically. It transpires that ^{99m}Tc-DPD, a particular tracer that has been little used of late for bone scintigraphy, appears to localize to cardiac amyloid deposits very sensitively,

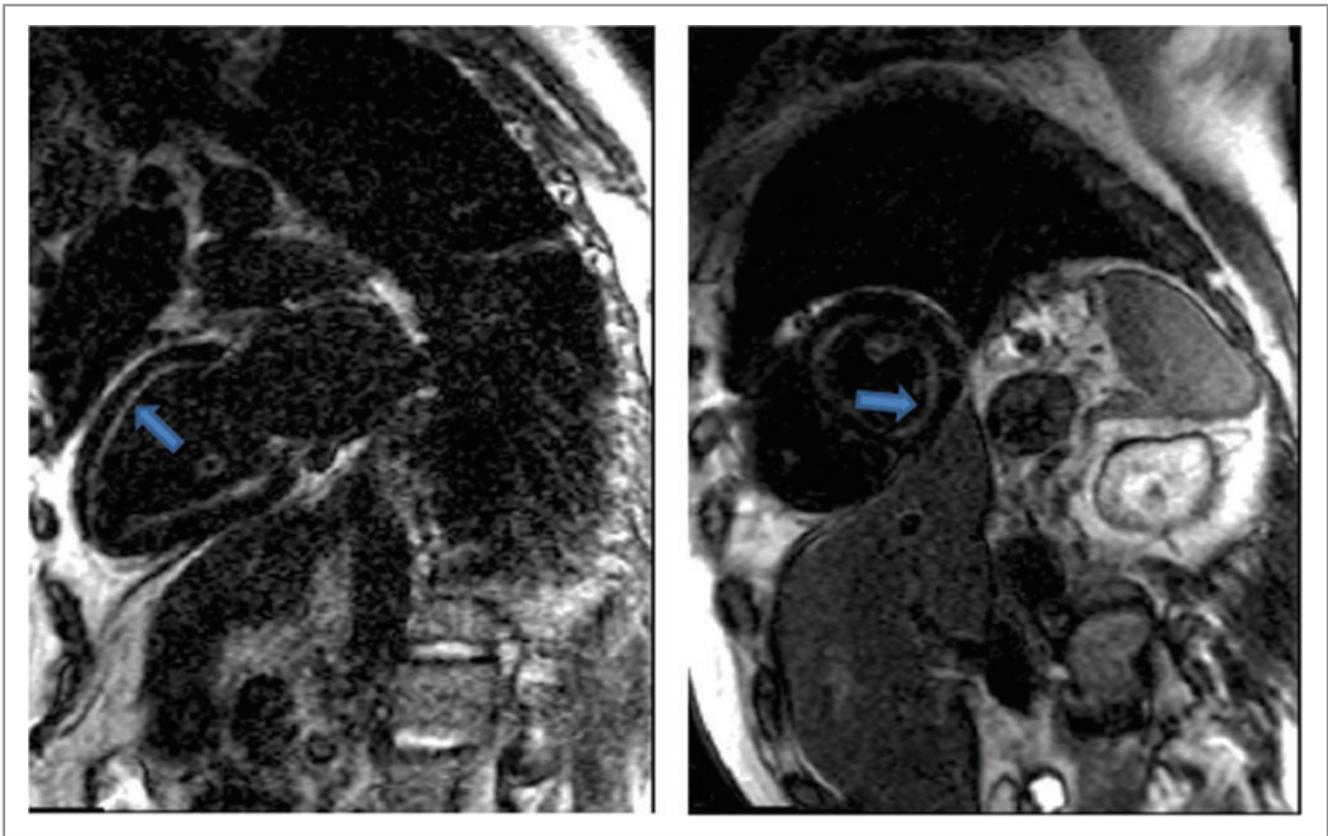


Figure 3. CMR with the classic amyloid global, subendocardial late gadolinium enhancement pattern in the left ventricle with blood and mid-/epimyocardium nulling together.

