A Focused Review on the Pathophysiology, Diagnosis, and Management of Cardiac Amyloidosis

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Amyloidosis is a systemic disorder that results from abnormal protein metabolism, producing amyloid fibrils that are subsequently deposited within vital organs. Cardiac involvement is typically associated with the specific subtypes of immunoglobulin light-chain, transthyretin, secondary amyloidosis, and dialysis-related amyloidosis. The hallmark of cardiac amyloidosis is the development of restrictive cardiomyopathy and heart failure, usually with a preserved left ventricular ejection fraction. The diagnosis is based on the integration of clinical signs and symptoms, echocardiography, cardiac magnetic resonance imaging, nuclear scintigraphy, electrocardiography, and cardiac biomarkers. Traditionally, management of heart failure symptoms and prevention of heart failure exacerbations have been the cornerstones of therapy. However, various treatments are currently under investigation that aim to eliminate or neutralize the underlying amyloidogenic substrate. Herein, we provide a focused review and discussion of the cardiovascular manifestations, epidemiologic and clinical characteristics, diagnostic modalities, and treatment strategies of cardiac amyloidosis.

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KEY WORDS

Amyloidosis • Heart failure • Cardiomyopathy

Amyloidosis is a heterogeneous group of disorders related to an abnormal protein metabolism, in which misfolded protein precursors deposit with proteoglycans and serum amyloid P protein, leading to organ infiltration and dysfunction.[1] The abnormal precursor proteins are termed *amyloid*, and consist of crossed β-pleated sheets that form amyloid fibrils resistant to protease catalysis.[2] To date, more than 30 proteins are identified as amyloidogenic, with a heterogeneous clinical presentation and natural history.[1-3] As a systemic disease, amyloidosis may affect all organ systems; the cardiovascular and renal systems are the most common. The phenotypic variation of the amyloid protein determines its organ predilection and clinical manifestations.[4]

The cardiovascular system is most commonly affected by the subtypes of immunoglobulin light-chain, transthyretin, secondary, and dialysis-related amyloidosis.[1,4] Infiltration by amyloid fibrils results in impaired cardiac cellular metabolism, calcium transport, and receptor regulation, which produces cellular edema.[3,4] There is also an associated derangement of the intracellular redox state, which increases the production of reactive oxygen species, and contributes to mitochondrial and sarcomere dysfunction.[5] Circulating amyloid, via activation of p38 mitogen-activated protein kinases, may trigger cardiomyocyte apoptosis and cell death.[6] Herein, we provide a focused review and discussion of the cardiovascular manifestations of this entity.

Cardiovascular Manifestations of Amyloidosis

Restrictive cardiomyopathy is the hallmark finding in cardiac amyloidosis that results from the interstitial deposits of amyloid fibrils. Once infiltrated, the myocardium becomes firm and noncompliant.[7,8] Clinically, this manifests in progressive diastolic dysfunction, elevated left ventricular (LV) filling pressures, and heart failure (HF) with preserved ejection. Common symptoms include exercise intolerance due to the inability to augment cardiac output, dyspnea, and peripheral edema. The natural history and prognosis varies significantly between the different subtypes; acquired light-chain amyloidosis demonstrates a more aggressive disease course, and senile or wild-type transthyretin amyloidosis has a more indolent progression. As with all restrictive cardiomyopathies, the chronically elevated LV filling pressures lead to left atrial enlargement, atrial fibrosis, and electromechanical remodeling, which are substrates for the development of atrial fibrillation.[9]

Pulmonary hypertension is frequently found in patients with cardiac amyloidosis; the most likely etiology is pulmonary venous hypertension from chronic diastolic dysfunction. Amyloid deposits in the pulmonary vascular bed may also contribute to pulmonary hypertension. Eventually, cor pulmonale and signs of right-sided HF may develop, which entail a poor prognosis, with a median survival of 73 days.[10]

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With the progression of the disease, patients may develop LV systolic dysfunction and, ultimately, expire. Rapezzi and colleagues[7] noted that 63% of patients with light-chain amyloidosis were alive 2 years after diagnosis, as compared with 98% of those with transthyretin amyloidosis.[7] The potential for coronary intramural or microvasculature amyloid infiltration has also been proposed, which can worsen LV diastolic dysfunction and result in myocardial ischemia and systolic impairment.[11,12]

Infiltration of the autonomic nervous system leading to orthostatic hypotension and syncope occurs in approximately 10% to 20% of patients.[13] The conduction system is also commonly affected, and the abnormalities may range from sinus node dysfunction to atrioventricular block.[14]

The prevalence of sudden cardiac death has been cited as high as 30% to 40%; however, ventricular arrhythmias are uncommon.[15,16] It is hypothesized that sudden death in this population is the result of cardiac electromechanical dissociation and a rapidly fatal hemodynamic collapse.[17]

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Pathogenesis, Epidemiology, and Characteristics of Cardiac Amyloid Subtypes

