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AMYLOIDOSIS IN CLINICAL PRACTICE: HOW TO DIAGNOSE

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Abstract: Amyloidosis is a rare disease in which insoluble amyloid proteins are deposited in the organs. Deposits cause tissue damage and organ dysfunction, especially in the heart, kidneys, and nerves. Cardiac amyloidosis (CA), particularly transthyretin (ATTR) and immunoglobulin light chains (AL) amyloidosis, has arisen as a frequently unrecognized cause of heart disease and death. Underdiagnosis was mainly due to a lack of recognition of the true prevalence and the non-specific signs of the disease. High clinical suspicion is required to promote early diagnosis. This article overviews various diagnostic tests for amyloidosis, emphasizing cardiac amyloidosis in innovative diagnostic methods. Furthermore, an algorithm of summary assessing the diagnosis of amyloidosis is presented.

Keywords: Amyloidosis, Light-chains, Transthyretin, Diagnose, Assessment, Algorithms

Introduction

Amyloidosis refers to a spectrum of complex rare, and deadly diseases caused by extracellular deposition of insoluble-misfolded proteins called amyloidogenic proteins. Thirty-six proteins can cause these extracellular amyloid depositions, resulting in damage to the cells and organs that cause disease when accumulation is sufficient to impair the affected organs' structure and integrity. Amyloidosis seems to be underdiagnosed. The clinical symptoms of the various types

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of amyloidosis largely overlap and rely on the affected organ. The heart is often affected by the most common types. Cardiac amyloidosis is a strong predictor of survival; the sooner it is found, the greater the patient's survival.[1–3] Unfortunately, delayed diagnosis is common in amyloidosis. Action should be taken to raise understanding, particularly better clinical outcomes. Signs and symptoms that may increase suspicion of a possible diagnosis of amyloidosis are generally non-specific; thus, diagnosis is elusive, and early diagnosis needs a high level of clinical suspicion. Amyloidosis suspicion should be initiated by determining the extra-cardiac or cardiac symptoms, followed by different diagnostic assessments. This article summarizes current knowledge on the optimal diagnostic assessment of patients with suspected amyloidosis with a particular focus on diagnostic assessments for cardiac amyloidosis in the most common types (transthyretin (ATTR) and immunoglobulin light chains (AL) amyloidosis).

Organ Involvement of Amyloidosis

Amyloidosis is often referred to as the "Great Imitator" because of its non-specific clinical presentation.[4] A consensus of the International Society of Amyloidosis (ISA) established the criteria for organ involvement. The criteria are mean wall thickness greater than 12 mm in echocardiography without other cardiac cause for cardiac involvement. 24-hr urine protein > 0.5 g/day, predominantly albumin for kidney involvement. Clinical symmetric lower extremity sensorimotor peripheral neuropathy for peripheral nerve involvement, whereas gastric-emptying disorder, pseudo-obstruction, and voiding dysfunction are criteria for autonomic nerve involvement. Total liver span > 15 cm in the absence of heart failure or alkaline phosphatase > 1.5 times the institutional upper limit of normal liver involvement. For soft tissue involvement, the criteria are tongue enlargement, clinical arthropathy claudication, presumed vascular amyloid skin myopathy by biopsy or pseudohypertrophy lymph node (may be localized), and carpal tunnel syndrome. Direct biopsy verification is still required for gastrointestinal tract involvement with symptoms.[5] When determining organs' involvement, the affected organs are the heart, kidney, liver, nerve, intestine, and soft tissue. Soft tissue involvement includes the skin, muscle, and temporal artery. Direct organ biopsy is not needed for diagnosis if the biopsy is verified at an alternative site with evidence of organ dysfunction.[6, 7]

Detecting Amyloid and its Classification

The detection of amyloid should begin with reasonable clinical suspicion of amyloidosis. Amyloid is a tissue-based diagnosis. If amyloidosis is suspected, the first step is to collect histologic evidence of amyloid, followed by a search for evidence of systemic amyloid deposition in tissue biopsy. A tissue specimen shows the presence of amyloid is positive for Congo Red stain.[8] Congo red results in a pale "salmon-pink" staining that reveals typical apple-green birefringence when viewed under polarized light microscopy.[9]