especially in patients with ATTR type (Figure 5). Indeed, asymptomatic cardiac ATTR deposits can be identified through ^{99m}Tc -DPD scintigraphy at an early stage when echocardiography, serum cardiac biomarkers, and perhaps even CMR remain normal.⁸² By contrast, uptake of ^{99m}Tc -DPD occurs in about one third of patients with cardiac AL amyloidosis, and ^{99m}Tc -DPD-SPECT-CT can help to distinguish the two types.⁸² The sensitivity of DPD scintigraphy for detecting cardiac amyloidosis of TTR type would appear to have considerable potential for diagnosis and screening.⁸³

Endomyocardial Biopsy

Endomyocardial biopsy has been considered to be the gold standard for demonstrating cardiac amyloid deposition.⁸⁴ Although cardiac involvement can reasonably be inferred in a patient with proven systemic amyloidosis through a combination of clinical features, ECG, echocardiography, and biomarkers, etc, endomyocardial biopsy is required when suspected cardiac amyloidosis is an isolated feature or when the cardiac amyloid fibril type cannot be identified by other means. In practice, endomyocardial biopsies are most commonly required to differentiate between AL and ATTR in older patients, some 5%

of whom have a monoclonal gammopathy of undetermined significance.⁸⁵ Endomyocardial biopsies should be considered in patients with a thickened left ventricle by echocardiography where hypertension, valvular disease, and a family history of hypertrophic cardiomyopathy have been excluded, particularly if the patient is young. Complications such as perforation remain a small but real risk and may not be well tolerated in restrictive cardiomyopathy.^{86,87} The presence of amyloid deposition should be confirmed by Congo red staining, and immunohistochemistry can usefully identify fibril type in about 60% to 70% cases (see Figure 6). Electron microscopy to confirm or refute the presence of amyloid fibrils has an occasional role when Congo red stains fail to produce definitive results.^{88,89} Proteomic typing of amyloid by mass spectrometry using tiny samples obtained through laser capture microdissection of tissue sections usually provides definitive results⁹⁰ and is critical when immunohistochemistry has not done so.

Treatment

Cardiac amyloidosis in general has a poor prognosis, but this differs according to amyloid type and availability and response