Immunoglobulin Light-chain Amyloidosis

Immunoglobulin light-chain protein is associated with a spectrum of plasma cell disorders, including amyloidosis, multiple myeloma, B-cell lymphoma, and Waldenström macroglobulinemia.[18] Modifications in the immunoglobulin variable regions determine the type of light-chain,

with a predominance of a λ-κ ratio of 3:1 in amyloidosis.[19] It constitutes approximately 85% of all new diagnoses, with an annual incidence of 3000 cases in the United States.[20,21] The median age at diagnosis is 73 years, and men account for 60% of the population.[20] The cardiovascular system is affected in up to 50% of patients, with the majority progressing to New York Heart Association (NYHA) functional class III or IV HF.[22,23] The median survival, without treatment, is approximately 1.8 years; this decreases to 7 to 9 months once HF symptoms develop.[24]

Transthyretin Amyloidosis

Transthyretin is a protein synthesized in the liver, which functions as a systemic transporter of thyroxine and Vitamin A. Different forms of protein misfolding result from the two types of transthyretin amyloidosis. The sporadic nongenetic form (also known as senile systemic or wild-type amyloidosis) originates from normal native transthyretin protein that undergoes post-translational modification, whereas or familial amyloid cardiomyopathy) arises from a genetically mutated transthyretin protein.

The exact prevalence of wild-type versus mutant-type transthyretin cardiac amyloidosis is difficult to obtain, given the broad regional differences in the type of mutation and their variable penetrance. However, relative frequencies have been previously reported in a US cohort of 100 endomyocardial biopsy-proven cases of cardiac amyloidosis. Figure 1 shows the results of this study, in which 22% of the biopsies corresponded to wild-type and 4% to mutant-type transthyretin amyloidosis.[25]

Wild-type transthyretin myocardial deposition is frequently found in the elderly, occurring in 10% to 25% of individuals over age 80 years, and in 50% of those over age 90.[26] However, deposition is typically mild and scattered, with <10% of individuals having moderate or severe infiltration.[27,28] It is far more common in elderly men, and has an 80% to 95% predominance in men.[29] Wild-type transthyretin amyloidosis typically has a more indolent course, with a median survival estimated at approximately 5 years.[26,29]

Over 100 mutations in the gene encoding for transthyretin are associated with the development of variant-type transthyretin amyloidosis.[29,30] Based on the mutation, the expressed phenotypes differ in their clinical presentation. In the Transthyretic Amyloidosis Outcomes Survey, cardiomyopathy was most commonly observed in the mutations involving the valine to isoleucine substitution at position 122 and leucine to methionine at position 111, a polyneuropathy was more prevalent with valine to methionine at position 30, and a mixed presentation occurred with glutamic acid to glycine at position 89.[31] The valine-isoleucine mutation is present in 3% to 4% of African Americans, who represent a high-risk population, and is typically expressed as a cardiomyopathy after age 50 years, with infiltration of both the left and right ventricles.[32,33] As compared with noncarriers, patients affected with the mutation have a 47% increased risk of HF.[34]

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Secondary Amyloidosis

Chronic inflammation as a result of rheumatic, autoimmune, and infectious diseases is associated with organ tissue deposition of the acute-phase reactant serum amyloid A protein.[35] The process is triggered by circulating tumor necrosis factor, interleukins, and transcription factors, which upregulate gene expression of the amyloid protein.[36,37] The most common disorders associated with secondary amyloidosis are rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthropathies, inflammatory bowel disease, and familial Mediterranean fever, with an estimated prevalence of 10% to 25%.[38,39] The development of cardiomyopathy is variable, and appears to be highest in patients with rheumatoid arthritis.[40] There does not appear to be an age predilection for secondary amyloidosis;

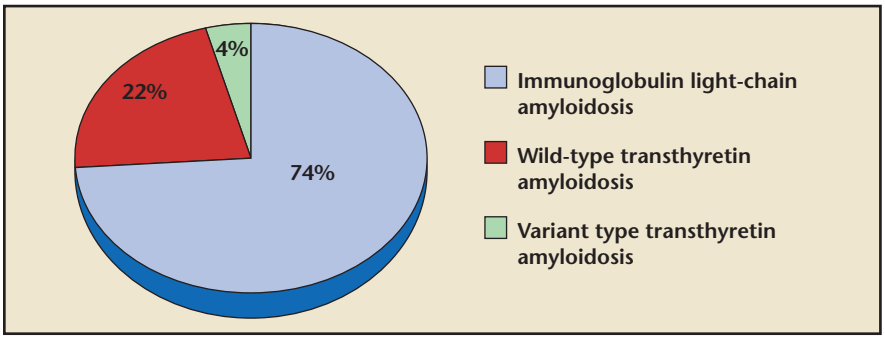

Figure 1. Relative frequency of biopsy-proven types of cardiac amyloidosis. Diagram shows the frequency of immunoglobulin light-chain cardiac amyloidosis, wild-type, and variant-type transthyretin cardiac amyloidosis by endomyocardial biopsy. Data from Crotty TB et al.[25]

it is suggested that cardiovascular manifestations may be related to poorly controlled long-standing inflammatory processes.[35,40]

