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A MULTIDISCIPLINARY APPROACH IN CARDIAC AMYLOIDOSIS

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Abstract

Cardiac amyloidosis is an infiltrative condition characterized by the extracellular deposition of insoluble amyloid proteins in myocardial tissue. This accumulation leads to structural and functional remodeling of the heart, resulting in progressive ventricular dysfunction and heart failure with a predominantly restrictive phenotype.

Etiologically, cardiac amyloidosis can be primarily classified into forms associated with immunoglobulin light chains (AL) and transthyretin (TTR), either in hereditary or wild-type variants. AL-type amyloidosis represents a secondary manifestation of a systemic plasma cell disorder, with cardiac involvement being associated with a poor prognosis. In contrast, TTR-type amyloidosis has a relatively slower and more favorable clinical course. The use of Tc-99m-labeled bone tracers in scintigraphy enables the confirmation of TTR-type amyloidosis due to specific cardiac uptake. In AL-type amyloidosis, the absence of uptake makes diagnosis confirmation through this method impossible. Conversely, compounds such as Pittsburgh Compound B (C-11 PiB), F-18 florbetaben, and F-18 florbetapir, used in PET-CT, have demonstrated specific uptake in cardiac AL-type amyloidosis.

These methods not only allow for the early identification of amyloid deposits but also reduce the need for cardiac biopsy, which was previously considered necessary in many cases.

This review aims to present current data on the integration of nuclear medicine technologies into modern cardiology practice, redefining the paradigm for diagnosing and monitoring cardiac amyloidosis. Nuclear cardiology offers a precise, non-invasive, and personalized approach with significant clinical implications, providing valuable support for practicing cardiologists.

Keywords: *cardiac amyloidosis, nuclear cardiology, transthyretin*

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Rezumat

Amiloidoza cardiacă este o afecțiune infiltrativă caracterizată prin depunerea extracelulară de proteine amiloide insolubile la nivelul țesutului miocardic. Această acumulare determină remodelarea structurală și funcțională a inimii, conducând la disfuncție ventriculară progresivă și insuficiență cardiacă cu fenotip predominant de tip restrictiv.

Din punct de vedere etiologic, amiloidoza cardiacă poate fi clasificată în principal în forme asociate lanțurilor ușoare de imunoglobuline (AL) și forme asociate transtiretinei (TTR), fie în varianta ereditară, fie cea de tip sălbatic.

Amiloidoza de tip AL reprezintă o manifestare secundară a unei afecțiuni sistemice a celulelor plasmatice, implicarea cardiacă fiind asociată cu un prognostic nefavorabil. În contrast, amiloidoza de tip TTR are un curs clinic relativ mai lent și mai favorabil. Utilizarea trasorilor osoși radiomarcați cu Tc-99m în scintigrafie permite confirmarea amiloidozei de tip TTR datorită captării specifice la nivel cardiac. În cazul amiloidozei de tip AL, lipsa captării face imposibilă confirmarea diagnosticului prin această metodă. În schimb, compușii Pittsburgh Compound B (C-11 PiB), F-18 florbetaben și F-18 florbetapir, utilizați în PET-CT, au demonstrat captare specifică în amiloidoza cardiacă de tip AL. Aceste metode permit nu doar identificarea precoce a depozitelor amiloide, ci și evitarea biopsiei cardiace, în multe cazuri considerate anterior necesare.

Astfel, acest review își propune să prezinte date actuale referitoare la integrarea tehnologiilor de medicină nucleară în practica cardiologică modernă, redefinind paradigma diagnosticului și a monitorizării amiloidozei cardiace. Medicina nucleară cardiologică are o abordare precisă, neinvazivă și personalizată, cu implicații clinice semnificative și de mare ajutor pentru cardiologii practicieni.

Cuvinte cheie: *amiloidoza cardiacă, cardiologie nucleară, transtiretină*

Introduction

Cardiac amyloidosis is an infiltrative condition characterized by the extracellular deposition of insoluble amyloid proteins in myocardial tissue. This accumulation leads to structural and functional remodeling of the heart, resulting in progressive ventricular dysfunction and heart failure with a predominantly restrictive phenotype. Amyloidosis is characterized by the misfolding and extracellular deposition of more than 30 distinct precursor proteins, with the most clinically relevant being immunoglobulin light chains (AL), transthyretin (ATTR), serum amyloid A (SAA), apolipoprotein AI/II, and fibrinogen. The pathological accumulation of amyloid fibrils within various organ systems progressively impairs their architecture and function, ultimately leading to organ failure if left untreated.[1,4,18]