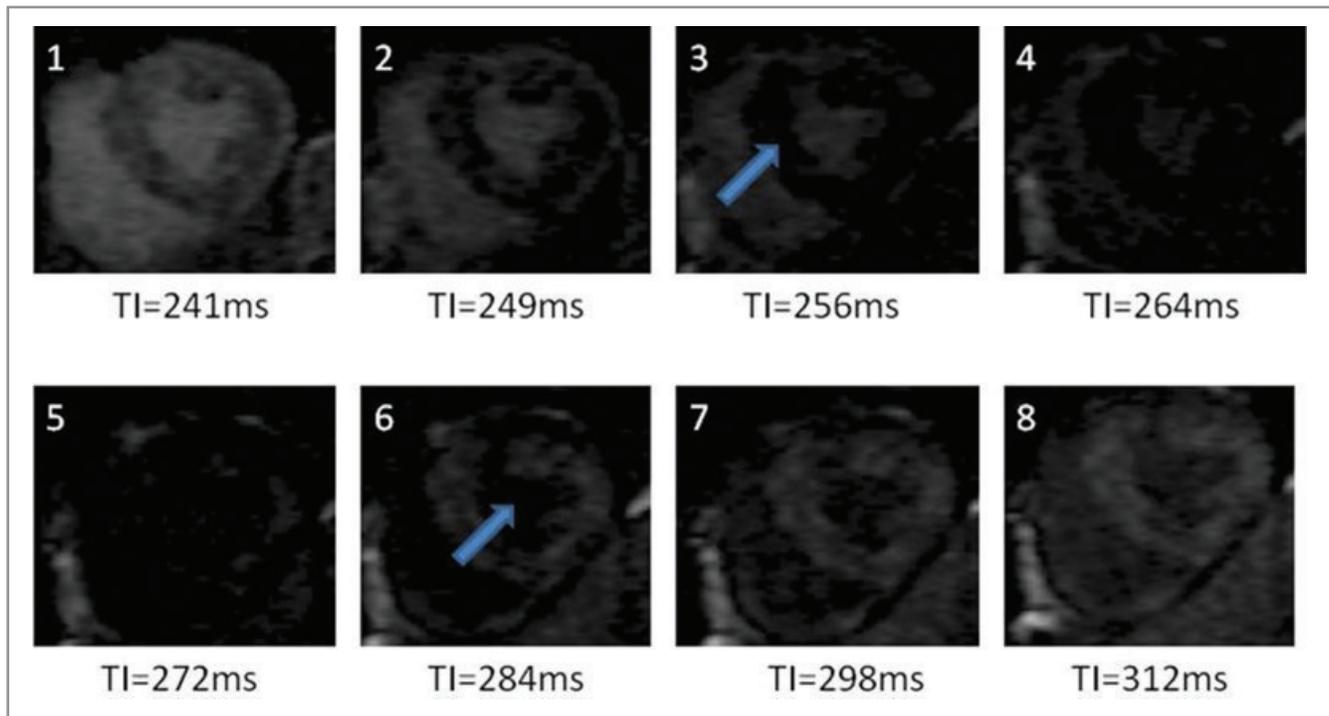


Figure 4. Sequential static images from a CMR TI scout sequence. As the inversion time (TI) increases, myocardium nulls first (arrow in image 3), followed by blood afterwards (arrow in image 6), implying that there is more gadolinium contrast in the myocardium than blood—a degree of interstitial expansion such that the “myocrit” is smaller than the hematocrit.

to therapy. Treatment may be classified as follows: supportive therapy (ie, modified heart-failure treatment including device therapy); therapies that suppress production of the respective amyloid fibril precursor protein (eg, chemotherapy in AL amyloidosis); and novel strategies to inhibit amyloid fibril formation or to directly target the amyloid deposits or stabilize the precursor protein (especially in ATTR with drugs such as tafamidis or diflunisal). Cardiac transplantation, although rarely feasible, can be very successful in carefully selected patients.

Supportive Treatment

Standard heart-failure therapy may be of limited benefit or even detrimental in cardiac amyloidosis. There is scant evidence for the use (or not) of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β -blockers. These may be poorly tolerated and may worsen postural hypotension or renal function. Restrictive cardiomyopathy leads to a heart-rate-dependent cardiac output in some cases, and some such patients may find difficulty in tolerating β -blockers. Digitalis and calcium channel blockers may be selectively concentrated in amyloidotic tissue and are relatively contraindicated on grounds of increased toxicity,^{91–93} especially the latter, which can lead to rapid worsening. Careful monitoring is needed to avoid significant drug interactions, for example,

β -blockers with thalidomide used in chemotherapy of AL amyloidosis causing bradycardia.⁹⁴

Maintenance of adequate filling pressures is vital because of the restrictive physiology, balancing peripheral edema and renal impairment with salt/water restriction and judicious use of diuretics. Patient education and participation, ideally with backup from a heart failure team, are critical to successful management. Contrary to standard heart failure management, maintenance of adequate blood pressure with an α -agonist such as midodrine may permit higher doses of loop diuretics, especially in patients with autonomic neuropathy.⁹⁵

Device Therapy

Pacemakers or implantable cardioverter defibrillators may not prevent sudden cardiac death, because this is thought to often be due to electromechanical dissociation.⁹⁶ In the absence of evidence, pacing indications remain within current standard guidelines. High defibrillator thresholds may be encountered, and the benefits of such devices remain uncertain.^{96–98} Biventricular pacing appears to play little role but may be the ideal pacing option to avoid decompensation of the stiffened ventricle as a result of induced dyssynchrony from right ventricular pacing.⁹⁹