Dialysis-related Amyloidosis

Amyloidosis in the setting of end-stage renal disease requiring hemodialysis results from the deposition of β-2-microglobulin amyloid fibrils.[4] β-2-microglobulin is normally cleared by the glomerular filtration system; therefore, its impact in dialysis-related amyloidosis is directly proportional to the severity of the renal impairment and the length of the time period of the hemodialysis treatment.[41] Postmortem studies have cited the prevalence of β-2-microglobulin amyloidosis to be 50% in patients who received dialysis for ≤10 years, and 100% after 15 to 20 years.[42,43] The most commonly affected organ is the skeletal system; the majority of patients present with bony deformities, tenosynovitis, and arthritis.[44] However, cardiac infiltration may occur, and is usually manifested as atrial fibrotic deposition with associated supraventricular arrhythmias, and a perivascular infiltrative pattern in the left ventricle.[45,46]

Diagnosis

Cardiac amyloidosis should be included in the differential diagnosis in any patient with a restrictive cardiomyopathy and congestive HF symptoms. Diagnostic modalities include transthoracic echocardiography, cardiac magnetic resonance imaging (MRI), nuclear imaging, tissue biopsy, electrocardiography, and cardiac biomarker testing. Figure 2 shows an updated diagnostic and treatment algorithm with the recently added nuclear scintigraphy imaging scans.

Echocardiography

Transthoracic echocardiography remains the most useful and cost-effective imaging modality for identifying and monitoring cardiac amyloidosis (Figure 3). As the amyloid fibrils infiltrate the myocardium, there is a concentric increase in the LV wall thickness, which typically exceeds 15 mm and produces a hyper-reflective "granular sparkling" pattern[46]; the latter, however, becomes less specific with greater use of harmonic echocardiography. With long-standing amyloidosis, there is often infiltration of the papillary muscles leading to mitral and tricuspid valve regurgitation; deposition may also be observed in the

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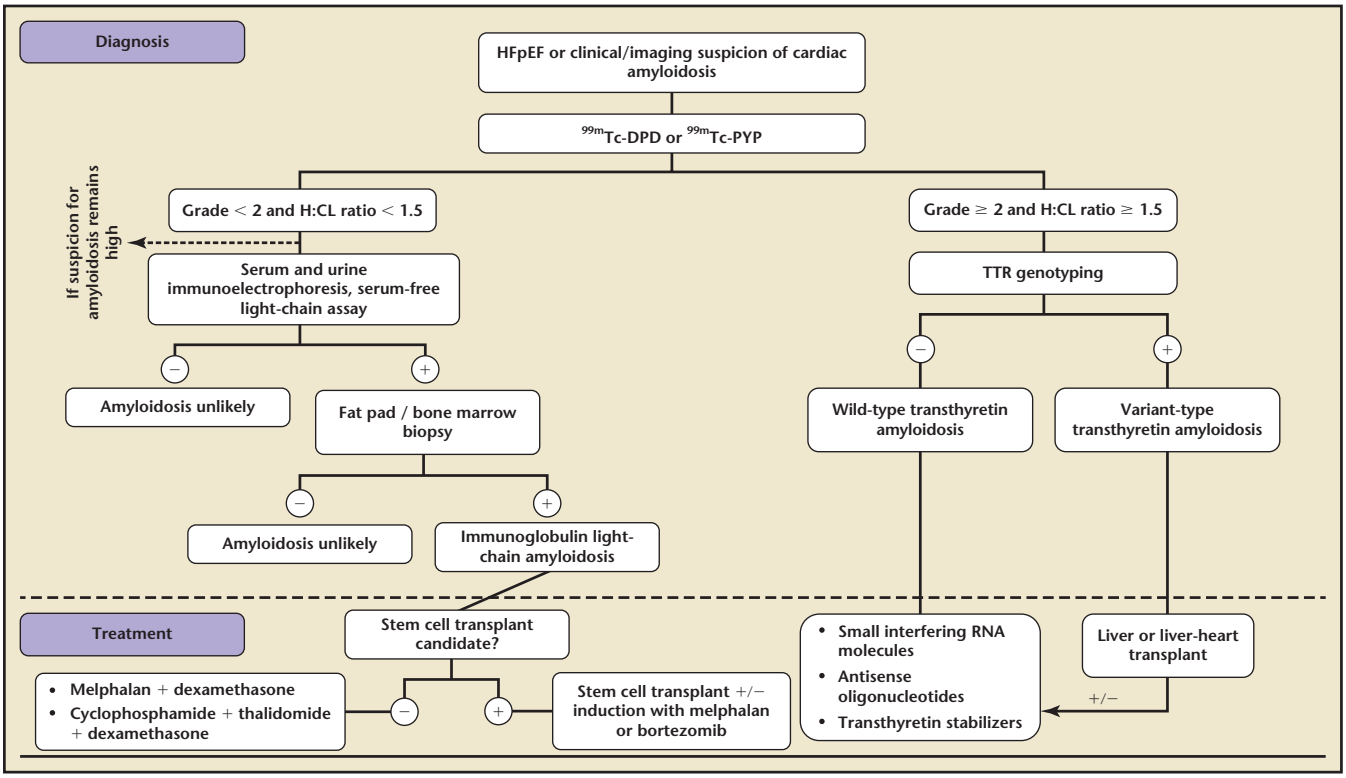

Figure 2. Proposed diagnostic and therapeutic algorithm for cardiac amyloidosis. Diagram shows a simplified algorithm for the approach to diagnosing cardiac amyloidosis that includes novel nuclear imaging scans. Novel pharmacologic treatment under current investigation has also been included. ^{99m}Tc-DPD, ^{99m}Tc-3,3-diphosphono-1, 2-propanodicarboxylic acid; ^{99m}Tc-PYP, ^{99m}Tc-pyrophosphate; H:CL ratio, heart-to-contralateral ratio; HFpEF, heart failure with preserved ejection fraction; TTR, transthyretin.