The protein forming the amyloid fibrils must then be identified to establish the type of amyloidosis. Immunohistochemistry (IHC) remains the most common method to characterize amyloid deposits, though it may be inconclusive or misleading, particularly outside of centers of

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expertise.[10] IHC entails using antibodies against usual or aberrant protein epitopes within amyloid as a form of amyloid typing. In a recent study of 142 biopsies examined at the National Amyloidosis Center in the United Kingdom, 108 (76%) were diagnosed with IHC, and 100% were in line with the findings of laser capture microdissection and mass spectrometry (LCM-MS) conducted on the same samples.[11] Despite these findings, the efficacy of IHC outside specialized centers is generally low due to multiple inconclusive or misleading results.[12] Without a validated antibody panel, the incidence of false positives and negatives is high. The other issue also complicates AL amyloid identification, as antibodies targeting kappa or lambda light chains may bind normal immunoglobulins to the specimen. Serum proteins may be embedded in amyloid deposits (a condition known as contamination), resulting in false-positive results.[13]

Lately, a mass spectrometric proteomic analysis of the amyloid deposits has been shown to classify the amyloid subtype with a high level of success and is known to be the gold standard. Given the disadvantages of antibody-based methods for classifying amyloid fibril proteins, direct chemical characterization of amyloid deposits is desirable.[14] LCM-MS has emerged as a promising method for detecting amyloid fibril proteins. LCM-MS has been reported to classify the amyloid subtype with 100% sensitivity and specificity. However, these complex, costly, and time-consuming methods are only available in highly advanced centers.[6]

Clinical Manifestation of Cardiac Amyloidosis

The majority of cases of CA can be traced to two precursor proteins: the monoclonal immunoglobulin light chain (AL) protein type formed by irregular clonal proliferation of plasma cells and the type of transthyretin (ATTR) protein originating from the liver and usually involved in the transport of thyroxine and retinol-binding protein.[15]

General symptoms such as nausea, weight loss, cachexia, and muscle weakness are reported in both age ranges and forms of amyloidosis. The most prominent initial CA appearance is heart failure (HF) with preserved or mid-range left ventricular (LV) systolic function and LV hypertrophy.[16] Infiltration of amyloid fibrils results in stiffening and thickening of the ventricles, resulting in reduced compliance and elevated pressure modifying the mechanics of ventricular activity manifested as diastolic dysfunction (DD). Besides, amyloid fibrils' cytotoxic symptoms result in apoptotic and fibrotic alterations, ultimately leading to systolic activity. This results in HF signs such as dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, abdominal distension, and lower extremity edema.[17] Syncope, falls, and symptomatic hypotension due to autonomic instability are commonly identified, and the combination of hypotension and LV hypertrophy should be a warning sign.[16]

The cardiac conduction system's involvement triggers first-degree, second-degree, or total heart blocks or arrhythmias, which can be symptomatic secondary to direct amyloid deposits in the conduction system.[18] In addition, amyloid can be found inside and/or near small arterioles of the heart, which may lead to clinical signs of angina pectoris or, in some cases, myocardial infarction.[19]

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Each type of CA is related to a distinct natural history of significance for differential diagnosis. When considering the overall population, AL-CA primarily affects the elderly, though occasional cases may also affect younger patients: the mean age of diagnosis is approximately 60 years. Medical conditions depend on the organs involved and the degree of organ activity.[19] In AL-CA, a sharp, functional regression is found in AL-CA from the initial presentation. As a result, suspicion of AL-CA should alert physicians to prompt and detailed diagnostic work, as further disease development significantly worsens the prognosis without implementing effective anti-plasma cell therapies.[16]