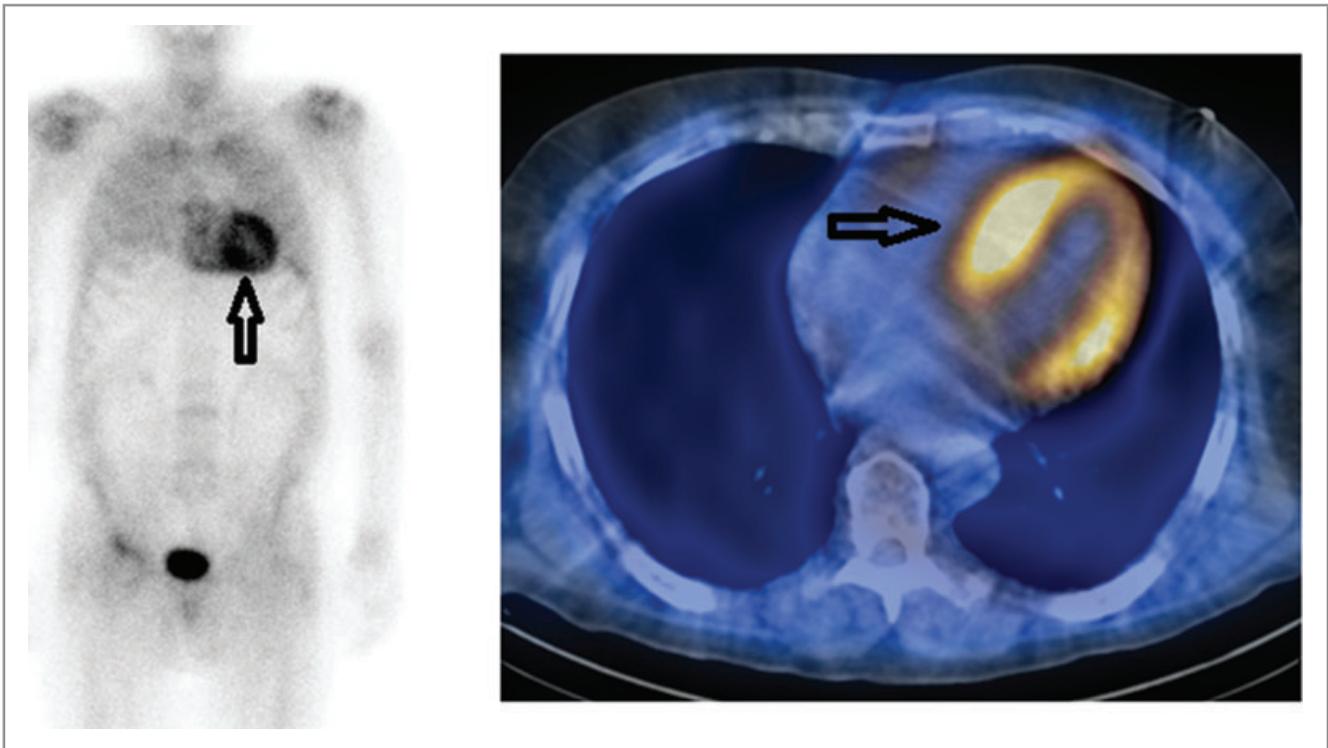


Figure 5. A positive ^{99m}Tc -DPD scan for TTR cardiac amyloid (left), showing uptake in the heart (arrow) and reduced bone uptake. The right-hand panel shows a fused CT/SPECT image showing myocardial uptake with greater uptake in the septum.