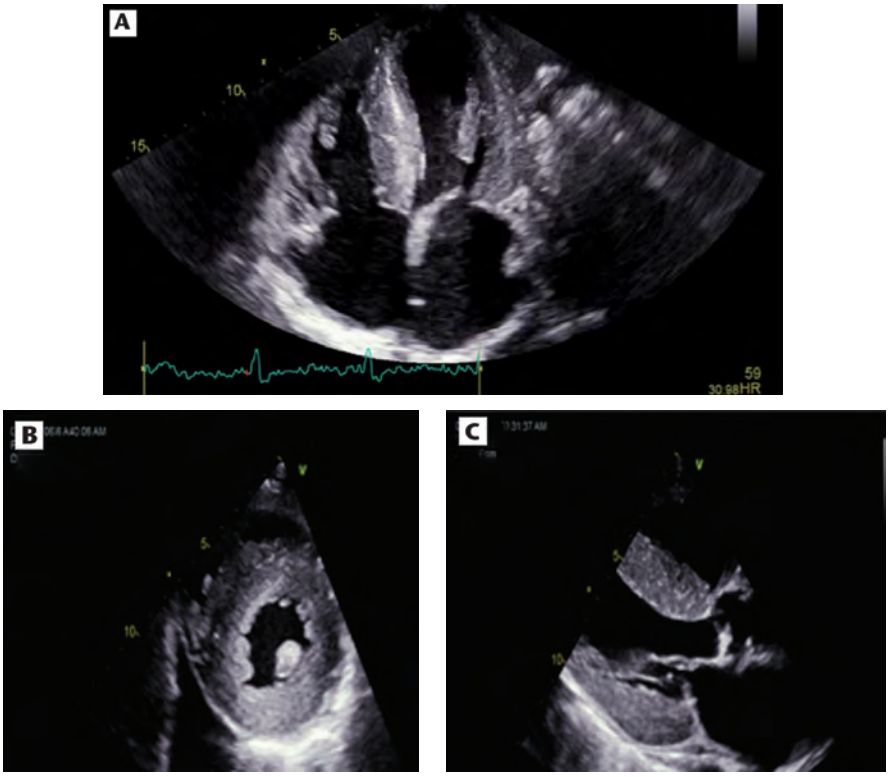

Figure 3. Transthoracic echocardiography in cardiac amyloidosis. Apical four-chamber view showing normal left ventricular size, increased left ventricular wall thickness, and a hyper-reflective "granular sparkling" pattern of the myocardium **(A)**. Corresponding parasternal short-axis **(B)** and long-axis **(C)** views are also shown.

atrial walls, interatrial septum, and pericardium.[47] As the LV compliance decreases, the initial phase of impaired diastolic relaxation progresses to a restrictive cardiomyopathy, resulting in elevated left atrial pressure with subsequent atrial dilatation.[48] Pulmonary venous hypertension subsequently ensues, which contributes to right-sided HF. Frequently, there is a coexistent small pericardial effusion, which is typically circumferential and of minimal hemodynamic significance. Finally, although the LV ejection fraction often remains preserved, the myocardial strain pattern is significantly reduced, which indicates the presence of subclinical LV systolic dysfunction occurring early in the disease process.[48,49] A specific pattern of longitudinal strain characterized by worse longitudinal strain in the mid and basal ventricle with relative sparing of the apex, classically described as a "cherry-on-top" strain pattern, may help distinguish LV infiltration due to amyloid infiltration from ventricular hypertrophy of hypertensive heart disease or hypertrophic cardiomyopathy.[50]

Cardiac Magnetic Resonance Imaging

Cardiac MRI has a sensitivity and specificity of 88% and 90%, respectively, for the diagnosis of cardiac amyloidosis (Figure 4).[51] This technique is centered on the prolonged retention of gadolinium in the extracellular myocardial space secondary to amyloid infiltration, which produces a characteristic delayed hyperenhancement and incomplete resolution of contrast from the myocardium. This imaging modality is able to detect a wide range of infiltrative patterns, including transmural versus subendocardial, global versus patchy, and infiltration of the atria, and may be used to quantify the extent of myocardial infiltration via the implementation of equilibrium contrast.[52,53] Additionally, late gadolinium enhancement is observed in patients with early cardiac amyloidosis and normal LV wall thickness, which would otherwise be undiagnosed by conventional transthoracic echocardiography. However, limitations include cost, lack of wide availability, inability to perform the scan in patients with pacemakers, and the contraindication of gadolinium use in patients with chronic kidney disease.[54]

