CME

Understanding and recognizing cardiac amyloidosis

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ABSTRACT

Cardiac amyloidosis is an infiltrative abnormality that causes myocardial thickening and dysfunction. Historically, it has been underrecognized as a cause of heart failure and was often misdiagnosed. In the past decade, the cardiology community has improved the understanding of the subtypes of these protein-based infiltrates and how they play a role in heart failure. This article reviews the pathophysiology, presentation, diagnosis, and management of cardiac amyloidosis.

Keywords: amyloid, transthyretin, light chain, cardiomyopathy, heart failure, infiltrative

Learning objectives

- Describe the different types of cardiac amyloidosis and their presentations.
- Explain the common cardiac and general patient features associated with cardiac amyloidosis.
- Summarize the workup and diagnosis for TTR and AL amyloidosis.
- Describe the current and emerging treatments for cardiac amyloidosis.

Amyloidoses are a group of degenerative diseases characterized by protein abnormalities that cause damaging fibrous deposits throughout the body. The most recognized diseases in this group are those affecting the nervous system, namely Alzheimer and Parkinson diseases. However, clinical research and literature in the past decade have shown increasing awareness of cardiac dysfunction caused by amyloidosis.[1] Investigations have shown that cardiac amyloidosis and its resulting toxic-infiltrative cardiomyopathy are much more common than previously believed and the condition is an underrecognized cause of heart failure, particularly diastolic heart failure.[2] This article discusses the effects of amyloidosis on the heart and how to recognize it in clinical practice.

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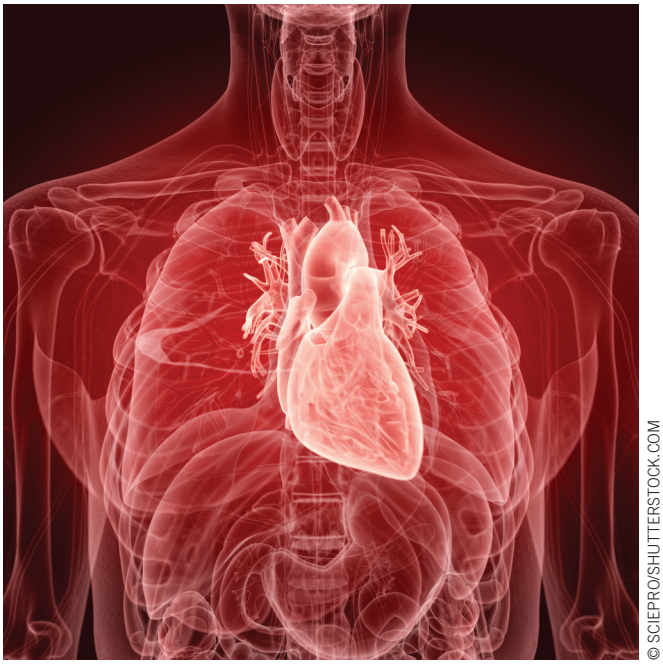


Nomenclature for amyloidosis uses the letter A for amyloid, followed by letter(s) indicating the main precursor protein being deposited. Light-chain amyloidosis is denoted **AL** (**A** for amyloid; **L** for light chain) and *transthyretin amyloidosis* is abbreviated **ATTR** (**A** for amyloid; **TTR** for transthyretin).

Pathophysiology More than 30 different amyloidogenic proteins have been identified.[3] The proteins commonly associated with cardiac amyloidoses arise from misfolded transthyretin (ATTR) or immunoglobulin light-chain aggregation (AL). These proteins can be deposited among one or more of the body's organs and interfere with normal organ function. The type of precursor protein, the tissue distribution, and the amount of amyloid deposition largely determine the specific clinical manifestations associated with each type of amyloidosis.[4] ATTR can be further classified by cause as either ATTR-m, which is due to a DNA mutation, or *wild type* transthyretin (ATTR-wt), which is acquired, and for which a mutation is not identified.

