Untangling Amyloidosis: Recent Advances in Cardiac Amyloidosis

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ABSTRACT

Cardiac amyloidosis (CA) is a highly underdiagnosed cause of heart failure. Amyloid light-chain (AL) and amyloid transthyretin (ATTR) cardiomyopathy are two major subtypes of cardiac amyloid. Amyloid fibril deposits cause cardiac dysfunction by mechanically infiltrating the myocardium or by direct cardiotoxicity. Achieving a timely diagnosis is important to initiate disease-modifying therapies and improve the survival of patients with CA. Therefore, physicians must be aware of “red flag symptoms” that increase suspicions for CA when assessing heart failure patients. Although endomyocardial biopsy is a definitive diagnostic tool, with recent advances in non-invasive imaging, non-biopsy diagnosis is feasible in ATTR CA. There have been major advances in treatments for both AL and ATTR CA, and survival of CA has improved. In addition to general management of heart failure, numerous treatment options are increasing for both AL and ATTR CA. Given the systemic nature of amyloids, multi-disciplined team approaches are crucial to management of CA. With recent development of diagnosis and treatment options for both AL and ATTR amyloidosis, it is no longer considered a non-treatable disease.

Keywords: Heart failure; Amyloidosis; Amyloid

INTRODUCTION

Cardiac amyloidosis (CA) is a rare disease but is likely a highly underdiagnosed cause of heart failure. According to data collected from Korea National Health Insurance, the age-standardized prevalence of amyloidosis was 0.93 persons per 100,000 persons in 2006 and 1.91 persons per 100,000 persons in 2015. Although incidences of amyloidosis have been increasing during past decades, the true prevalence of CA is uncertain. Recent studies suggested that the prevalence of wild-type amyloid transthyretin (wATTR) CA is substantially underestimated in older patients with heart failure, reporting 13% of wATTR incidence in heart failure with preserved ejection patients aged >60 years.

Up to 36 proteins are known to cause amyloid fibrils, and most CA is affected by either immunoglobulin amyloid light-chain (AL) or amyloid transthyretin (ATTR). With the introduction of a series of effective therapies for AL amyloidosis and promising new
treatments for ATTR amyloidosis, awareness among cardiologists needs to be raised because
these diagnoses are often delayed due to the various non-specific heart failure symptoms.

All types of CA share a common pathologic mechanism of extracellular deposition of amyloid
in the heart, which results in restrictive cardiomyopathy. However, the pathophysiology,
clinical presentation, and prognosis of AL and ATTR amyloidosis are different.

**PATHOGENESIS OF CA**

**AL amyloidosis**

AL amyloidosis is a hematologic disorder of plasma cells, mainly monoclonal gammopathy or
multiple myeloma (10%), and (rarely) B cell lymphoma. It is caused by the proliferation of an
abnormal clone of plasma cells as a monoclonal population of plasma-cell immunoglobulin
light chains, which form beta-pleated sheets, ultimately polymerizing into amyloid fibrils.

In addition to the effects of infiltration of the myocardium, light chain cardiotoxicity
was suggested from observation of clinical improvement after successful hematologic
improvement as evidenced by lack of changes in echocardiographic parameters. Recent
studies elucidated the mechanisms of light chain toxicity in cellular levels. Light chains
directly damage cardiomyocytes by impairing the lysosomal function, which results in
defective autophagy, increased reactive oxygen species, and eventually cellular death. Direct cardiac toxicity of light chains can be observed from more accelerated cardiac
deteriorations and higher levels of cardiac biomarkers in AL CA compared to ATTR CA.