Nuclear Imaging

The use of nuclear scintigraphy with conventional technetium bone isotopes is generally associated with a low sensitivity for the diagnosis of cardiac amyloidosis, resulting in a high false-negative rate.[55]

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However, the ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) and ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) isotopes have a predilection for specifically binding to transthyretin-related amyloid cardiac fibrils, which is most likely the result of its affinity for the increased calcium reservoirs found in the hearts of afflicted individuals (Figure 5).[56,57] In small, prospective studies, the differentiation of transthyretin-related versus immunoglobulin light-chain cardiac amyloidosis was made with a sensitivity and specificity of 100% utilizing the ^{99m}Tc-DPD isotope, and 97% and 100% with

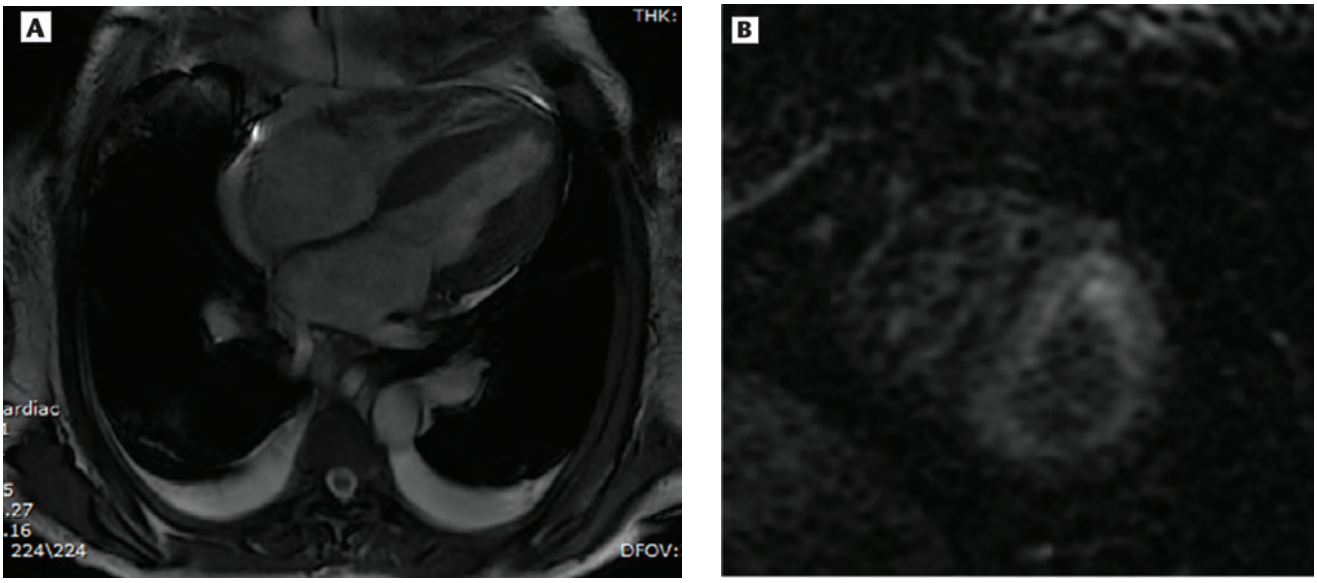

Figure 4. Characteristic appearance of cardiac amyloidosis on cardiac magnetic resonance imaging. **(A)** Four-chamber end-diastolic sagittal view of the heart shows diffuse biventricular hypertrophy with reduced cavity size, biatrial enlargement, and trace pericardial and bilateral pleural effusions. **(B)** Cardiac magnetic resonance imaging with gadolinium demonstrates diffuse late gadolinium enhancement of the left ventricular myocardium.

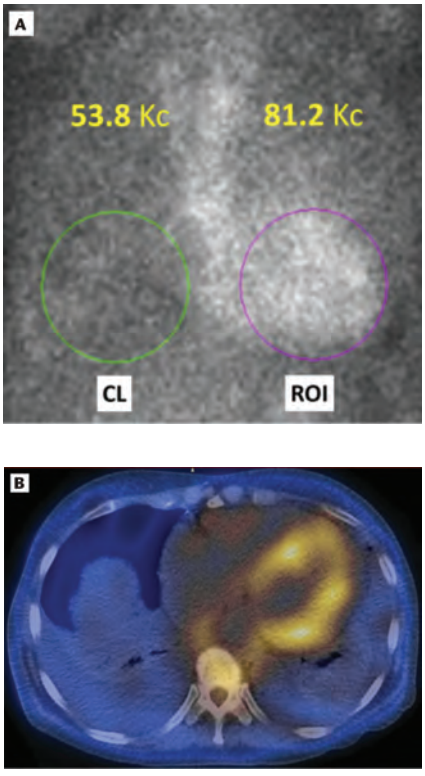

Figure 5. ^{99m}Tc-pyrophosphate nuclear scintigraphy in transthyretin amyloidosis. Quantitative evaluation of ^{99m}Tc-pyrophosphate uptake with planar imaging demonstrating mean heart (region of interest [ROI]) to contralateral (CL) ratio (ROI:CL) ≥1.5, suggestive of transthyretin amyloidosis (ATTR) cardiac amyloidosis **(A)**. Semiquantitative evaluation with single-photon emission computed tomography imaging in the same patient demonstrating intense diffuse myocardial uptake, greater than that of the adjacent ribs, also suggestive of ATTR cardiac amyloidosis **(B)**.