AL AMYLOID

Immunoglobulin light chain (AL) amyloid is a subtype of amyloidosis in which a plasma cell or B-cell dyscrasia produces excess immunoglobulin light chains that can be

Key points

- Cardiac amyloidosis is a toxic-infiltrative cardiomyopathy believed to be an underrecognized cause of heart failure with preserved ejection fraction.
- Common noncardiac symptoms of systemic amyloidosis include peripheral neuropathies, carpal tunnel syndrome, and orthostasis.
- Cardiac biopsy and cardiac PYP scan are diagnostic for AL and TTR amyloidosis, respectively.
- Intolerance to guideline-directed medicines and therapies for heart failure may be the first clue that a patient has cardiac amyloidosis.

deposited in organs as insoluble fibrils.[5] In patients with AL amyloid, a plasma cell clone forms and secretes excess light chains. Due to the underlying plasma cell dyscrasia, multiple myeloma and/or monoclonal gammopathy of undetermined significance (MGUS) also may be present.[6] The excess light chains that are formed and secreted are prone to misfolding, leading to a pathologic molecular conformation. These misfolded light chains can then aggregate, form into amyloid fibrils, and deposit in organs, leading to toxicity and dysfunction. The organs most commonly affected by AL amyloid deposition are the heart, kidneys, and liver; the autonomic and peripheral nervous systems also can be affected.[6] In AL amyloid, the resulting cardiac dysfunction is not simply due to amyloid deposits between myocardial cells leading to an infiltrative cardiomyopathy; the circulating free light chains also are directly toxic to the myocardium, and can have cytotoxic effects on cardiomyocytes.[3]

ATTR-M AMYLOID

Transthyretin, also known as prealbumin, is an abundant protein produced mainly by the liver and secreted into the bloodstream.[7] This transport protein carries the thyroid hormone thyroxine (T4) and retinol-binding protein (RBP). RBP is the transport protein for retinol (vitamin A1); in other words, this protein **trans**ports **thy**roxine and **retin**ol. In a patient with ATTR-m, an inheritable DNA mutation ultimately leads to protein instability and misfolding. As with AL amyloid, the misfolded proteins aggregate into insoluble amyloid fibrils, which then deposit into a variety of tissues. In ATTR-m, amyloid fibril deposition most commonly occurs in the nervous and/or cardiac systems, causing restrictive heart failure and peripheral neuropathy.[7] ATTR-m has variable myocardial involvement based on its genotype. Although ATTR-m is hereditary, determining a clear family history can prove difficult because not all carriers will develop the disease.

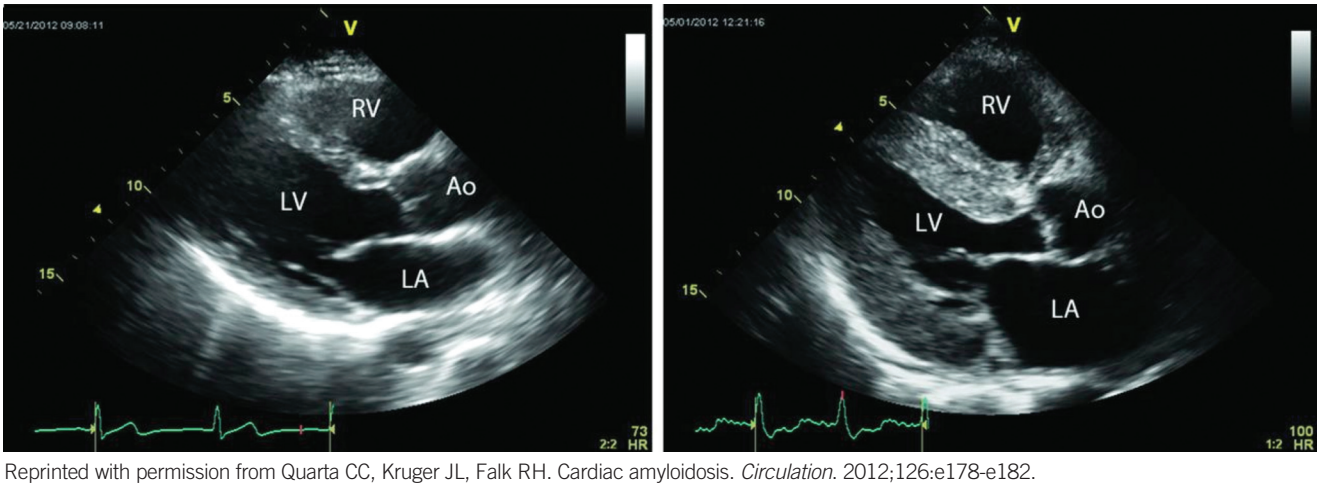
ATTR-WT AMYLOID

In patients with ATTR-wt amyloid, the transthyretin synthesized in the liver contains an acquired amyloidogenic defect.[4] In these patients, the precursor transthyretin protein becomes prone to misfolding with advanced patient age. Amyloid deposition is predominantly cardiac in wild type amyloidosis, with occasional carpal tenosynovial tissue involvement.