From an etiological perspective, cardiac amyloidosis can be primarily classified into forms associated with immunoglobulin light chains (AL) and transthyretin (TTR), either in hereditary or wild-type variants. Early diagnosis and precise characterization of the amyloid type are essential for the timely initiation of specific treatment and for improving patient prognosis.[2,14]

AL-type amyloidosis represents a secondary manifestation of a systemic plasma cell disorder, with cardiac involvement being associated with a poor prognosis. In contrast, TTR-type amyloidosis has a relatively slower and more favorable clinical course. The use of Tc-99m pyrophosphate allows for the confirmation of TTR-type amyloidosis due to specific cardiac uptake. In AL-type amyloidosis, the absence of uptake makes diagnosis confirmation through this method impossible.[4,15] Additionally, Tc-99m methylene diphosphonate (MDP) and F-18 NaF tracers have been reported to show positive uptake in TTR-type amyloidosis but negative for the AL form. Conversely, compounds such as C-11 PiB, F-18 florbetaben, and F-18 florbetapir have demonstrated specific uptake in cardiac AL-type amyloidosis, highlighting the utility of these tracers in characterizing this clinical form.[9,22]

Myocardial scintigraphy with bone tracers such as 99mTc-DPD, 99mTc-PYP, and 99mTc-HMDP represents a standardized and validated technique for the differential diagnosis of transthyretin amyloidosis, with particularly high sensitivity and specificity. This method not only allows for the early identification of amyloid deposits but also avoids cardiac biopsy, which was previously considered necessary in many cases.[23]

Furthermore, positron emission tomography (PET) with amyloid-specific tracers such as 18F-florbetapir and 18F-flutemetamol provides additional benefits in characterizing AL-type amyloidosis, offering functional information on the metabolic activity and distribution of amyloid deposits. These advanced imaging tools facilitate not only etiologic diagnosis but also disease staging and therapeutic efficacy monitoring.[20]

Mechanism of disease

Transthyretin (prealbumin) is a plasma protein involved in the transport of thyroxine and retinol, primarily synthesized in the liver and, to a lesser extent, in the brain.

Pathophysiological mechanism of transthyretin in cardiac amyloidosis: in ATTR amyloidosis, transthyretin undergoes a folding error during monomer synthesis, leading to the formation of amyloid fibrils, which predominantly deposit in the central nervous system (CNS) and the heart. Amyloid-

related tissue changes can be displayed as mechanical disarrangement, disruption of cell membrane integrity, inflammatory reactions, hypoxic cell damage and/or alteration of the structure of the extracellular matrix.

Due to its involvement in multiple organs, it presents with a wide range of symptoms, including carpal tunnel syndrome, gastrointestinal disturbances, urinary incontinence, erectile dysfunction, and glaucoma. At the cardiac level, it progressively leads to heart failure with dyspnea and fatigue. The main clinical features of ATTR amyloidosis are cardiomyopathy and neuropathy. **Wild-type ATTR (**ATTRwt) amyloidosis usually presents as heart failure in elderly male patients, but bilateral carpal tunnel syndrome, lumbar spinal stenosis and biceps tendon rupture can precede the onset of cardiac symptoms by a decade or more.[3,21,24]

One of the challenges when evaluating patients for cardiac amyloidosis is the wide range of differential diagnoses that needs to be considered with similar clinical and imaging manifestations of increased left ventricular wall thickness.

Possibilities include hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction and other reasons for heart failure with preserved ejection fraction. Other infiltrative diseases that can mimic cardiac amyloidosis include Anderson Fabry disease, Danon disease, sarcoidosis, hemochromatosis and Loeffler's endocarditis. Differential diagnoses should be evaluated thoroughly, as part of the assessment for cardiac amyloidosis.[11]

ATTR is primarily classified into two main categories: **hereditary ATTR (ATTRh)** and **wild-type ATTR (ATTRwt). Hereditary ATTR (ATTRh),** this form is associated with over 120 amyloidogenic TTR mutations that can cause tetrameric structural instability. It typically manifests in men under 60 years of age and presents clinically as a progressive, painful, and debilitating sensorimotor neuropathy. Myocardial involvement is relatively rare, but when present, it leads to congestive heart failure. **Wild-type ATTR (ATTRwt),** this form occurs predominantly in men over 60 years old. Clinical manifestations are more prevalent, with approximately 50% of patients presenting with carpal tunnel syndrome. Cardiac involvement is significantly more pronounced, manifesting as restrictive cardiomyopathy, restrictive heart failure, conduction disturbances, atrial fibrillation, and degenerative aortic stenosis.[6,7]