^{99m}Tc-PYP.[58,59] Thus, nuclear scintigraphy with these specific isotopes can aid in noninvasively distinguishing the type of cardiac amyloid infiltration, which may provide important clinical and therapeutic insight.

Tissue Biopsy

Tissue biopsy can be performed from affected organs or other noninvolved sites, such as the abdominal fat pad. Fat pad aspiration is especially useful in patients with multiorgan amyloidosis, in which the sensitivity and specificity for diagnosis may be as high as 85% and 100%, respectively.[60,61] The advantage of utilizing the abdominal fat pad for biopsy is its ease of approach, and a smaller likelihood of significant bleeding. In the case of a negative tissue biopsy result and a high suspicion of cardiac amyloidosis, an endomyocardial biopsy may be considered, and can be performed with a high diagnostic yield in specialized centers.[62,63] Under light microscopy, the amyloid fibrils bind Congo red resulting in apple-green birefringence under polarized light (Figure 6), and thioflavin T leading to a yellow-green immunofluorescent staining (Figure 7). Finally, immunohistology is typically used to identify the subtype of amyloid disease present, which can also be accomplished via mass spectroscopy or amino acid sequencing.[64]

Electrocardiography and Cardiac Biomarkers

A common electrocardiographic pattern found in patients with cardiac amyloidosis is a low voltage in the limb leads (QRS voltage amplitude ≤0.5 mV), and a pseudomyocardial infarction pattern (Q waves in 2 or more continuous leads with nonobstructive coronary artery disease) (Figure 8).[65] These characteristics are more commonly observed in patients with immunoglobulin light-chain amyloidosis, in which the prevalence is approximately 50%, as compared with the transthyretin or secondary amyloidosis subtypes.[7,66] When combining the presence of LV wall thickness ≥19.8 mm and low QRS limb-lead voltage, a noninvasive diagnosis of cardiac amyloidosis is suggested with a sensitivity and specificity of 72% and 91%, respectively.[67] Other possible electrocardiographic findings in patients

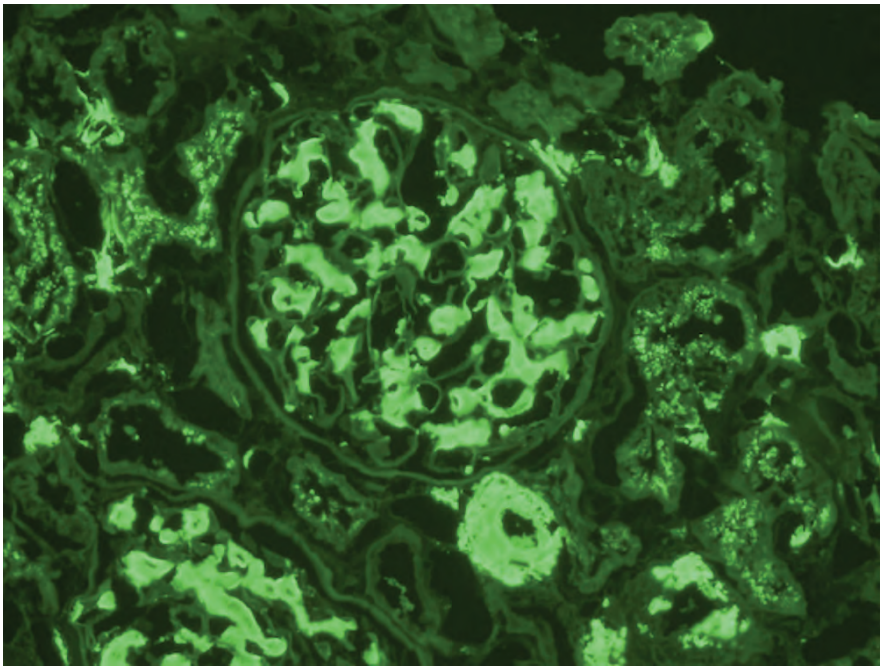

Figure 6. Light microscopy of amyloid fibrils. Binding of Congo red by the amyloid fibrils results in apple-green birefringence under polarized light.

with cardiac amyloidosis are atrial fibrillation, which is especially common in patients with advanced disease and restrictive physiology, and conduction system disease manifesting as atrioventricular and bundle branch blocks.