CLINICAL PRESENTATION

Noncardiac symptoms Amyloid cardiomyopathy typically is predated by extracardiac symptoms, which can be significant clinical clues for diagnosis. Ophthalmologic, orthopedic, neurologic, and gastrointestinal abnormalities can all be warning signs of cardiac amyloidosis, particularly in patients with ATTR.[8] ATTR can lead to deposits in the soft tissues, causing nerve entrapment syndromes.[2] Bilateral carpal tunnel syndrome is the most common noncardiac manifestation of ATTR and can precede clinical heart failure by 5 to 10 years.[9] Lumbar spinal stenosis, associated

FIGURE 1. Echocardiogram of a healthy patient (left) and one with cardiac amyloidosis (right). Myocardial wall thickening in amyloidosis eventually impairs cardiac function, as the left ventricle (LV) is reduced in size. Amyloid in the myocardium also thickens the interventricular septum. (RV, right ventricle; LA, left atrium; Ao, aorta.)



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with ATTR-wt, occurs due to thickening of the ligamentum flavum, causing compression and narrowing of the spinal canal.[10] Macroglossia and spontaneous periorbital bruising can be symptoms of AL cardiomyopathy. When hepatic infiltration occurs, the liver often is hard and nonpulsatile on examination.[11] Sensory abnormalities such as peripheral neuropathy can be a feature of both AL amyloidosis and ATTR. Patients with lower extremity neuropathies describe numbness in the feet or a sensation of "walking on rolled-up socks."[11]

Cardiac When amyloidosis affects the heart, the amyloid fibril deposits in the myocardium cause biventricular wall thickness and stiffness, effectively inducing a restrictive cardiomyopathy. Therefore, it is not surprising that the clinical presentation of cardiac amyloidosis is heart failure. Left ventricular (LV) diastolic dysfunction and dilated atria contribute to dyspnea. Just as commonly, several typical right heart failure findings can be seen, including jugular venous distension, lower extremity edema, and abdominal distension. These findings are caused by the restrictive nature of the cardiac infiltrates and the resulting reduced ventricular filling.[11] The reduced ventricular filling limits stroke volume and can progress to orthostasis, syncope, and low-output heart failure.[7]

Patients with cardiac amyloidosis often are diagnosed with heart failure with preserved ejection fraction, which can appear phenotypically as hypertrophic cardiomyopathy.[2] Clinicians should have a high level of suspicion for amyloidosis in patients previously diagnosed with heart failure with preserved ejection fraction who do not also have longstanding hypertension or ischemia. In the quest to identify this cause of heart failure as early as possible, recognizing the constellation of cardiac and systemic symptoms (Table 1) could significantly improve identification of amyloid cardiomyopathy.

DIFFERENTIAL DIAGNOSIS

Other conditions that can present with symptoms similar to cardiac amyloidosis include hypertensive cardiomyopathy, restrictive cardiomyopathy from previous chest radiation, and high-output heart failure. Other forms of infiltrative cardiomyopathy should be on the differential diagnosis, including sarcoidosis, iron overload cardiomyopathy from hemochromatosis, metastatic cancer, and glycogen storage disorders such as Fabry disease.

TABLE 1. Red flags for amyloid cardiomyopathy

- Echocardiogram findings with reduction in longitudinal strain and apical sparing
- Atrioventricular block and LV wall thickness
- Infiltrative hypertrophic features on echocardiogram
- History of bilateral carpal tunnel syndrome
- Mild increase in troponin levels on multiple occasions
- Symptoms of polyneuropathy and/or dysautonomia
- Spinal stenosis
- Macroglossia and/or periorbital purpura (AL type)
- Nephrotic syndrome (AL type)

TABLE 2. Criteria for diagnosing ATTR cardiomyopathy

- Heart failure/red flag and increased LV wall thickness (greater than 14 mm in men over age 65 years or women over age 70 years)
- Abnormal bone scintigraphy and normal serum free light chain ratio and serum/urine protein electrophoresis with immunofixation
- Confirmation on biopsy

MAKING THE DIAGNOSIS

Along with a detailed history and physical examination, the diagnostic evaluation of cardiac amyloidosis includes laboratory studies and cardiac imaging. Initial diagnosis begins with clinical suspicion based on the patient's presenting symptoms and examination findings. A diagnosis of AL cardiac amyloidosis can be confirmed with a positive tissue biopsy, a plasma cell dyscrasia on laboratory analysis, and typical cardiac imaging findings.