**ATTR amyloidosis**

Transthyretin (TTR) is a transport protein of thyroxine and retinol-binding protein/
vitamin A complex and is mostly found in serum and cerebrospinal fluid. TTR is secreted
predominantly by the liver (95%); a smaller portion (<5%) is produced by the choroid plexus
and retinal pigment epithelium. TTR is composed of 4 beta-sheet-rich proteins. When
TTR is destabilized from the tetramer by proteolytic cleavage into unstable monomers,
misfolding of monomers results in aggregates of amyloid fibrils. The TTR gene is found
on chromosome 18, and more than 120 single mutations in 127 amino acid sequences have
been identified. TTR mutations in hereditary amyloid transthyretin (hATTR) increase the
TTR amyloidogenic propensity by reducing tetramer stability or increasing the instability of
monomers. The hATTR has autosomal-dominant patterns of inheritance, but penetrance
is highly variable according to mutation. The variability of TTR mutations differs according
to geographic and/or ethnic groups. In Korea, the asparatic acid to alanine substitution at
position 38 (Asp38Ala) mutation is currently the most common. Among the variants of
TTR predominantly involving the heart, the valine to isoleucine substitution at position
122 (V122I) is the most commonly detected mutation. In wATTR amyloidosis, the genes
of TTR are normal, and age appears to be involved in the instability of TTR; however, the
mechanisms are not yet clear. In contrast to AL CA, the mechanism of cardiac dysfunction is
predominantly infiltration of extracellular amyloid deposits within the myocardium, leading
to increased cardiac and vascular stiffness. There are some reports suggesting that pre-
fibrillar protein aggregates exhibit proteotoxicity in ATTR.
Clinical features of CA

CA presents with symptoms of biventricular heart failure, arrhythmia, or sudden death. The symptom of dyspnea is due to left ventricular diastolic dysfunction and increased atrial stiffness, as reflected by prominent v waves in the pulmonary wedge pressure tracing in the absence of mitral regurgitation. Atrial involvement also causes thrombus formation, even in patients with sinus rhythm, which may cause systemic embolism. Peripheral edema, ascites, hepatomegaly, and raised jugular venous pressure are often observed. Some patients present with exertional syncope or pre-syncope likely due to low stroke volume, which is associated with poor prognosis. Microvascular angina due to perivascular infiltration is also frequently observed. Symptoms from involvement of other organs from patients in the Samsung Medical Center amyloid registry are described in Table 1 (unpublished data).

DIAGNOSTIC ALGORITHM

Early signs and symptoms of CA are non-specific and may mimic other diseases. Delayed diagnosis is still an important issue in clinical practice. More than 20% of AL CA patients experience more than two years of delayed diagnosis, and time delay is even longer in patients with ATTR CA. Table 2 summarizes red-flag signs that should raise suspicions for CA. The diagnostic algorithm of CA in patients presenting with symptoms of heart failure is summarized in Figure 1. In patients with suspected CA, screening for

| Table 1. Clinical presentation and involvement of organs according to subtype of amyloids |
|---------------------------------|---------------------------------|---------------------------------|
| Organ involvement              | All organs except central nervous system | Heart, peripheral and autonomous nerve system, ligaments |
| | AL amyloidosis (n=324) | hATTR amyloidosis (n=40) | wATTR (n=5) |
| Heart | 75% | 63% | 100% |
| Kidney | 65% | 0% | - |
| Autonomic/peripheral nerve system | 10% | 56%/52% | 60% |
| Gastrointestinal tract and liver | 15% | 26% | - |
| Connective tissue/soft tissue | 15% | 22%/15% | - |

Unpublished data from the Samsung Medical Center amyloid registry.

AL = amyloid light-chain; hATTR = hereditary amyloid transthyretin; wATTR = wild-type amyloidosis transthyretin.

| Table 2. Red flag symptoms for cardiac amyloidosis |
|---------------------------------|---------------------------------|
| Cardiac amyloidosis | |
| Echocardiography | - Unexplained increased in wall thickness (>12 mm) with non-dilated LV |
| | - Thickening of RV free walls, valves, or interatrial septum |
| | - Small pericardial effusion |
| | - Reduced LV GLS with apical sparing pattern despite pEF |
| ECG | - Low voltage* or pseudo infarct-pattern |
| Clinical features | - Intolerance to beta blocker, ACEI, or ARB |
| | - Low normal blood pressure with previous history of hypertension |
| Labs | - Mild increase in troponin level on repeated occasions |
| AL cardiac amyloidosis | - ATTR cardiac amyloidosis |
| MGUS | - AV block in presence of increased LV wall thickness |
| | - Unexplained conduction block needing pacemaker |
| Symptoms of HF pEF with nephrotic syndromes | - Autonomic signs and symptoms (orthostatic hypotension, alternating constipation/diarrhea, sweating abnormalities) associated with peripheral neuropathy |
| Macroglossia and periorbital purpura | - Carpal tunnel syndrome, particularly if bilateral |
| Peripheral neuropathy | - Newly diagnosed HCMP in elderly patients |
| | - Newly diagnosed low flow, low gradient stenosis in elderly patients |

ACEI = angiotensin-converting-enzyme inhibitor; AL = amyloid light-chain; ARB = angiotensin II receptor blockers; ATTR = amyloid transthyretin; AV = atrioventricular; ECG = electrocardiography; GLS = global longitudinal strain; LV = left ventricle; MGUS = monoclonal gammopathy of undetermined significance; pEF = preserved ejection fraction; RV = right ventricle.