Multidisciplinary approach to the management of cardiac amyloidosis

The gold standard for diagnosing amyloidosis remains endomyocardial biopsy, followed by

histopathological analysis using specific staining techniques such as Congo red and immunohistochemistry. Despite its diagnostic accuracy, this approach has notable limitations: it is an invasive procedure, requires specialized expertise, and is not readily accessible on a large scale. Moreover, it lacks the ability to reliably differentiate between amyloid subtypes without adjunct techniques.[3]

In clinical practice, when biopsy is not feasible, a multimodal diagnostic approach is recommended. This includes biomarker assessment (NT-proBNP and Troponin T for cardiac involvement), electrocardiography (ECG) and transthoracic echocardiography (TTE) for structural and functional cardiac evaluation, cardiac magnetic resonance imaging (MRI) to assess tissue characteristics and late gadolinium enhancement (LGE) patterns, radionuclide scintigraphy with bisphosphonate tracers (e.g., 99mTc-PYP, 99mTc-DPD) to detect transthyretin amyloid deposits, positron emission tomography/computed tomography (PET/CT) with amyloid-specific tracers in certain cases, genetic testing to identify amyloidogenic TTR mutations in hereditary ATTR.

Therefore, in ATTR amyloidosis, biomarkers are stratified based on the assessment of cardiac, renal, and thyroid involvement: cardiac markers (NT-proBNP, Troponin T), renal markers: urea, creatinine, creatinine clearance, proteinuria, thyroid markers: TSH, free T4 (FT4), and free T3 (FT3). This integrative approach enhances diagnostic accuracy, facilitates disease staging, and informs therapeutic decisions while minimizing the need for invasive procedures.[5,17]

A classic feature encountered in cardiac amyloidosis is a low-voltage ECG tracing, which is discordant with the ventricular hypertrophy identified through imaging studies. Additionally, a pseudo-infarction pattern may appear in up to half of the patients with AL-type amyloidosis. Furthermore, conduction disturbances, such as atrioventricular blocks, can be observed in approximately 22% of cases. Intraventricular blocks are frequently observed, being more common in patients with ATTR amyloidosis. However, electrocardiographic criteria for left ventricular hypertrophy can be found in 10-15% of patients with cardiac amyloidosis, often reflecting pre-existing ventricular myocardial conditions, such as hypertensive heart disease or significant valvulopathies.[3,8]

Echocardiography, the standard exploration for all patients with heart failure, is the imaging investigation that most frequently raises suspicion of cardiac amyloidosis. Traditionally, a particular aspect of the myocardium described as "granular and sparkling" has been considered diagnostic. However, with the development of new imaging techniques, this feature has lost its diagnostic sensitivity and specificity.

Classically, cardiac amyloidosis is characterized by concentric or asymmetric biventricular thickening of the LV walls, despite normal or even lower cavity dimensions. Since patients with AL amyloidosis tend to become symptomatic earlier, greater maximum myocardial wall thickness has been observed at the time of diagnosis compared to patients with ATTR amyloidosis. The extracellular deposition of amyloid leads to an increase in the thickness of the ventricular myocardium, contributing to its rigidity and, consequently, to diastolic dysfunction. Advanced diastolic dysfunction, characterized by pseudonormalization or a restrictive filling pattern, is found in most patients. Elevated biventricular filling pressures, together with direct infiltration of the atrial wall, lead to biatrial dilation, low

velocities, or even the absence of the A-wave. These findings are often observed in patients with advanced restrictive cardiomyopathy, even if sinus rhythm is maintained.