Cardiac imaging includes an echocardiogram and/or a cardiac MRI. Classically described features are found on each of these imaging modalities. Although these findings can support a diagnosis of an infiltrative cardiomyopathy, they cannot definitively diagnose amyloid nor differentiate between the different subtypes of cardiac amyloidosis. Classic echocardiogram findings of cardiac amyloidosis include increased LV wall thickness to greater than 14 mm, biatrial enlargement, and diastolic dysfunction. A classical pattern of myocardial strain (*relative apical sparing*) also can be seen on echocardiography in patients with cardiac amyloidosis.[3] A finding of *delayed gadolinium enhancement* on cardiac MRI suggests cardiac amyloidosis; the MRI contrast agent gadolinium occupies the interstitial space that has been expanded by amyloid infiltration. This abnormal enhancement occurs in a noncoronary artery distribution.

A 12-lead ECG may show low voltage in the QRS complex across the precordial leads. The ECG may be most useful for diagnosis in patients with discordance between lower voltage on the ECG and LV hypertrophy on cardiac imaging (which would typically be expected to cause high voltages on ECG). Signs of conduction system disease, such as prolongation of the P wave, PR interval, or QRS complex, also are more common and are related to amyloid infiltration of the myocardium.

If the patient's presentation along with imaging and laboratory findings are suggestive of cardiac amyloidosis, obtain further studies to confirm that cardiac amyloidosis is present. Typical diagnostic algorithms begin with determining whether the patient has a plasma cell dyscrasia. This is done by serum and urine electrophoresis with immunofixation as well as serum free light

chains.[6] The immunofixation studies determine whether abnormal proteins are present, and the serum free light chain assay quantifies the amount of abnormal proteins. If a plasma cell dyscrasia is found on these studies, suspect AL amyloid.

Biopsy is mandatory for a confirmatory diagnosis of AL amyloidosis.[6] The tissue sample can be obtained from the right ventricular endocardium (endomyocardial biopsy), bone marrow, or a fat pad (typically from the abdomen). Positive biopsy samples need to undergo mass spectrometry for more specific amyloid typing. If there is clinical suspicion for cardiac amyloidosis and no plasma cell dyscrasia is found on laboratory results, should consider a workup for ATTR (Table 2). Unlike AL, ATTR can be diagnosed without a biopsy, by using a pyrophosphate (PYP) nuclear imaging scan.[7] The PYP localizes to cardiac TTR deposits and is highly sensitive for TTR amyloid.[7] If this myocardial uptake of PYP is deemed strongly positive, TTR amyloidosis can be confirmed. After a positive scan, patients will need TTR DNA sequencing to determine TTR subtype (ATTR-m or ATTR-wt).

The most recent guidelines for staging patients with systemic AL amyloidosis suggest that overall mortality correlates additively with three serum assays: plasma free light chain difference (dFLC) greater than 18 mg/dL, N-terminal pro B-type natriuretic peptide (NT proBNP) greater than 18,000 pg/mL, and cardiac troponin-T greater 0.025 ng/mL.[12] NT-proBNP and troponin-T have shown to be strong predictors for survival in AL patients. In ATTR, serum troponin and proBNP levels often are persistently elevated, sometimes disproportionately for the degree of heart failure.[13] Cardiac specialists use these biomarkers to determine prognosis for these patients.