ATTR-CA is characterized by a more insidious and steadily progressing condition with extreme symptoms that occur years after the initial manifestations. Wild-type transthyretin amyloidosis (ATTRwt) is characterized by a late development of the condition (usually after the seventh decade of life) and often occurs in men. The heart is primarily affected by up to 90 % of patients.[20] In the absence of hypertension, the appearance of unexplained left ventricular hypertrophy can still increase the suspicion of ATTRwt-CA in older men.[21] The carpal tunnel is the leading site of extra-cardiac manifestation. Carpal tunnel syndrome (CTS) occurs in up to 70% of patients with ATTRwt-CA 5–10 years before cardiac manifestations.[22]

Clinical presentation of variant or familial transthyretin amyloidosis (ATTRv) amyloidosis depends on mutation and other factors such as diagnosis age, inheritance pattern, gender, geographical conditions, and ethnicity.[23] The cardiac symptoms in patients with ATTRv-CA are somewhat similar to those in patients with ATTRwt-CA, but the neurological effects can be more significant such as sensorimotor polyneuropathy.[19]

It has not been possible to distinguish AL, ATTRv, and ATTRwt precisely by transthoracic echocardiography (TTE). A significant cohort study involving 233 patients with a clear-cut diagnosis of the amyloid precursor type (AL, n=157; ATTRv, n=61; ATTRwt, n=15) compared the clinical profiles of the three main types of systemic cardiac amyloidosis. The key results were that mean age at diagnosis was higher in AL, mean LV wall thickness was higher in ATTRwt-CA, LVEF was mildly depressed in ATTRwt-CA, ATTRv-CA showed lower QRS voltage less frequently (25 vs. 60 % in AL, $P < 0.0001$), and AL patients had higher hemodynamic dysfunction.[24] These variations in the disease's progression may be due to distinct underlying pathophysiological pathways of cardiac damage in AL-CA vs. ATTR-CA.[16] (**Table I**) highlights the characteristic clinical manifestations and approaches to diagnostic assessments of AL-CA and ATTR-CA, respectively.

Table 1. Clinical Manifestation and Diagnostic Assessment of Cardiac Amyloidosis

	AL-CA	**ATTR-CA**
General symptoms	Nausea, weight loss, cachexia, muscle weakness	
Initial symptoms	HF* with preserved or mid-range LV systolic function and LV hypertrophy *HF signs: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, abdominal distension, lower extremity edema	

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Other symptoms	Autonomic instability: Syncope, falls, symptomatic hypotension	
	Angina pectoris	
	Higher hemodynamic dysfunction	Neurological extra-cardiac effects more significant: CTS and sensorimotor polyneuropathy
Age of diagnosis, sex	Sixth decade, equal	Seventh decade, male > female
Progressivity	sharp, functional regression found from the initial presentation	steadily progressing condition with extreme symptoms that occur years after the initial presentation
ECG	Pseudoinfraction pattern	
	Arrhythmia: atrial fibrillation	
	Low QRS voltage	LV hypertrophy
Echocardiography	Increased LV wall thickness ≥12 mm	
	Relative sparing of the apical area: “the cherry on the top” or “the cupcake” appearance	
	Restrictive loading with sequential biatrial dilation and sometimes secondary insufficiency of atrioventricular valves	
CMR	Diffuse, subendocardial, or transmural LGE	
	Increased myocardial mass, substantial thickening of the myocardium, enlargement of the atria, and thickening of the interatrial septum	
	Increased Native T1	
Bone-tracer scintigraphy	Cardiac uptake grade < 2	Cardiac uptake grade 2 or 3 of visual Perugini scale uptake scan along with negative serum and urine examination for elevated free light chains and monoclonal gammopathy
EMB	Congo Red stain: positive	
	Under polarized light microscopy: Typical apple-green birefringence	
	fat pad biopsy ≥ 70%	fat pad biopsy < 70%

AL: light chain; ATTR: transthyretin; CA: cardiac amyloidosis; HF: heart failure; LV: left ventricle; CTS: carpal tunnel syndrome; ECG: electrocardiogram; LGE: late gadolinium enhancement; CMR: cardiac MRI; EMB: endomyocardial biopsy

Diagnostic assessments for cardiac amyloidosis

Electrocardiogram

While Electrocardiogram (ECG) may be normal even at advanced stages of CA, it could provide indications for amyloid infiltration and further reinforce the diagnosis in accordance with imaging findings. The appearance of low voltage on 12-lead electrocardiography (all limb leads are less than 5 mm in height) hints at the cardiac activity of amyloid. This is more