A value of the A-wave velocity below 30 cm/s is associated with an increased risk of intracavitary thrombus formation in patients with AL amyloidosis, even without documented supraventricular arrhythmias. Myocardial infiltration can also lead to interatrial septum and valvular thickening, with different degrees of regurgitation. Pericardial effusions in small amounts are frequently associated, but large effusions and cardiac tamponade are rather exceptions.[3,11,17]

Unlike left ventricular diastolic function, which is affected even in the early stages of the disease, global systolic function, evaluated based on the ejection fraction (EF), is usually preserved until the advanced stages of the disease. However, myocardial deformation impairment, highlighted by calculating the global longitudinal strain (GLS), can be observed even in the early stages. This impairment exhibits a particular pattern of 'apical sparing,' with severe longitudinal dysfunction at the basal segments and preservation at the apical segments. Recently, a significant dissociation between preserved global systolic function, expressed as left ventricular EF, and reduced GLS, expressed as the EF/GLS ratio, has been described as a sensitive and reproducible method for differentiating cardiac amyloidosis from other forms of ventricular hypertrophy. Furthermore, GLS can be used as a predictor of survival in patients with AL-type amyloidosis, providing additional information beyond clinical data and biomarkers.[3,17]

Myocardial deposition of amyloid fibers increases the extracellular volume and leads to the accumulation of gadolinium-based contrast agents. For this reason, the identification of late gadolinium enhancement (LGE) on cardiac MRI is extremely useful for the diagnosis of cardiac amyloidosis. Cardiac MRI is valuable as a screening method for identifying patients with cardiac amyloidosis, with a sensitivity and negative predictive value of 100%, and a specificity and positive predictive value of approximately 80% for the diagnosis of amyloidosis in patients with multiple myeloma. Furthermore, cardiac MRI provides prognostic information for this group of patients.

Gadolinium is primarily an extracellular agent, meaning it preferentially accumulates in tissues with a large extracellular volume. In cardiac amyloidosis, the extracellular volume fraction often increases due to the intramyocardial deposition of amyloid.

Cardiac amyloidosis presents a pathognomonic LGE pattern, specifically a diffuse subendocardial distribution that does not follow coronary territories; however, other patterns, patchy, diffuse, or transmural, have

also been described. Transmural LGE has been associated with a worse prognosis compared to other distribution patterns. Although a very useful technique, classical LGE imaging is highly operator-dependent and reliant on the correct acquisition of images. Furthermore, cardiac amyloidosis is recognized as one of the most challenging pathologies for LGE imaging. The technique known as "phase-sensitive inversion recovery" (PSIR) helps mitigate operator subjectivity and may prevent errors that could mask cardiac amyloidosis, being, in fact, the recommended technique for LGE imaging in cardiac amyloidosis.[8,20,21]

Phosphate-based isotopes with bone avidity also exhibit high affinity for ATTR-type amyloid deposits. A scintigraphy showing poor tracer uptake, accompanied by elevated levels of monoclonal plasma cells or light chains in blood and urine, is suggestive of AL-type amyloidosis and requires biopsy confirmation of amyloid deposits. In contrast, an examination demonstrating abnormal myocardial tracer uptake alongside normal plasma cell levels has a specificity and positive predictive value of 100% for the diagnosis of ATTR amyloidosis, without requiring biopsy confirmation of amyloid deposits.

During evaluation, monoplane acquisitions can be performed to identify radioactive tracer uptake and visually assess the Perugini score: 1 – low uptake, subcostal intensity, 2 – significant uptake, intensity equal to the ribs, 3 – important uptake, supracostal intensity. Additionally, visual assessment can be complemented by the H/C ratio (intensity measured in the heart region (H) relative to the contralateral lung (C)). A Perugini score of 2 or higher, or an H/C value equal to or greater than 1.5, strongly suggests ATTR cardiac amyloidosis.

Axial plane imaging using hybrid SPECT/CT is not routinely recommended but is reserved for cases where the accuracy of a Perugini visual score cannot be established or when there is suspicion of radioactive tracer accumulation behind the sternum. The most used tracers are technetium-based isotopes containing phosphate groups (99mTc-DPD, 99mTc-PYP, and 99mTc-HMDP), which have good sensitivity and specificity for the non-invasive identification of cardiac TTR amyloidosis. Despite structural similarities with these isotopes, 99mTc-MDP demonstrates lower sensitivity in identifying TTR-type amyloid deposits, and its routine use is not recommended. [12,13,16]

Tissue biopsy remains the gold standard in diagnosing amyloidosis, despite advances in non-invasive imaging techniques. Since the treatment of different forms of amyloidosis involves distinct therapeutic agents and may be associated with significant toxicity, it is essential that diagnosis includes Congo red staining or other amyloid-specific dyes and identification of the precursor protein, combined with polarized light evaluation.

