Journal of Geriatric Cardiology (2019) 16: 567–574

Perspective · **Open Access** ·

Approach to a patient with cardiac amyloidosis

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J Geriatr Cardiol 2019; 16: 567–574. doi:10.11909/j.issn.1671-5411.2019.07.010

Keywords: Cardiac amyloidosis; Heart failure; The elderly

1 Introduction

Cardiac amyloid (CA) is characterized by inexorably progressive heart failure making early diagnosis and treatment imperative. This article will review the pathophysiology, clinical presentation, diagnosis, prognostication and treatment of patients with CA.

2 Pathophysiology

CA is the result of extracellular deposition of a misfolded protein into cardiac tissue, forming insoluble aggregations of rigid, nonbranching 10 nm wide fibrils. This causes impaired cardiac function by disrupting cardiac architecture, direct myotoxicity and ischemic injury secondary to infiltration of intramyocardial vessels.[1–3] Amyloid deposits demonstrate a pathognomonic affinity for Congo red, with apple green birefringence under polarization.[1] Nearly all cases of clinically significant CA are caused by one of six proteins: immunoglobulin light chain, immunoglobulin heavy chain, serum amyloid A, transthyretin (TTR), apoliprotein A1, or atrial naturitic factor.[1] Of these, immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) account for > 90% of cases in the United States (US).[4]

2.1 Immunoglobulin light chain cardiac amyloidosis (AL-CA)

In AL amyloidosis, amyloid deposits are formed by kappa or lambda light chain proteins which are produced by a clonal population of malignant plasma cells. The myocardium is involved in around 50% of cases.[5] In addition to mechanical damage mediated by cardiac fibril deposition, the soluble AL protein has directly toxic effects on myocardial tissues, mediated via p38α mitogen-activated protein kinases (MAPK) signaling.[6] Brain natriuretic peptide (BNP) is also upregulated by p38 MAPK signaling, and thus serum BNP reflects both the amyloid disease activity and cardiac injury.[7]

2.2 Transthyretin cardiac amyloidosis (ATTR-CA)

Transthyretin, a transporter of thyroxine and retinol, can form amyloid deposits in both its wild type and mutant forms.[8] Wild type transthyretin amyloid (ATTRwt) affects elderly patients and predominantly affects the heart and peripheral nerves. In mutant transthyretin amyloidosis (ATTRm), the tropism and age of clinical onset can be affected by mutations of the TTR gene, of which over 90 mutations have been identified. The Val122Ile mutation is present in 4% of African Americans in the US, and causes predominately CA. The Val30Met mutation causes familial amyloid polyneuropathy. The Thr60Ala is found in Northern Ireland, and may be seen in younger CA patients (Table 1).[9]

2.3 Clinical features

Clinically, CA is characterized by features of restrictive cardiomyopathy such as dyspnea (92%) and syncope. Characteristic physical signs include jugular venous distension (52%), rales (54%), prominent edema (81%), and hepatomegaly.[10] Systolic blood pressure < 100 mmHg, and impaired 6 min-walk test are both indicative of a high degree of cardiac impairment, and each have prognostic significance.[11,12]

3 Diagnosis and prognostication

The diagnosis of CA requires demonstration of amyloid infiltration in an affected tissue, though not necessarily cardiac tissue. Upon demonstration of amyloid deposits, the causative protein must be identified for appropriate therapy. The following points are general principles for amyloidosis diagnosis.