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prevalent in AL-CA (45%) but less common in ATTR-CA (23–31%).[25] The total amplitudes of S waves in V1 and R waves in V5 or V6 greater than 3.5 mV are believed to be an indicator of left ventricular hypertrophy (LVH), and less than 1.5 mV is shown to be consistent with poor results in all three forms of amyloidosis with cardiac involvement.[26]

Pseudoinfarction pattern seen by Q waves or slow R-wave progression in precordial leads, atrioventricular block, or bundle branch block is another finding. Atrial fibrillation is the most frequent arrhythmia with a high rate of relapse.[27] However, ECG can not be used alone as a screening method for patients with confirmed CA or at risk for CA.

Laboratory testing

As there is no single parameter for diagnosing ATTR-CA, the goal of laboratory research in patients with suspected CA is primarily to look for AL-amyloidosis-causing plasma cell disease markers. This involves elevated serum-free light chain immunoglobulins, pathological kappa or lambda free light chain ratio, and monoclonal gammopathy in serum and urinary immunosuppression with confirmed sensitivity >95% to identify AL amyloidosis.[28] The serum-free light chain is a quantitative test tracking light chains with greater sensitivity than immunosuppressive electrophoresis.[29] It calculates the ratio of kappa to lambda, ranging from 0.26 to 1.65 with a ratio of more than 1.65, indicating the quantity of kappa light chain and less than 0.26 the number of clonal lambda chains.[30]

Besides, biomarkers play a significant role in patients' follow-up with identified monoclonal gammopathy of undetermined significance (MGUS). In the case of MGUS with an irregular free light chain ratio with the elevation of the involved light chain, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and urinary albumin should be tracked during follow-up to detect the progression of MGUS to systemic amyloidosis. In Mayo clinical study, patients were classified as Mayo stage I, II, and III based on the levels of the following biomarkers; NT-proBNP (≥332 pg/ml), Cardiac troponin T (≥0,035 ng/ml), or troponin I (≥0,1 ng/ml). Stage I patients had none, stage II patients either had one of these, and stage III patients had all of these results. This study demonstrated a median survival of 26, 11, and 4 months at stages I, II, and III, respectively, demonstrating their status as risk stratification in AL-CA. Elevated NT-BNP is a responsive proxy for cardiac infiltration and, in particular, higher than 152 pmol/L is associated with a poor prognosis in AL.[31]

Echocardiography

TTE is essential for the initial assessment of patients with diagnosed CA. While early-stage subtle anomalies are non-specific, some findings strongly predict CA in the proper clinical sense. LV hypertrophy without dilation is almost abundant, whereas outflow obstruction is very rare. Increased LV wall thickness ≥12 mm has been confirmed to be an early symptom of cardiac amyloidosis, and thus, caution should be taken when testing patients with suspected amyloidosis to not skip a diagnosis before developing severe LV hypertrophy.[32] CA is characterized by LV diastolic dysfunction, which eventually progresses towards restrictive loading with sequential biatrial dilation and sometimes secondary insufficiency of atrioventricular valves. LV systolic function is almost always pathological despite maintaining a normal to moderately diminished

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ejection fraction before the late disease. The global longitudinal strain (GLS) of the LV is deeply reduced by the relative sparing of the apical area, giving a characteristic appearance in the bull's eye plot called "the cherry on the top" or "the cupcake" appearance.[16]

Cardiovascular magnetic resonance imaging

Cardiac MRI (CMR) with a combination of native and contrast-enhanced imaging offers a precise anatomical and functional assessment of myocardium and tissue characterization, which is of accelerated value in assessing cardiomyopathies. CA has the characteristic presence of a diffuse, subendocardial, or transmural late gadolinium enhancement (LGE) of a non-ischemic pattern of prognosis.[33]