*Only 50% of AL cardiac amyloidosis and 30% of ATTR cardiac amyloidosis cases meet low-voltage ECG criteria of QRS amplitude <5 mm in limb leads or <10 mm in precordial leads.

monoclonal gammopathy should be performed and includes serum-free kappa/lambda ratio and serum and urine immunofixation. Screening by electrophoresis is inadequate because 20% of patients with AL amyloidosis have only immunoglobulin light chains, with no intact immunoglobulin protein. In addition, both urine and serum must be studied by immunofixation because one-third of patients have negative immunofixation of the serum. Up to 40% of patients with ATTR CA can have monoclonal gammopathy of unknown significance, for which scintigraphy alone cannot ensure a proper diagnosis.

Classic imaging features of ATTR CA are described in Figure 2 and Table 3. Recent advances with nuclear imaging have enabled non-invasive diagnosis of ATTR CA without need for invasive cardiac biopsy. Three technetium-labeled radiotracers, Tc-99m-pyrophosphate (PYP), Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and Tc-99m-hydroxymethylene diphosphonate (HDMP), are clinically used for identification of ATTR CA. The mechanisms for myocardial retention of radiotracers are not fully understood. From large-scale international studies, the sensitivity of grade 2 (cardiac uptake equal to that of bone) or grade 3 (cardiac uptake exceeding that of bone) tracer uptake for detecting TTR amyloid deposits was >99%, with a specificity of 86% in the absence of monoclonal protein in heart failure patients with suspicious features on echocardiography. Clinicians should be aware that about one-third of AL CA patients can show grade I or even higher myocardial retention. Presence of monoclonal protein is an important differential diagnostic clue for AL and ATTR CA. However, up to 40% of ATTR CA patients have monoclonal gammopathy of unknown significance. In such cases, a definitive diagnosis should be made by tissue biopsy from the affected organ. Abdominal fat pad biopsy by needle aspiration is reported to have 70–80% sensitivity for identifying amyloid deposition; however, false negatives and
false positives may occur in less experienced centers. In our center, we prefer to perform endomyocardial biopsy because, in addition to tissue confirmation, we can also assess cardiac hemodynamics and coronary physiology.

Table 3. Imaging studies in diagnosis of ATTR CA

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<th>Study</th>
<th>Advantages/limitations</th>
<th>Limitation</th>
<th>Typical features suggestive of ATTR CA</th>
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<tr>
<td>Echocardiography</td>
<td>Cost-effective, commonly available, can identify diastolic function</td>
<td>Typical features may be variably present</td>
<td>Thickened myocardium (&gt;12 mm), small LV cavity sized valve, restrictive diastolic function, thickened interatrial septum, pericardial effusion, and apical sparing regional longitudinal strain patterns</td>
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<td>Cardiac MRI</td>
<td>Detailed information about cardiac function and tissue characterization</td>
<td>Limited in patients with renal dysfunction</td>
<td>Diffuse subendocardial or transmural late gadolinium enhancement, increased myocardial native T1, increased extracellular volume fraction, suboptimal myocardial nulling</td>
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<td>Bone scintigraphy</td>
<td>High specificity for diagnosis with grade 2 or 3 uptake</td>
<td>Cannot rule out AL amyloidosis</td>
<td>Grade 2 or 3 tracer uptake in conjunction with no evidence of monoclonal gammopathy by serum/urine testing</td>
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AL = amyloid light-chain; ATTR = amyloid transthyretin; CA = cardiac amyloidosis; LV = left ventricle; MRI = magnetic resonance imaging.
TREATMENT