(1) Endocardial biopsy is the gold standard for diagnosis

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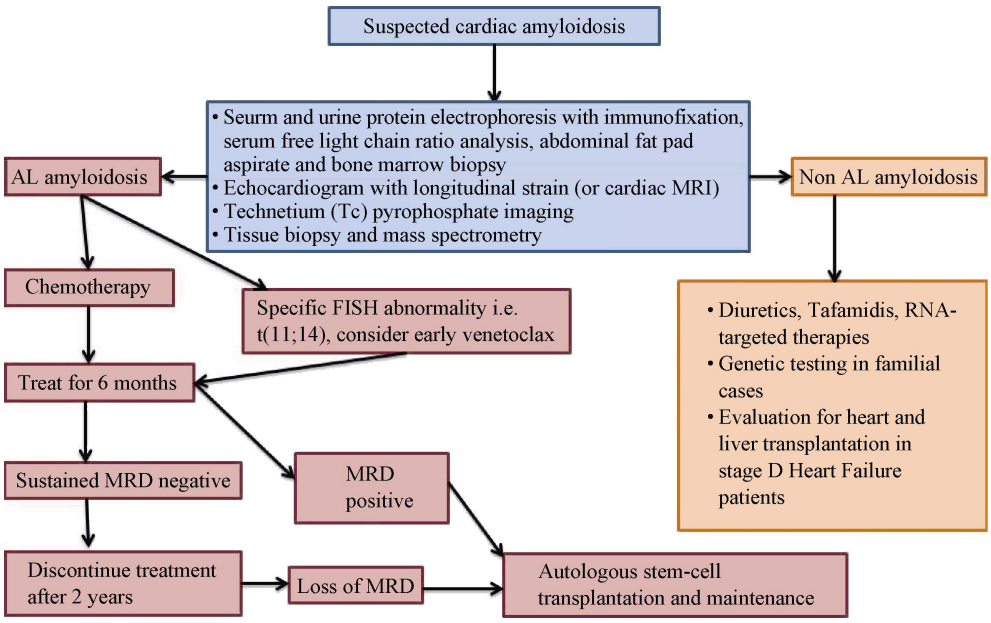

Figure 1. Treatment algorithm AL amyloidosis. AL: light chain amyloidosis; MRD: minimum residual disease.

Table 1. Characteristics of patients with amyloidosis.

	AL[4]	ATTR wild type (senile systemic amyloidosis)[9]	ATTR mutant[9]	
			Thr60Ala	Val122Ile
Incidence	8.9 per million person years[2]		Present in 1% of north western Irish population.[62]	1.3 million US African American patients carry Ile 122 allele, 13,000 homozygous patients[63]
Gender M: F	2: 1	20: 1	2: 1	3: 1
Age, yrs	60–70	70–80	45	70
Organs involved	Any tissue except CNS. Cardiac in 33%–50% of patients.	Cardiac, nerves	Cardiac, autonomic neuropathy, peripheral neuropathy	Primarily heart

AL: light chain amyloidosis; Ala: alanine; ATTR: transthyretin amyloidosis; CNS: central nervous system; Ile: isoleucine; Thr: threonine; US: United States; Val: valine.

of CA, but is associated with about 1% risk of severe complication (right atrial perforation and cardiac tamponade).[13] It is thus not routinely performed if amyloid deposits can be demonstrated in other tissues.

(2) Fat pad biopsy is approximately 79%–100% sensitive in cases of AL amyloidosis. Samples greater than > 700 mm^2 are reported to have sensitivity is 100%. Fat pad sampling is only 12% sensitive for diagnosis of ATTR.[14,15] Salivary gland biopsy is 58% sensitive in patients with negative fat pad sampling, and rectal biopsy is 85% sensitive overall.[16]

(3) Upon diagnosis of CA, it is essential to verify the amyloidogenic protein. Protein identification can be accomplished with high specificity via mass spectrometry of the biopsy tissue. Alternatively, immunohistochemistry can identify the amyloidogenic protein if mass spectrometry is not available.[17]

(4) Serum or urine paraprotein by serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation or free light chain assay can identify monoclonal gammopathy related AL amyloidosis (Table 2).

(5) Coexistent multiple myeloma is present in 20% of patients with AL amyloidosis at the time of diagnosis, and is associated with inferior survival at 1 year (39% *vs*. 81%). Thus, patients diagnosed with AL amyloidosis should be evaluated for multiple myeloma, using positron emission tomography (PT) or magnetic resonance imaging (MRI) to evaluate for skeletal lesions, and bone marrow biopsy to evaluate for bone marrow infiltration.[18]

(6) AL only: bone marrow examination should be performed to evaluate for clonal plasma cells, and to obtain

Table 2. Prognostic markers in AL amyloidosis.