Recording global function, wall motion, myocardial mass, wall thickness, atrial scale, and the inter-atrial septum is part of a regular CMR test. Increased myocardial mass, substantial thickening of the myocardium, enlargement of the atria, and thickening of the interatrial septum can be accurately observed in nearly all patients.[34]

T1 mapping is a more recent method that offers a quantitative analysis of myocardial relaxation time. Native T1 increases amyloid penetration and correlates with systolic and diastolic dysfunction markers.[35] It is an early disease predictor of good diagnostic precision for CA in the event of a high pre-test probability. Because contrast administration is unnecessary, it is of concern to patients with significantly impaired renal function in whom gadolinium-based contract agents are contraindicated.[36] Currently, CMR is useful for confirming a suspected diagnosis, but access to CMR is limited due to limited local availability and a lack of radiologist expertise.[37]

Bone-tracer scintigraphy

Cardiac uptake of ^{99m}Tc -phosphate derivatives was seen for the first time in the 1980s as an incidental discovery in patients with ATTR-CA undergoing scintigraphy for metastatic bone disease. A small study in 2005 showed a diagnostic benefit of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) for ATTR-CA.[38] A grade 2 or 3 visual Perugini scale uptake scan along with negative serum and urine examination for elevated free light chains and monoclonal gammopathy showed 99%, 100 %, and 100% for sensitivity, positive predictive value, and specificity, respectively, for ATTR-CA. The following is the grading system proposed as a basis for assessing radionuclide uptake:

Table 2. Visual Perugini Scale Assessing Radionuclide Uptake[38]

Grade 0	No cardiac uptake, regular osseous structures
Grade 1	Minor cardiac uptake, with osseous structures appearing comparatively pale
Grade 2	Moderate cardiac uptake, with osseous structures partly indistinct,
Grade 3	Strong cardiac update, markedly increased extra-cardiac retention in the soft tissue, with very indistinct osseous structures

The key benefits of scintigraphy are its comparatively low cost, its proven reimbursement in Germany, its wider availability compared to CMR, and the independent image performance of the patient-specific variables.[39] Despite this paradigm change, bone tracer scintigraphy does not

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include quantitative analyses of tracer absorption, and the diagnosis of scintigraphy at the early stage of ATTR-CA disease has not been adequately studied.[40] This result needs to be confirmed in further research since it is of considerable significance to the subset of patients with ATTRv-CA

Endomyocardial tissue biopsy

The recommendations of the American College of Cardiology/American Heart Association note that endomyocardial biopsy (EMB) should not be done in the regular assessment of patients with heart disease but that it could be helpful in those with heart failure where a new condition that may affect the treatment is suspected.[41] While the endomyocardial biopsy is relatively safe, common complications include ventricular wall perforation, cardiac tamponade, pneumothorax, arrhythmias, puncture location, and bleeding. The left ventricular endomyocardial biopsy is consistent with a decreased pericardial effusion rate (6.6% vs. 17.1% for right ventricular endomyocardial biopsy).[42] EMB can be excluded in the event of undeniably positive ATTR-CA scintigraphy (grade 2 or 3 cardiac uptake) without laboratory evidence of plasma cell proliferation or clinical suspicion of AL-CA. These results are diagnostics for ATTR-CA.[43]

The type of amyloidosis determines the diagnostic accuracy of an extra-cardiac biopsy and the tissue examined. An extra-cardiac biopsy result (abdominal fat pad, gingiva, skin, salivary gland, or gastrointestinal tract) is higher in AL and lower in ATTRwt. In AL-CA, fat pad biopsy results are greater than 70% and are highly related to total body amyloid load. Fat aspiration was only 14% positive in ATTRwt CA patients in a study of 131 individuals with ATTR-CA with a positive EMB. While a fat pad biopsy is the preferred initial approach, a negative result is inadequate to rule out the diagnosis, and an endomyocardial biopsy should be conducted.[44]

The accumulation of data on diverse diagnostic modalities has contributed to the widespread introduction of validated diagnostic algorithms for presumed amyloidosis. An overview of the common approach to cardiac and extra-cardiac amyloidosis is discussed in (**Fig. 1**.). Overall, amyloidosis is a multi-faceted systemic disorder with a complex pathophysiology.