Amyloid-Specific Treatment

Reducing Amyloid Fibril Precursor Protein Production

Treatment of amyloidosis is currently based on the concept of reducing the supply of the respective amyloid fibril precursor protein. In AL amyloidosis, therapy is directed toward the clonal plasma cells using either cyclical combination chemotherapy or high-dose therapy with autologous stem cell transplantation. Most chemotherapy regimes in AL amyloidosis comprise dexamethasone combined with an alkylator (oral melphalan or others). Addition of thalidomide, for example, in the risk-adapted cyclophosphamide, thalidomide, and dexamethasone regime used widely in the United Kingdom, improves response rates but probably at cost of greater toxicity.¹⁰⁰ Dexamethasone, although a very useful agent in all patients with AL amyloidosis, including those with cardiac involvement, has to be used with great caution in patients with cardiac amyloidosis because of a high risk of fluid overload in absence of adequate and rapid changes to diuretic therapy. Close coordination between the treating hematology and cardiology teams is critical to steer the patient successfully through the treatment course.¹⁰¹ High-dose melphalan followed by autologous stem-cell transplantation is generally contraindicated in patients with advanced cardiac amyloidosis. Although it has been argued that autologous stem cell transplantation is the best

treatment for suitable patients,^{102–104} its role in the era of novel agents, discussed below, is less certain.

The newer treatment options include bortezomib (a proteasome inhibitor)¹⁰⁵ and the newer immunomodulatory drugs lenalidomide and pomalidomide. Bortezomib combinations appear to be especially efficient in amyloidosis with high rates of near-complete clonal responses, which appear to translate into early cardiac responses.^{106–108} Phase II (bortezomib in combination with cyclophosphamide or doxorubicin) and phase III (bortezomib, melphalan, and dexamethasone compared to melphalan and dexamethasone as front-line treatment) trials are underway.

AA amyloidosis is the only other type of amyloidosis in which production of the fibril precursor protein can be effectively suppressed by currently available therapies. Anti-inflammatory therapies, such as anti-tumor necrosis factor agents in rheumatoid arthritis, can substantially suppress serum amyloid A protein production, but very little experience has been obtained regarding cardiac involvement, which is very rare in this particular type of amyloidosis.

TTR is produced almost exclusively in the liver, and TTR amyloidosis has lately become a focus for novel drug developments aimed at reducing production of TTR through silencing RNA and antisense oligonucleotide therapies. ALN-TTR01, a systemically delivered silencing RNA therapeutic,¹⁰⁹ is already in phase I clinical trial. Liver transplantation has been used as