Markers associated with poor prognosis	Prognostic significance (HRs for OS)
Serum markers	
N-terminal pro-BNP	≥ 1,800 pg/mL (HR 1.4)[64] (AL only)
Free light chain difference (Involved - Uninvolved Light Chains)	≥ 18 mg/dL (HR 1.4)[64] (AL only)
Troponin T	≥ 0.03 ng/mL (HR 2.4)[64] (AL only)
Soluble suppression of tumorigenicity 2	≥ 30 ng/mL (HR 2.7)[65] (AL only)
Osteopontin	≥ 426.8 ng/mL[66] (AL only)
Growth Differentiation Factor -15	≥ 7575 pg/mL[67] (AL only)
Cytogenetic Abnormalities	t(11:14), trisomy karyotype, -17p[19,20] (AL only)
Echocardiogram	
Left ventricular ejection fraction	< 45%[68]
Left ventricular diastolic deceleration time	< 150 ms[69]
Cardiac MRI findings	
Late gadolinium enhancement	Transmural pattern (HR 4.9)[21]
Increased myocardial T2	Reflective of myocardial edema (HR 1.32)[70]

AL: light chain amyloidosis; BNP: brain natriuretic peptide; HR: hazard ratio; MRI: magnetic resonance imaging; OS: overall survival.

fluorescence in-situ hybridization (FISH) analysis of the clonal plasma cells. The most frequent cytogenetic abnormality in AL is t(11;14), occurring in approximately 40%–60% of patients.[19] The presence of trisomies, deletion 17p or t(11;14) are each associated with adverse outcome.[19,20]

(7) Cardiac MRI (CMR): Circumferential subendocardial late gadolinium enhancement by CMR is highly sensitive (76%–97%) and specific (86%–94%) for the diagnosis of CA.[21]

(8) Echocardiogram: the most characteristic structural findings on echocardiogram are septal and posterior wall thickening at least > 12 mm, and with mean thickness of 16 mm at the time of diagnosis.[10,22] Myocardial speckling has low sensitivity (26%) and modest specificity (71%–81%).[22]

(9) Nuclear imaging: Technetium-labeled phosphates (e.g., Technetium-99m 3, 3-diphospho-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), technetium-99m pyrophosphate (^{99m}Tc-PYP)), have been found to have strong affinity for ATTR deposits in the heart, and much weaker affinity for AL amyloid deposits. This makes technetium-labeled phosphate scintigraphy useful to non-invasively distinguish AL-CA from ATTR-CA (sensitivity 84%–97%, specificity 94%–100%).[23–26]

4 Management

4.1 Heart failure therapy

CA clinically presents as heart failure and arrhythmias, which are the most frequent cause of death.[27] Cardiac function is often tenuous, requiring intensive management by a heart failure specialty service to maintain optimal function and minimize treatment delays.[27] Loop diuretics and aldosterone antagonists are mainstays in maintaining euvolemia.[28] Anecdotally, higher doses of diuretics are sometimes required if concurrent nephrotic range proteinuria and hypoalbuminemia are present.[27]

Contrary to patients with other kinds of cardiomyopathy, treatments with beta blockers have not been shown to have beneficial effect, and in fact are often unmanageably toxic. Similarly, renin angiotensin-aldosterone system inhibitors often cause marked hypotension even at low doses, possibly due to concurrent autonomic nervous system dysfunction from amyloidosis.[27] Non-dihydropyridine calcium channel blocking agents appear to have particularly high toxicity in these patients, due to selective concentration in the amyloidotic tissues, and should be avoided.[29]

The prognosis of patients with CA and cardiogenic shock is dismal.[30] Implantation of left ventricular assist devices (LVAD) in patients with CA is technically feasible, though is a class IIB recommendation by International Society of Heart and Lung Transplant (ISHLT) guidelines. CA patients receiving LVADs have worse 2-year survival than patients receiving LVADs for other indications, but some patients have been successfully bridged to heart transplants.[31]

4.2 Role of heart transplantation

4.2.1 AL amyloidosis

Orthotopic heart transplantation may be considered for patients with AL-CA who achieve a good hematologic response but none-the-less continue to have severe heart failure.[32] It is a class IIa indication per the ISHLT guidelines and cardiac transplantation showed a 1 year survival of 50%, and 5 year survival of only 20%.[32] However, more recent

series have demonstrated significant improvements, with 1 and 5 year survivals of 89.5% and 65%, respectively.[33,34]

