Chapter 2

Imaging of Systemic Amyloidosis

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Abstract In systemic amyloidosis, several imaging techniques can be used to detect the presence, extent, and localization of amyloid deposits, to monitor their progression and regression, and to assess organ involvement and dysfunction. The presence of heart involvement is the main prognostic determinant and most efforts have been directed to the evaluation of cardiac amyloidosis. Heart involvement is classically diagnosed based on increased ventricular wall thickness and myocardial echogenicity (often referred to as “granular sparkling”) at echocardiography. However, more refined echocardiographic techniques, such as myocardial integrated backscatter, tissue Doppler, and strain imaging can provide evidence of early heart involvement and add functional and prognostic information. Magnetic resonance imaging (MRI) and cardiac scintigraphy with radiolabeled phosphate derivatives showed good sensitivity and specificity in the detection of heart involvement. In particular, scintigraphy with radiolabeled aprotinin can detect early amyloid deposits in the heart. Scintigraphy has the advantage of specific tissue characterization. The prototype of a specific amyloid tracer is iodinated serum amyloid P component (I-SAP). Scintigraphy with I-SAP is a useful complement for the diagnosis and provides an estimation of amyloid load, and serial studies can reveal disease progression and regression. However, I-SAP scintigraphy cannot image the heart. Anatomo-functional imaging, via ultrasound, computed tomography, and MRI scanning, is useful in the diagnosis and follow-up of localized amyloidosis. Accurate imaging of amyloid deposits can now be combined with the biochemical assessment of organ, particularly cardiac, damage and with reliable measurement of the circulating precursors. This will improve the care of patients with amyloidosis and shed light on the pathogenesis of organ damage.

Keywords Amyloidosis, Imaging, Diagnosis, Scintigraphy, I-SAP, Aprotinin, Ultrasound scan, Echocardiography, Magnetic resonance imaging, Computed tomography

Introduction

The ability to image a pathologic process provides with an objective means to assess the presence and extent of a disease, as well as to monitor response to treatment or determine whether relapse has occurred. Several imaging modalities have been developed for systemic amyloidosis with the purpose to detect organ involvement, to determine its extent, to monitor progression and regression of amyloid deposits, and to characterize known lesions, differentiating them from other pathologies. More recently, refined imaging techniques have been used to provide functional information
on the organs involved by amyloidosis. In systemic amyloidoses, one of the most important prognostic determinants is the presence of heart involvement that can be detected and studied by echocardiographic techniques and magnetic resonance imaging. Scintigraphy with amyloid-specific tracers is a useful complement in diagnosing amyloidosis and an accurate means to assess amyloid load at diagnosis and during the course of the disease. Anatomic imaging, such as computed tomography and magnetic resonance imaging, is useful in the diagnosis and follow-up of localized extracardiac amyloidosis.

In this chapter, we review the specific tools that have been developed to image amyloid deposits and the applications of common imaging techniques to amyloidosis.

**Nuclear Imaging**

Scintigraphy is a biochemical imaging modality and has the potential advantage of specific tissue characterization over anatomical imaging, such as computed tomography, ultrasound scan, and magnetic resonance imaging. The clinical impact of nuclear imaging in amyloidosis is mainly contingent upon the specificity of radiotracers for amyloid deposits. In the last two decades, the scintigraphic scan of amyloid deposits in vivo has been attempted with several tracers, some specifically designed for imaging amyloidosis and others originally developed for different purposes, like bone tracers, that proved useful also in studying amyloid deposits, particularly in the heart. Several tracers have been proposed to identify myocardial amyloid involvement that were recently reviewed [1]. Amyloid deposits can be identified by the use of $^{99m}$Tc (technetium)-aprotinin, $^{99m}$Tc-(pyro)phosphate, $^{67}$Ga (gallium), and $^{111}$In (indium)-antimyosin antibody, whereas cardiac innervation can be evaluated by $^{123}$I-MIBG (metaiodobenzylguanidine) scintigraphy. Myocardial perfusion can be evaluated with $^{99m}$Tc-sestamibi and $^{201}$Tl (thallium), and ventricular function has been characterized by the use of conventional radionuclide ventriculography.

In recent years, the combination of amyloid-specific tracers with tomographic techniques, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), was used to provide accurate high-resolution localization of amyloid deposits.