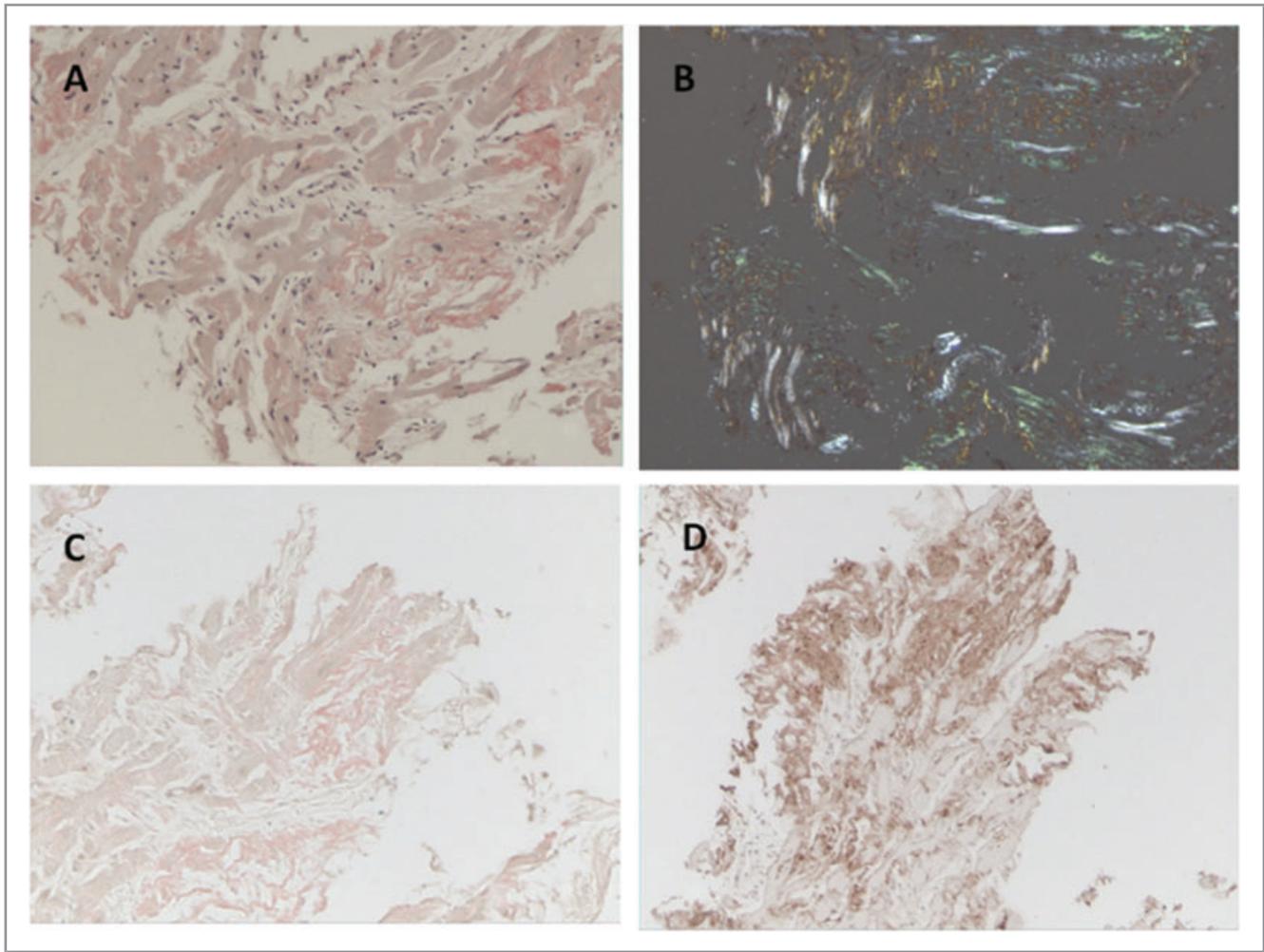


Figure 6. An endomyocardial biopsy of a patient with cardiac AL amyloidosis stained as follows: (A) Congo red only; (B) Apple-green birefringence under polarized light; (C) Congo red with lambda overlay (negative); (D) Congo red with kappa overlay (positive).

a treatment for variant ATTR for 20 years, to remove genetically variant TTR from the plasma. Although this is a successful approach in ATTR Val30Met, it has had disappointing results in patients with other ATTR variants, which often involve the heart. The procedure commonly results in progressive cardiac amyloidosis through ongoing accumulation of wild-type TTR on the existing template of variant TTR amyloid.¹¹⁰ The role of liver transplantation in non-Val30Met-associated hereditary TTR amyloidosis thus remains very uncertain.

Inhibition of Amyloid Formation

Amyloid fibril formation involves massive conformational transformation of the respective precursor protein into a completely different form with predominant β -sheet structure. The hypothesis that this conversion might be inhibited by stabilizing the fibril precursor protein through specific binding to a pharmaceutical has lately been explored in TTR amyloidosis. A key step in TTR amyloid fibril formation is the dissociation of the normal

TTR tetramer into monomeric species that can autoaggregate in a misfolded form. In vitro studies identified that diflunisal, a now little used nonsteroidal anti-inflammatory analgesic, is bound by TTR in plasma, and that this enhances the stability of the normal soluble structure of the protein.^{111,112} Studies of diflunisal in ATTR are in progress. Tafamidis is a new compound without anti-inflammatory analgesic properties that has a similar mechanism of action. Tafamidis has just been licensed for neuropathic ATTR, but its role in cardiac amyloidosis remains uncertain, and clinical trial results are eagerly awaited. Higher-affinity “superstabilizers” are also in development.¹¹³

Eprodisate is a negatively charged, sulfonated molecule with similarities to heparan sulfate, which is being pursued as a treatment for AA amyloidosis. Eprodisate is thought to inhibit the pro-amyloidogenic interactions of glycosaminoglycans with SAA during fibril formation in AA amyloidosis. A phase III trial showed benefits in terms of progression of AA-amyloid-associated renal dysfunction,¹¹⁴ and further studies are currently being conducted.