Although it is a nonspecific marker of HF, the serum B-type natriuretic peptide (BNP) concentration may be a useful clinical adjunct in assessing patients with cardiac amyloidosis. In the setting of elevated LV filling pressures, there is an upregulation of BNP secretion by the ventricles. This leads to the formation of pro-BNP, an active hormone that assists in diuresis, natriuresis, and volume homeostasis.[68,69] It has been shown that, in patients with immunoglobulin light-chain amyloidosis, serum BNP levels are elevated in symptomatic as well as asymptomatic patients, which may serve as an early marker of cardiac involvement.[70] Furthermore, serum BNP levels are a powerful predictor of all-cause mortality and cardiovascular events in both acutely decompensated and chronic HF, and may be more prognostic than LV ejection fraction or NYHA functional class.[71]

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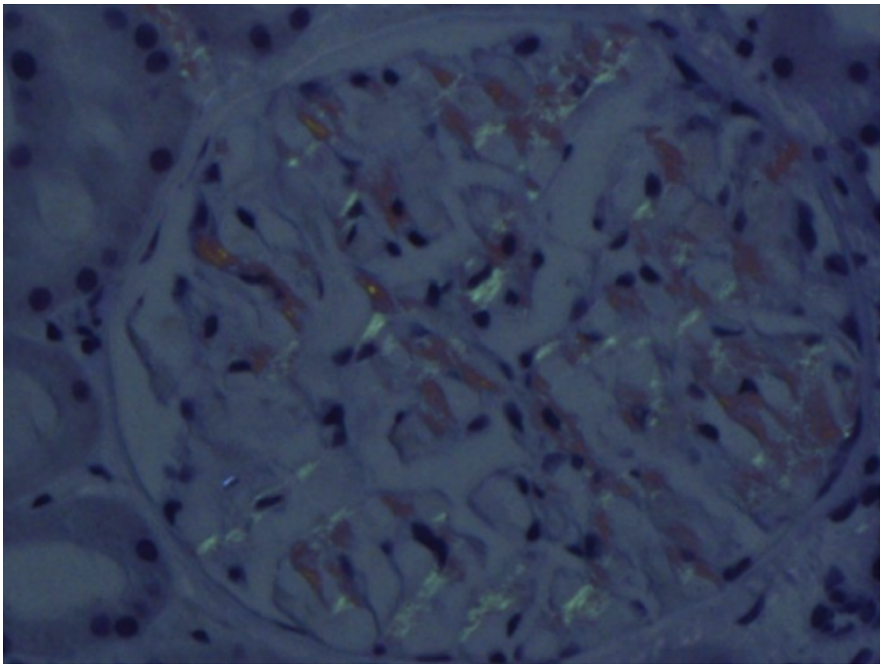

Figure 7. Immunofluorescent staining of amyloid fibrils. Binding of thioflavine T by the amyloid fibrils results in a yellow-green staining pattern.

Treatment

The primary goal of therapy in cardiac amyloidosis is centered in treating the specific protein subtype, whereas the other spectrum of therapeutics includes managing the associated symptoms. Novel targeted therapies and better understanding of the physiopathology has led to improved outcomes over the past 15 years. The 4-year survival was observed as 54% from 2010 to 2014 versus 31% between 2005 and 2009 ($P < .001$).[72]

The chemotherapy drug of choice is tailored depending on the type of amyloid protein. For immunoglobulin light-chain cardiac amyloidosis the options are less limited when compared with transthyretin amyloidosis. In selected patients with immunoglobulin light-chain amyloidosis, the treatment is centered on autologous stem cell transplantation with or without an initial induction phase with either high-dose

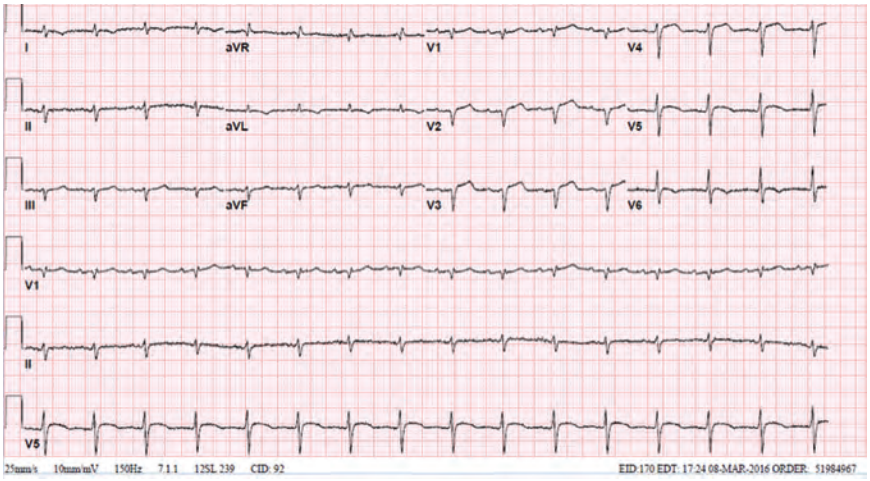

Figure 8. Twelve-lead electrocardiogram in a patient with cardiac amyloidosis. Note the low-voltage QRS amplitude (≤0.5 mV) in the limb leads, and a pseudomyocardial infarction pattern in leads V1-V3.

melphalan or bortezomib, which targets the plasma cell dyscrasia.[73] A good clinical response has been noted in 77% of patients who undergo stem cell transplantation, with small differences between those receiving induction chemotherapy prior to transplant compared with those who do not.[72] The response to therapy, both chemotherapy alone or with autologous stem cell transplantation, depends largely on the level of cardiac involvement, as well as the levels of biomarkers such as pro-BNP and troponin at the time of diagnosis.[73] Regimens such as oral melphalan with dexamethasone, or the combination of cyclophosphamide, thalidomide, and dexamethasone, constitute alternative options for patients deemed not candidates for stem cell transplantation.[74] The presence of NYHA functional class III or IV symptoms is considered a contraindication to advanced therapy, because the median survival in this group despite treatment is approximately 7 months.[24] The major challenge that remains is the overall limited awareness of this disease, which results in a late diagnosis, given the fact that the presenting symptoms often mimic many other disorders.