Therapy for CA includes optimal treatment of heart failure and specific therapies according to subtype of amyloid. Generally, standard heart failure medications, especially beta blockers, angiotensin-converting-enzyme inhibitors, and angiotensin II receptor blockers, are poorly tolerated. Diuretics are the mainstay of heart failure therapy. Digoxin toxicity could occur even in ranges of therapeutic levels because of altered binding properties. Atrial arrhythmia often accompanies heart failure, and anti-arrhythmic agents with negative inotropic or chronotropic effect should be avoided. Catheter ablations may be not be effective, likely due to the multifocal nature of the disease; high recurrence rates have been reported after catheter ablation. Sudden cardiac death in CA patients is mostly reported to be from pulseless electrical activity, and there is no evidence for benefit of prophylactic implantable defibrillator use. The role of a left ventricular assist device in CA patients with advanced heart failure is limited due to the small size of the cardiac chambers and right ventricular dysfunction. Heart transplant could be considered in selected patients with severe CA without significant involvement of other organs. For AL CA, patients with refractory heart failure after achieving complete hematologic responses (normalization of free light chain ratio) could benefit from heart transplantation. Some centers consider patients with severe AL CA limited to the heart and intolerant to chemotherapy because of cardiac function to be possible candidates for heart transplant with concomitant high-dose chemotherapy.

Specific treatments for AL and ATTR CA are summarized in Table 4. For ATTR amyloidosis, various pharmacological strategies are under development. A recent multi-center, randomized ATTR-ACT trial demonstrated the efficacy of tafamidis in ATTR CA patients. Tafamidis reduced mortality compared with placebo (29.5% vs. 42.9%; hazard ratio, 0.70; 95% confidence interval [CI], 0.51–0.96) and also reduced cardiovascular-related hospitalizations (0.48 vs. 0.70 per year; relative risk, 0.68; 95% CI, 0.56–0.81). Consistent improvements in mortality and hospitalizations were realized regardless of subtype of ATTR (hATTR vs. wATTR); however, patients with New York Heart Association Class III heart failure symptoms were observed to have a higher risk of cardiovascular-related hospitalization, suggesting that

<table>
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<th>Table 4. Treatment for AL and ATTR amyloidosis</th>
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<td><strong>Treatments</strong></td>
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This table is modified from Table 2, Cleve Clin J Med 2017;84:12-26. AL = amyloid light-chain; ASO = anti-sense oligonucleotide; ATTR = amyloid transthyretin; CA = cardiac amyloidosis; hATTR = hereditary amyloid transthyretin; PPI = proton pump inhibitor; sRNA = small interfering RNA; TTR = transthyretin; TUDCA = tauro-deoxycholic acid; wATTR = wild-type amyloid transthyretin. *High-dose chemotherapy with autologous stem cell transplantation is generally reserved for suitable CA cases; consultation from cardiology is important because stem cell collection is often accompanied by fluid retention, and atrial arrhythmia can follow chemotherapy.
earlier treatment with tafamidis is likely to improve the prognosis in ATTR CA patients. The U.S. Food and Drug Administration (FDA) approved tafamidis for ATTR cardiomyopathy in 2019; it has approved patisiran and inotersen only for ATTR neuropathy not for ATTR cardiomyopathy. From a randomized trial investigating the efficacy of patisiran for ATTR polyneuropathy, patisiran significantly reduced N-terminal pro-brain natriuretic peptide level, LV wall thickness, and worsening of longitudinal strain in the ATTR CA subgroup.\(^{36}\)

Regardless of amyloid subtype, because amyloid is a systemic disease and involves multiple organs, a multi-disciplinary team approach is important for improved survival of patients. Our center established an amyloid clinic in 2009 involving cardiologists, hematologists, neurologists, pathologists, nuclear medicine physicians, and gastroenterologists. The multi-disciplinary team approach significantly improved the survival of CA patients (Figure 3). Of note, as seen in Figure 3, early mortality reflected by 1-year survival did not change despite the multi-disciplinary team approach. This is because early mortality can be only reduced by early diagnosis. Therefore, the role of cardiologists in early diagnosis is extremely important to improve early mortality even in a multi-disciplinary team setting.

**CONCLUSIONS**

CA affects a considerable proportion of patients presenting with heart failure. With advancements in contemporary imaging techniques, cardiologists now have the means to facilitate early diagnosis of CA and improve the prognosis of patients with CA. Despite major advances in diagnosis and treatments for both AL and ATTR CA, delayed diagnosis from lack of physician awareness is still a critical issue. Establishing a multi-disciplinary team-based amyloid clinic is of tremendous importance in successful diagnosis and treatment of CA patients. Hopefully, this review will contribute to raise awareness of physicians and increase the recognition that CA is no longer a non-treatable disease; it is now possibly becoming a curable condition.
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