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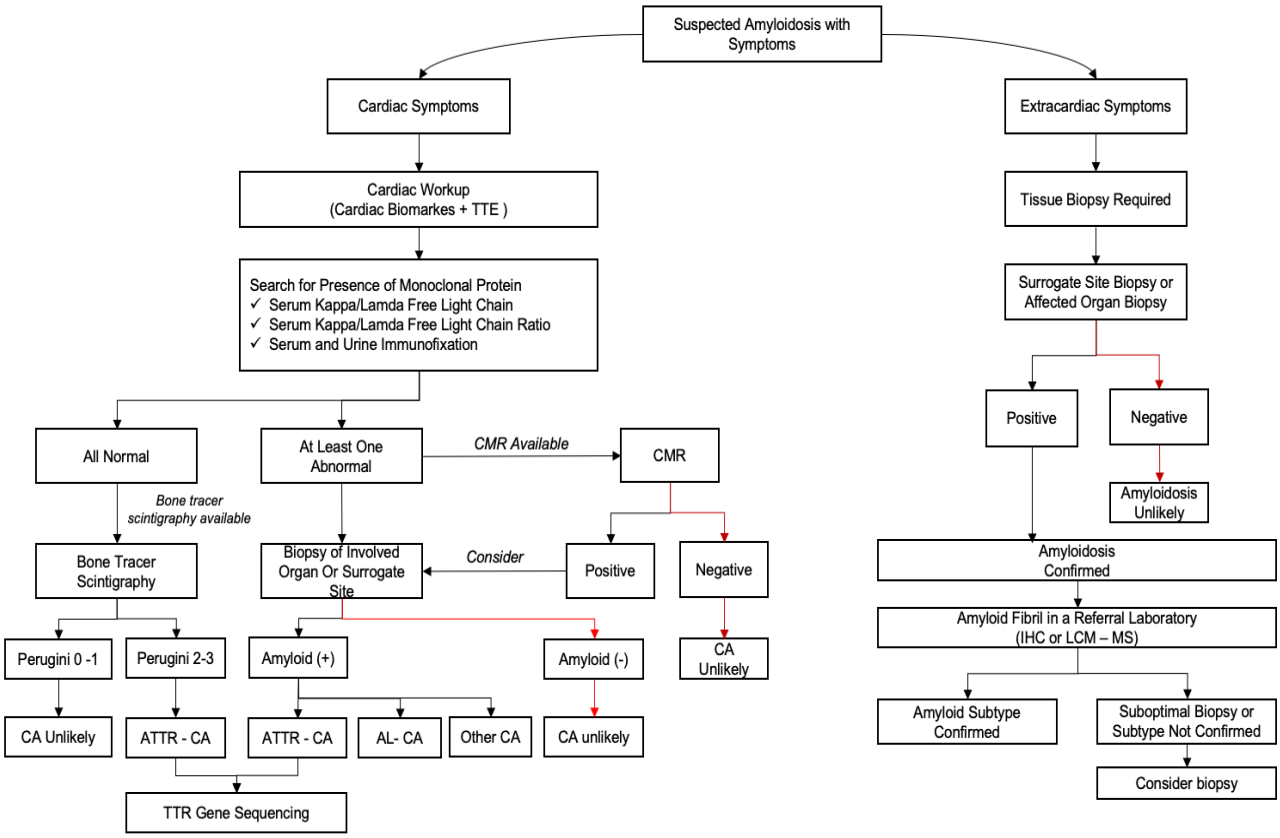

Figure 1. Summary of Common Approach Cardiac and Extracardiac Amyloidosis
*AL: light chain; ATTR: transthyretin; CA: cardiac amyloidosis; CMR: cardiac MRI; IHC: immunohistochemistry; LCM-MS: laser capture microdissection and mass spectrometry; TTE: transthoracic echocardiography.

Current Management Strategy For Cardiac Amyloidosis

The management of CA is divided into two main sections. The first is the treatment and prevention of further complications, and the second is the specific treatment that stops or delays amyloid deposition.