Targeting Amyloid Deposits by Immunotherapy

Amyloid deposits are remarkably stable, but the body evidently has some limited capacity to remove them. After treatment that prevents the production of new amyloid, for example, successful chemotherapy in AL type amyloid deposits are gradually mobilized in the majority of patients, though at different rates in different organs and different individuals. Unfortunately clearance of amyloid is especially slow in the heart, and echocardiographic evidence of improvement is rare, even over several years. The concept of passive immunotherapy to enhance clearance of amyloid has proved successful in experimental models and is variously now in clinical development.

The challenge of developing a therapeutic monoclonal antibody that is reactive with all types of amyloid has lately been addressed by targeting SAP because this is a universal constituent of all amyloid deposits and an excellent immunogen. Anti-SAP antibody treatment is clinically feasible because circulating human SAP can be depleted in patients by the bis-D-proline compound CPHPC, thereby enabling injected anti-SAP antibodies to reach residual SAP in the amyloid deposits.³ The unprecedented capacity of this novel combined therapy to eliminate amyloid deposits in mice is encouraging and should be applicable to all forms of human systemic and local amyloidosis.

Cardiac Transplantation in Amyloidosis

Cardiac transplantation has played a disappointingly small role, because of the multisystem nature of amyloidosis, advanced age, treatment-related complications, and rapid disease progression. Further, patients with AL amyloidosis must be deemed likely to be sufficiently fit to undergo chemotherapy afterward, to address the underlying bone marrow disorder. As a result, only a few dozen cardiac transplantations have ever been performed for amyloidosis. However, the long-term outcome can be good in highly selected patients with AL amyloidosis.¹¹⁵ Cardiac transplantation followed by successful peripheral blood autologous stem cell transplantation was associated with better survival in selected patients, as reported¹¹⁶ from most major amyloidosis units in the United Kingdom,¹¹⁵ France,¹¹⁷ Germany,¹¹⁸ and the United States.¹¹⁹ A suitable patient with AL amyloidosis is likely to be young (<60 years); to have isolated Mayo stage III cardiac amyloidosis, NYHA III or IV symptoms after adequate diuretics, good renal/liver function, no significant autonomic neuropathy, and low-level bone marrow plasmacytosis; and to be eligible for autologous stem cell transplantation after the heart transplantation. Even in such patients, outcomes are probably inferior to other indications.¹²⁰ For variant ATTR, combined cardiac and liver transplantation has been performed in a few dozen cases throughout the world.^{115,116,121,122} Although most patients with wild-type ATTR are too elderly for cardiac transplantation, the

absence of extracardiac involvement renders younger patients with wild-type ATTR excellent candidates. The 2 patients with wild-type ATTR who presented to our center before age 60 survived 10 and 20 years, respectively, after cardiac transplantation.

Conclusion

Cardiac amyloidosis remains challenging to diagnose and to treat. Key “red flags” that should raise suspicion include clinical features indicating multisystem disease and concentric LV thickening on echocardiography in the absence of increased voltage on ECG; the pattern of gadolinium enhancement on CMR appears to be very characteristic. Confirmation of amyloid type is now possible in most cases through a combination of immunohistochemistry, DNA analysis, and proteomics. Unlike other causes of heart failure, supportive treatment is mainly focused on diuretics therapy. Although developments in chemotherapy have greatly improved the outlook in AL amyloidosis, the prognosis of patients with advanced cardiac involvement remains very poor. Senile cardiac amyloidosis is probably greatly underdiagnosed, but CMR and DPD scintigraphy show great potential to address this unmet need in the aging population. A variety of novel specific therapies are on the near horizon, with potential to both inhibit new amyloid formation and enhance clearance of existing deposits.

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