4.2.2 Transthyretin

Heart transplantation in patients with ATTRwt-CA offers the possibility of prolonged graft function because the rate of amyloid re-accumulation is very slow, however because ATTRwt-CA generally presents in elderly patients, this approach is rare.[33]

For patients with mutations associated with CA, such as Thr60Ala or Val122Ile, heart transplantation can be combined with liver transplantation to simultaneously address the source of amyloidogenic protein (liver) and the primary end-organ involved (heart).[35]

4.3 Treatment of conduction disorders

Symptomatic electrical conduction abnormalities, such as heart block, sick sinus syndrome, chronotropic incompetence are highly prevalent in CA and can be effectively managed with permanent pacemaker implantation.[36] Though sudden cardiac death is a common in patients with CA, the role of prophylactic implantable cardioverter defibrillators (ICD) remains controversial. Trials have not demonstrated a survival benefit to ICD implantation, possibly because cardiac death in these patients is most often the result of pulseless electrical activity, which is not amenable to defibrillation.[37] However, in one series of CA patients implanted with an ICD, 28% went on to receive appropriate shock, and 75% of patients who were shocked survived the arrhythmia event. Thus, implantation can be considered in patients with moderate cardiac involvement, particularly in patients with history of syncope or non-sustained ventricular tachycardia.[38]

Atrial fibrillation is common in this population, putting patients with atrial fibrillation and CA at high risk for stroke. The decision to anticoagulate these patients must be carefully considered as they are also at high risk for bleeding, whether from gastrointestinal involvement of amyloidosis (present in 3%–7% of cases), or from acquired clotting factor deficiencies.[39,40] Achieving adequate rate control in this population can be a significant challenge, as anti-chronotropic agents such as beta blockers and calcium channel blockers are poorly tolerated, as described above. Additionally, digoxin should be avoided as amyloid fibrils can bind digoxin, resulting in an elevated risk of digoxin toxicity.[41]

4.4 Plasma cell directed therapy in AL amyloidosis

4.4.1 Goals of therapy

The goal of anti-plasma cell therapies in AL amyloidosis is to reduce the plasma cell clone, achieve minimum residual disease (MRD) negativity and thus reduce production of the amyloidogenic light chain proteins. The classes of drugs available for treatment are proteasome inhibitors, immunomodulatory agents (IMiDs), monoclonal antibodies and conventional chemotherapy. Based on performance status, AL amyloid patients are divided into two categories: those who are eligible for autologous stem cell transplant (ASCT) and those who are ineligible for ASCT.

4.4.2 Initial therapy

The depth and rapidity of response to therapy is highly correlated to survival in these patients, as patients responding within 30 days survive longer than those with later or no response.[42] The routinely used initial therapy is a combination of cyclophosphamide, bortezomib and dexamethasone (CyBorD), which achieves a response in 94% of patients, with complete hematologic response in 71%.[43] CyBorD is also the first line therapy for transplant ineligible patients, if they are robust enough to tolerate it. Evidence is accumulating to suggest that earlier incorporation of the IMiD class of medications (thalidomide, lenalidomide, pomalidomide) may result in improved survival, and these agents may be included in first line treatments in the future.[44] However, drugs like lenalidomide and thalidomide are typically less well-tolerated in patients with AL amyloidosis, so an induction regimen without one of these agents is often preferred. Induction therapy can also slow amyloid production and limit further organ damage while awaiting ASCT. Following ASCT, further therapies are considered based on the degree of response achieved.

4.4.3 Novel agents

Daratumumab is a monoclonal antibody directed against CD38. Its use in 129 patients with relapsed/refractory AL resulted in deep hematologic responses without significant toxicity. It is among the most promising new therapies for AL amyloidosis.[45] Venetoclax is a BCL-2 inhibitor which has recently garnered attention for its activity in multiple myeloma, particularly in the case of multiple myeloma with t(11;14). Venetoclax is thus an attractive option in AL amyloidosis, which frequently has t(11;14). To date, one case has been reported of refractory AL amyloidosis, in which a complete response was achieved with single agent venetoclax.[46].