The prognosis for patients with amyloidosis varies considerably depending on the nature and extent of organ involvement as well as the disease progression at the time of diagnosis. AL amyloidosis carries the worst prognosis, with a median survival time of 4 to 6 months after a patient is diagnosed with heart failure.[5] ATTR is characterized by years of relative stability despite progressing disease; patients with this form may live for 3 to 10 years after diagnosis, depending on their therapeutic options.[2]

MANAGEMENT

The management and treatment of cardiac amyloidosis requires a focus on two different areas: management of the cardiac symptoms and cardiac-related complications along with treatment of the underlying disease to suppress further amyloid formation and deposition.[14]

Several nondisease modifying therapies have been shown to help manage cardiac symptoms and cardiac-related complications in patients with cardiac amyloidosis. Loop diuretics are commonly used for controlling congestive symptoms in patients with AL and TTR cardiac amyloidoses and are a mainstay of treatment for these types.[3] Use caution, however, when using diuretics in patients with cardiac amyloidosis. Achieving a balance between symptom management with decongestion and hypotension can be challenging. Because of amyloid deposition, the ventricles are stiff and noncompliant, and may lack the preload to maintain cardiac output. In these cases, diuresis can sometimes lead to hypotension and orthostasis. Encourage patients to restrict sodium intake and to weigh themselves daily. Educate patients about orthostatic hypotension and encourage them to wear compression stockings to minimize this effect.[14]

TABLE 3. Evaluating for AL amyloidosis

- Urine protein electrophoresis with immunofixation (abnormal if monoclonal protein is detected)
- Serum protein electrophoresis with immunofixation (abnormal if monoclonal protein is detected)
- Serum kappa/lambda free light chain ratio (abnormal if ratio is <0.26 or >1.65)
- Confirmation with endomyocardial or fat pad biopsy if laboratory results are believed to be false-negative

Conventional heart failure therapies such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) typically are poorly tolerated and should be avoided.[11,14] Hypotension is a common cause of intolerance because of involvement of the autonomic nervous system and may limit diuresis. If a patient is intolerant of guideline-directed medicines and therapies for heart failure, clinicians should have an increased suspicion for cardiac amyloidosis.[11,14]

Treatment of the underlying cause of cardiac amyloidosis is directed at reducing the amount of underlying precursor protein that ultimately forms into amyloid fibrils.[2] The treatment of the underlying causes of amyloidosis is different depending on whether it is AL or TTR amyloid.[14]

For AL amyloid, the treatment goal is to stop the growth of abnormal cells that produce amyloid; therapy consists of chemotherapy with or without autologous stem cell transplantation.[6] These therapies have mainly evolved from treatment of multiple myeloma. Overall survival depends on the patient's hematologic response and degree of cardiac involvement at the time of diagnosis. Although overall survival with AL amyloid is improving, 1-year mortality is at 24%.[3] Given AL cardiomyopathy's devastating and rapid trajectory, clinicians must rule this disease out quickly if they suspect an amyloid process (Table 3).

Hope is on the horizon for both types of cardiac amyloidosis, as several drugs are being researched and developed to stop amyloid production and clear existing amyloid fibrils. Treatments involving TTR silencer therapies and RNA interference approaches are entering late phases of clinical trials.[2] The transthyretin stabilizer, tafamidis, has demonstrated benefits in all-cause mortality and cardiac-related

hospitalizations. This drug was recently approved by the FDA for treating ATTR.[15]

Advanced heart failure therapies such as LV assist devices are contraindicated in patients with small ventricular cavities, and generally are not recommended for patients with cardiac amyloidosis.[16] Cardiac transplantation remains the gold standard treatment for advanced heart failure; however, extracardiac amyloid organ dysfunction can preclude a patient's candidacy for transplantation.[16] The extent of light chain and transthyretin organ involvement before transplant as well as the risk of required immunosuppression must be rigorously evaluated during transplant workup. Among patients with AL, those with amyloidosis related to multiple myeloma are excluded from transplant consideration.[16] In patients with ATTR, because transthyretin amyloid is primarily produced in the liver, dual transplant of heart and liver can be considered. However, patients with dual transplant have been shown to have similar survival rates as those undergoing heart transplant alone.[7,16]

CONCLUSION

Amyloid cardiomyopathy is a toxic-infiltrative disease that is now recognized as a significant cause of heart failure. This disease is in the early stage of discussion, study, and discovery. Diagnostic clues include unexplained ventricular hypertrophy, inappropriately low ECG voltages, and unexplained heart failure occurring with characteristic dysfunction of other organs. Techniques such as advanced echocardiography and nuclear imaging increase the likelihood of accurate diagnosis, but there is no substitute for clinician awareness. Refer patients with suspected amyloid cardiomyopathy to a high-volume amyloid center for consultation. When possible, patients should be treated in the context of clinical trials that can further the understanding of this disease and provide them with the most innovative therapies. **JAAPA**

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