Endomyocardial biopsy should be performed in patients with plasma cell proliferation and inconclusive imaging results or in those suspected of having AL amyloidosis to differentiate it from ATTR amyloidosis or other monoclonal gammopathies. Identification of precursor proteins depends on tissue analysis expertise, using techniques such as immunohistochemistry, electron microscopy, or mass spectrometry. Monoclonal gammopathies are relatively common in patients with suspected ATTR amyloidosis, occurring in up to 10% of cases, requiring a rigorous diagnostic algorithm to avoid misdiagnosis.[3,15,20]

In general, untreated cardiac TTR amyloidosis follows a slow progressive course, with a

better prognosis than the AL type. This statement is particularly valid in the context of ATTR-wt, where the median survival without treatment ranges between 3 and 3.5 years. The prognosis for patients with AL amyloidosis has seen remarkable improvement over time, with a four-year survival rate of 90% in patients successfully treated with stem cell transplantation. The median survival of patients with treated cardiac amyloidosis can exceed 10 years.[6]

The spectrum of clinical manifestations in ATTR-wt is highly heterogeneous and may differ from the classic phenotype. Women can present with the disease in a significant proportion, with asymmetric left ventricle hypertrophy and systolic dysfunction not being uncommon, while only a minority exhibit low-voltage QRS complexes. Clinicians should therefore be aware of the wide clinical spectrum of ATTR-wt to correctly identify the condition in populations with heart failure with preserved ejection fraction, a condition for which several etiologic treatments are currently being studied.[6,14]

Treatment should be guided by experienced centres, using a multidisciplinary approach (cardiology, haematooncology, neurology, nephrology, gastroenterology). Treatment with tafamidis 61 mg should be considered for patients with cardiac ATTRwt amyloidosis and dyspnea, NYHA class I—III. The optimal timing to start treatment for ATTRwt amyloidosis remains unclear, though it is known that there is a long latency period before organ damage manifests. Patients treated at earlier stages of the disease are reported to have a greater survival benefit.

The pharmacological treatment of heart failure in cardiac amyloidosis aims to reduce the congestive symptoms caused by infiltrative cardiomyopathy. Unlike other therapeutic interventions for heart failure, there are no large randomized clinical trials to guide treatment choices, with recommendations typically based on small studies or personal experience. Diuretics are the primary treatment option and are often used in combination, such as a loop diuretic and an aldosterone antagonist.

Orthostatic hypotension is frequently encountered in AL amyloidosis, caused by autonomic nervous system involvement or the toxicity of chemotherapeutic agents, which can severely limit diuretic therapy. For vasopressor support and diuresis, peripheral vasoconstrictors such as midodrine can be used to counteract orthostatic hypotension.[19,21,24]

Conclusions

Overall, amyloidosis has gained a lot of attention in the last couple of years. This is mainly based on much better diagnostic tools and treatment options. However, the diagnosis and treatment remain challenging,

and misdiagnosis may pose a danger to the patient, and potential treatment may be unintentionally withheld. Further, amyloidosis remains a multiorgan disease and a multidisciplinary approach.

Management of cardiac amyloidosis requires a multidisciplinary approach, involving cardiologists, hematologists, nephrologists and other specialists. Close monitoring and coordination of care are essential to ensure high-quality treatment.[10]

Significant advances have occurred in multimodality cardiac imaging for assessing cardiac amyloidosis. Echocardiography, MRI and nuclear imaging all play important and complementary roles in this clinical scenario. Echocardiography is first-line for chamber quantification, assessing diastolic function and myocardial deformation.

MRI uniquely offers tissue characterization and quantification of infiltration on top of chamber quantification. Nuclear imaging is the only currently available non-invasive modality able to distinguish ATTR from AL cardiac amyloidosis. Each modality also plays a role in risk stratification for adverse outcomes. Contemporary imaging plays a central role in helping improve the diagnosis and management outcomes of cardiac amyloidosis. It remains to be seen whether we can use these non-invasive imaging tools to follow disease progression/regression after initiation of novels therapies especially with ATTR cardiac amyloidosis.

Cardiological follow-up should be carefully integrated into clinical management, with evaluations recommended every 3–6 months, including clinical and laboratory evaluation (NT-pro BNP, troponin T, creatinine, proteinuria, albuminuria), and a comprehensive evaluation including ECG, 24-hour ECG, TTE every 6–12 months, ergometry, depending on disease severity and treatment.

Regular blood pressure and body weight home monitoring may be considered in order to adapt diuretic dose targeting euvolaemia.[11,24]

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