Specific treatment for AL-CA should be carried out by multidisciplinary teams consisting of oncohaematology and cardiology specialists, and patients should be referred to specialized centers whenever possible.[45] AL-CA patients not only have a hematologic malignancy, but their multiorgan involvement allows them highly vulnerable and prone to treatment toxicity. Therapeutic methods are based on risk assessment, characterized by the degree of cardiac involvement, and the hematological response also drives cardiac response.[46] The cardiologist's role in the specific treatment includes cardiac assessment for initial hematologic treatments, including autologous stem cell transplantation consideration, heart transplant evaluation, and cardiac monitoring during chemotherapy.[47]

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Over the last decade, therapies for AL amyloidosis have evolved significantly. Autologous stem cell transplantation (ASCT) has been shown to have included results; however, only a subset of patients with cardiac involvement are eligible. According to the Mayo group, 25% of patients are eligible for ASCT69, but only 3.4 % (23 of 668 patients) of patients with explicit heart failure with AL amyloidosis treated at their center over 20 years had a heart transplant.[48]

A novel, successful, and selective ATTRwt and ATTRv therapeutic alternatives are becoming more widely available. An early diagnosis is critical for treating neurological, cardiac, and other systemic symptoms, as therapy is more successful in the early stages of the disease. [49] Effective therapies either suppress the development of mutated (liver transplantation) and overall TTR (genetic silencers) or preserve circulating TTR molecules (stabilizers), avoiding dissociation or cleavage into amyloidogenic fragments. Several new compounds are being studied, including agents targeting amyloid fibrils removal.[47]

Recent treatment options differentiate between ATTRv and ATTRwt and, in the case of ATTRv, depend on the presence of cardiomyopathy, polyneuropathy, or both. A concise overview of ATTR treatments that are either available or in phase III trials. Tafamidis should be considered a choice in ATTR-CA patients with reasonably estimated survival, whereas Patisiran could be considered in ATTRv patients with cardiac involvement who are administered gene silencers due to symptomatic neurological disease.[47]

Tafamidis is a benzoxazole derivative that binds to TTR in the blood at the T4 binding site and lacks nonsteroidal anti-inflammatory action.[50] In a 30-month study, 441 individuals with ATTR-CA and NYHA class I-III HF were randomly instructed to receive tafamidis 80 mg, 20 mg, or placebo daily. In patients with NYHA class I or II HF, tafamidis was associated with a decreased all-cause mortality compared to placebo (29.5 % versus 42.9%) and a 32% reduced risk of cardiovascular hospitalizations. On the other hand, subjects with NYHA class III symptoms had greater rates of cardiovascular-related hospitalization with tafamidis medication than with placebo; this finding emphasizes the need for early identification and treatment.[51, 52]

Patisiran (Onpattro, Alnylam), a siRNA approved in the United States for ATTRv with associated polyneuropathy, targets the 3′ untranslated regions of the TTR mRNA.[53] Patisiran is formulated as a lipid nanoparticle to target hepatocyte uptake. In a phase II study of patients with ATTRv-associated polyneuropathy, serum TTR levels were lowered by more than 80% following the second dosage of patisiran, administered at 0.3 mg/kg every three weeks.[54]

Heart transplantation may be considered in certain patients with end-stage cardiomyopathy caused by ATTR-CA or AL-CA who have responded to light-chain depleting treatment. Extra-cardiac involvement, such as neuropathic, gastrointestinal, or hepatic disease manifestations, which might impair posttransplant outcomes, should be carefully considered when selecting heart transplant candidates.[55]

Conclusion

Amyloidosis is a rare but critical condition that needs to be suspected, mainly where clinical presentations are not typical. Early diagnosis provides access to all treatment options before developing advanced organ dysfunction. Accurate sub-typing is essential to the treatment of

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amyloidosis. Multimodality imaging is expected to play a pivotal role in all facets of CA. Repurposed bone scintigraphy and laboratory tory testing can exclude or validate diagnosis in most suspected ATTR-CA cases, although tissue biopsy for histopathological analysis is still the preferred test for AL amyloidosis and other clinical scenarios.

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None

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

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