**Serum Amyloid P Component Scintigraphy**

The prototype of a specific amyloid tracer is radiolabeled serum amyloid P component (SAP). All amyloid deposits contain SAP, a glycoprotein that reversibly binds amyloid fibrils independently from the protein of origin [2]. The circulating SAP is in constant dynamic equilibrium with the SAP bound to amyloid deposits, the latter representing as much as 200 times in quantity the blood pool in patients with systemic amyloidosis [3]. Serum amyloid P component can be conjugated with the short half-life $^{123}$I that is used for scintigraphic imaging [4] or with the longer half-life $^{125}$I for metabolic studies [3]. In patients with amyloidosis, $^{123}$I-SAP localizes rapidly to the amyloid deposits, in proportion to their quantity, and persists there, whereas in healthy subjects and in patients with diseases other than amyloidosis, it is almost exclusively confined to the blood and is rapidly catabolized in the liver, and the associated radioactivity is released back in the circulation and excreted in the urine within 14 days [3]. In patients with amyloidosis, I-SAP is initially cleared from the blood more rapidly reflecting extravascular localization to the deposits [3]. This specific dilution phenomenon, due to the constant equilibrium between SAP bound
to amyloid deposits and the blood pool, renders it possible to use I-SAP to evaluate amyloid deposits quantitatively and repeatedly in vivo. In particular, the combination of whole-body $\gamma$ counting with measurement of radioactivity in 24-h urine collection allows to derive the size of the extravascular compartment [5].

Scintigraphy with $^{123}$I-SAP was developed by Pepys and Hawkins and its use in patients was first reported in 1988 [6]. Since then, several thousands of scans have been performed by the London group. Scintigraphy with $^{123}$I-SAP can demonstrate amyloid deposits in the kidneys, liver, bones, spleen, and adrenal glands. The organ distribution of amyloid deposits detected by $^{123}$I-SAP scan can sometimes suggest a particular type of amyloidosis. For example, bone uptake is pathognomonic of immunoglobulin light-chain (AL) amyloidosis [4]. However, SAP scintigraphy cannot detect amyloid deposits in the heart, due to blood pool content, movement, intense uptake of I-SAP into the adjacent spleen, and lack of a fenestrated endothelium in the myocardium, hindering the access of the large 127 kDa tracer within the timescale determined by the short half-life of $^{123}$I [7]. Myocardial uptake has been demonstrated using the longer half-life $^{131}$I that, however, is unsuitable for routine clinical studies [8].

It has been reported that SAP scintigraphy can demonstrate articular $\beta_2$-microglobulin amyloid deposits [9, 10], but interpretation is difficult, because synovial effusion found in pathological joints represents an extension of the blood pool I-SAP background. Localized amyloid deposits are not imaged by I-SAP scans [11], and the chief value of SAP scintigraphy in localized amyloidosis is to rule out systemic disease [12].

Although the diagnosis of amyloidosis needs to be based on a tissue biopsy [13], given the very high specificity of $^{123}$I-SAP for amyloid deposits, SAP scintigraphy has been proposed as a diagnostic tool. In a study on 189 consecutive patients with systemic amyloidosis, the diagnostic sensitivity of $^{123}$I-SAP in AL amyloidosis and amyloidosis reactive to chronic inflammation (AA) was 90% [11]. Conversely, in patients with hereditary transthyretin (ATTR) amyloidosis, sensitivity was much lower (48%), particularly in subjects carrying non-Met30 TTR mutations (sensitivity 13%) [11]. Indeed, in patients with ATTR amyloidosis, typically involving the heart and peripheral nervous system, that cannot be imaged by SAP scintigraphy, amyloid deposits can be identified only if they are also present in other organs, such as the spleen and kidneys. On the other hand, SAP scintigraphy demonstrates that the distribution of amyloid within individual organs can be inhomogeneous, accounting for false negative biopsy results [14]. Moreover, SAP scintigraphy provides information on the distribution and amount of amyloid that cannot be derived from tissue biopsies. The diagnostic sensitivity of SAP scintigraphy can be improved by combination with the determination of the extravascular compartment, which is greatly increased in patients with systemic amyloidosis. Increased extravascular retention of $^{123}$I-SAP alone had a 65, 61, and 22% diagnostic sensitivity in AA, AL, and ATTR amyloidosis, respectively [5].