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For the variant-type transthyretin amyloidosis, treatment strategies to date are still insufficient, and definitive therapy constitutes liver transplantation.[75] The best experience with liver transplantation has been in relatively younger patients with Val30Met and V122I variants.[76] Simultaneous liver and heart transplantation in patients with familial transthyretin amyloidosis with significant cardiac involvement has demonstrated good results in selected patients .[77,78]

There are ongoing investigations of various drugs for transthyretin amyloidosis aiming at inhibiting the different steps in the production, misfolding, and deposition of the transthyretin protein. Some of these agents include the small interfering RNA molecules and antisense oligonucleotides that arrest the transcription of transthyretin protein from the nucleus of the hepatocytes. Phase 1 trials demonstrated efficacy in reducing the levels of both mutant and nonmutant transthyretin in a dose-dependent manner, with an acceptable adverse event rate.[79,80] Whether this will result in a clinical benefit has yet to be determined. The other class of drugs is the transthyretin stabilizers that bind transthyretin in the plasma to maintain its normal soluble native tetrameric structure. Diflunisal and tafamidis have been used solely in the variant-type, specifically in treating familial amyloid polyneuropathy, and have demonstrated slowing of disease progression.[81-83] Figure 2 provides a simplified diagnostic and therapeutic approach to cardiac amyloidosis. Finally, in secondary and dialysis-related amyloidosis, treatment of the underlying disease trigger is the standard of care.

The pharmacologic management of cardiac amyloidosis is aimed at the relief of pulmonary and systemic venous congestion, and reducing HF exacerbations.[84] Loop diuretics are used to achieve optimal volume homeostasis. Nondihydropyridine calcium channel blockers and β-blockers may be used to decrease the heart rate, enhance myocardial relaxation, increase LV filling time, and potentially improve diastolic function.[85-87] Care must be taken to tailor therapy to the individual patient, as excessive bradycardia may cause exercise-induced dyspnea and HF symptoms as a result of chronotropic incompetence. In patients with atrial fibrillation, heart rate control is important, as the absence of atrial systole may reduce the cardiac output by as much as 15% to 30%.[88,89] Additionally, oral anticoagulation with warfarin or a non-vitamin K antagonist oral anticoagulant are recommended to reduce the risk of thromboembolism. Permanent pacemaker implantation is indicated for patients with symptomatic or advanced atrioventricular

block.[90,91] Finally, in limited observational and retrospective studies, there has been no demonstrable benefit in the use of implantable cardioverter defibrillators for the primary prevention of sudden cardiac death in patients with cardiac amyloidosis.[17,92] This is thought to be due to the high incidence of electromechanical dissociation in this population; thus, the devices are traditionally not recommended.

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Cardiovascular involvement in patients with amyloidosis is a challenging clinical dilemma. A thorough understanding of the underlying amyloidogenic substrate, diagnostic modalities and their limitations, and treatment of the specific type of amyloid protein and the restrictive cardiomyopathy, is critical in order to improve outcomes. ■

Conclusions

Amyloidosis is a group of systemic disorders with a variable clinical presentation, including cardiovascular manifestations. When considering cardiac amyloidosis in a differential diagnosis, it is paramount to use an integrative approach, with incorporation of all clinical parameters, imaging modalities, and laboratory data. Although transthoracic echocardiography is well validated with numerous characteristic findings, at times it may be difficult to differentiate cardiac amyloidosis from other infiltrative disorders of the myocardium or hypertrophic cardiomyopathy.[48] Cardiac MRI is a sensitive and specific test, but has limited availability, as well as a high cost and significant clinical contraindications. A confirmatory tissue biopsy from an abdominal fat pad is useful in patients with multiorgan involvement, and can also be obtained from the endomyocardium, if clinically indicated. Finally, electrocardiographic and cardiac biomarkers are nonspecific for cardiac amyloidosis, and are more useful in combination with imaging findings, or as prognostic indicators.

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MAIN POINTS

- Immunoglobulin light-chain, transthyretin, secondary, and dialysis-related amyloidosis are the subtypes commonly associated with cardiovascular sequelae.
- The hallmark manifestation is a restrictive cardiomyopathy leading to heart failure.
- Wild-type transthyretin amyloidosis is an indolent process with the most favorable prognosis, whereas immunoglobulin light-chain disease confers a rapid clinical course and poor outcomes without early-onset treatment.
- Transthoracic echocardiography is the most useful screening modality given its ease of use, cost effectiveness, and robust diagnostic parameters.
- Therapy is centered on treating the specific subtype of amyloidosis, which is currently in multiple trials, and has shown improvement over the past decade.
- A cornerstone of the management of these patients is directed toward controlling systemic and pulmonary venous congestion and reducing HF exacerbations.

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