4.4.4 Autologous stem cell transplant

The role of early transplantation has debated due to the development of highly active non-transplant regimens. Additionally, ASCT carries risk of mortality up to 5%. In the

presence of cardiac involvement, the transplant related mortality could increase up to 10%. Patients with severe cardiac involvement have a high risk of transplant related mortality, and may not be appropriate candidates. Elevations of troponin T (TnT > 0.06 μg/mL) or elevated N- terminal pro-BNP (NTproBNP > 5000 pg/mL) are associated with marked excess risk of mortality and is a relative contraindication to transplant.[47,48]

4.4.5 Prognosis

Among patients with AL-CA who achieved normalization of the free light chain ratio, 64% of patients subsequently had an organ response, defined as NT-proBNP reduction of > 30% and > 300 pg/mL with a baseline NT-proBNP of ≥ 650 pg/mL. The majority of patients who went on to have an organ response (75%) did so within one year of starting treatment, however some patients do not achieve the maximum cardiac response until 2–3 years after induction therapy.[49,50] Patients who achieve a complete cardiac response (nadir NT-proBNP < 450 pg/mL) had a 5-year survival of 96%, compared to 74% in patients who achieved a very good partial cardiac response (> 60% reduction in NT-proBNP) and just 43% in patients who achieved a partial cardiac response (30%–59% reduction in NT-proBNP).[50]

4.5 Transthyretin directed therapies in transthyretin amyloidosis

Transthyretin is produced in the liver and hence, orthotopic liver transplantation has been established treatment for mutant ATTR for over 20 years, with overall survival greater than 50% at 20 years.[51,52] However, liver transplant is not widely utilized for this indication, due to the scarcity of organs and the cost and morbidity attendant to the procedure.

Recently, tafamadis, a TTR binding agent, has emerged as an option for reducing or stopping ATTR amyloid aggregation. Tafadamis was assessed in 264 patients with ATTR-CA, and demonstrated a 30% reduction in all-cause mortality compared to placebo.[53] There was additionally a slower decline in 6-min walk test and slower decline in a measure of quality of life, indicating the progressive nature of ATTR-CA was significantly slowed by tafadamis.[53] Patisiran, a ribonucleic acid interference (RNAi), binds transthyretin messenger ribonucleic acid and prevents translation into transthyretin protein, thus dramatically reducing the serum level of transthyretin. Treatment with patisiran resulted in a 55% reduction in mean NT-proBNP, and improved measures of LV wall thickness and longitudinal strain.[54] Inotersen, a modified antisense oligonucleotide, which inhibits synthesis of transthyretin, has also demonstrated efficacy in improving neuropathy symptoms, however have failed to show efficacy in CA.[55]

4.6 Anti-amyloid deposit treatments

Effective treatments to address the amyloid deposits and end organ damage would represent an enormous improvement in the treatment of these patients. A phase 1a/b study of a fibril reactive monoclonal antibody (11–1F4), which opsonizes the fibrils and facilitating their removal, has demonstrated cardiac response in 8 of 12 treated patients.[56] Serum amyloid protein (SAP), which is universally present on amyloid deposits, is another attractive target. An antibody to SAP, dezamizumab, appeared safe and improved amyloid deposits in hepatic tissues, however there was no improvement in renal and cardiac amyloid deposits.[57] Doxycycline has inhibitory effects on matrix metalloproteases, and in a trial of 30 AL-CA patients, those receiving doxycycline had better outcomes as compared to matched control group.[58,59] Epigallocatechin-3-gallate, which is abundant in green tea, is also currently being studied in CA clinical trials.[60,61]

5 Conclusion

CA has historically been a disorder associated with marked morbidity and mortality, due to the severe heart failure it is associated with. Diagnosis, prognosis and management of these patients requires a multidisciplinary approach. The opportunity to reverse end-organ damage in both AL-CA and ATTR-CA may offer encouraging improvements in both quality and quantity of life for patients with these diseases.

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