Serum amyloid P component scans can identify extensive amyloid deposits in organs in which they have not been suspected clinically [11, 14]. For example, in the study by Hazenberg et al., 86% of patients with AA amyloidosis and 76% of patients with AL had amyloid deposits in the spleen that were clinically relevant only in 8 and 18% of subjects, respectively [11]. Adrenal uptake was seen in 20% of patients with AA amyloidosis, but adrenal failure was present just in 3% [11]. Although certain organs can continue to function in a normal way despite the presence of substantial amyloid deposits, they may nevertheless fail under stress, and the possibility of recognizing asymptomatic amyloid deposits may improve the assessment of
eligibility to toxic therapies, thus preventing otherwise unexpected treatment-related toxicity. Conversely, in some cases, clinically relevant organ involvement may not be accompanied by significant tracer uptake. In the same study, 90% of AA and 83% of AL patients had clinical signs of renal involvement, but kidney I-SAP uptake was detected only in 67 and 31% of cases, respectively [11]. Moreover, SAP scintigraphy revealed a poor correlation between the quantity of amyloid present in a particular organ and the severity of organ dysfunction [14]. These observations support the hypothesis that, in AL and AA amyloidoses, the amount of amyloid deposited is not the only determinant of organ dysfunction.

Scintigraphy with $^{123}$I-SAP also provides prognostic information. Measurements of whole-body amyloid load by SAP scintigraphy correlate with the risk of death and progression to end-stage renal disease in AA amyloidosis [15]. Additional prognostic information may come from the determination of I-SAP tissue retention [7]. Hazenberg et al. demonstrated that in AL amyloidosis extravascular retention of $^{123}$I-SAP has a prognostic impact that is independent from the presence of cardiac involvement [5]. Moreover, serial SAP scans demonstrate regression of amyloid deposits in a significant proportion of patients in whom it has been possible to reduce or eliminate the supply of the amyloidogenic precursor. This includes reduction of serum amyloid A protein (SAA) by control of the underlying inflammatory disease in AA amyloidosis [15]; effective chemotherapy with reduction of the involved circulating free light chains (FLC) in AL amyloidosis [16]; liver transplantation in ATTR amyloidosis [17], in hereditary fibrinogen amyloidosis (AFib) [18], and in familial apolipoprotein AI amyloidosis (AApoAI) [19]; and renal transplantation in β2-microglobulin dialysis-associated amyloidosis (β2m) [20].

Despite the useful diagnostic and prognostic information it can provide, the clinical use of SAP scintigraphy is hampered by several important limitations, such as the inability to image cardiac amyloid deposits and the unavailability of I-SAP in most centers. Availability of I-SAP is limited because it is not a commercial product, SAP is isolated from human sera, and $^{123}$I-SAP is produced at a high cost. Attempts of labeling SAP with the cheaper $^{99m}$Tc have been made, but conjugation of SAP with $^{99m}$Tc is technically difficult. Moreover, $^{99m}$Tc-SAP is a less specific ligand of amyloid fibrils than I-SAP, part of the $^{99m}$Tc separates from SAP in the circulation, and $^{99m}$Tc-labeled degradation products are cleared incompletely, increasing the background signal in the kidneys and liver [14].

$^{99m}$Tc-Aprotinin Scintigraphy for Cardiac Imaging

The observation of the presence of antiproteases in amyloid deposits led our group to hypothesize that a radiolabeled antiprotease could be a specific tracer for amyloid deposits. We chose $^{99m}$Tc-conjugated aprotinin, a low molecular weight protease inhibitor that was used as a cortical renal tracer. It has been reported that aprotinin binds specifically to amyloid fibrils, probably through pairing of the β structures of the antiprotease with exposed structures of the same type on the amyloid deposits [21]. Aprotinin is known to accumulate in the kidneys masking the whole abdominal area, thus, we evaluated the capability of $^{99m}$Tc-aprotinin to detect extra-abdominal, particularly cardiac, amyloid deposits (Fig. 2-1) [22]. In 1995, in a first series of 25 patients with systemic amyloidosis, we observed cardiac uptake in 10 of 14 (71%) subjects fulfilling echocardiographic criteria of heart involvement and in 1 patient who subsequently developed overt cardiac amyloidosis. Cardiac biopsies were available in four cases (three positive and one negative) and were all concordant with $^{99m}$Tc-aprotinin uptake [22]. In the same study, localization to the neck
region (thyroid, salivary glands, and tongue) was also detected in eight patients with AL amyloidosis [22]. In 2001, in a subsequent study on 78 patients with systemic AL amyloidosis followed for a median of 31 months, the sensitivity and specificity of $^{99m}$Tc-aprotinin scintigraphy to detect cardiac involvement were 95 and 97%, respectively, and the scans were able to detect cardiac involvement before it became apparent at echocardiography [23, 24]. Further clinical studies at our center were hampered by a ban on bovine derivates that precluded further use of aprotinin in patients. In 2002 Schaad and coworkers found $^{99m}$Tc-aprotinin uptake in several localizations (heart, tongue, submandibular glands, intestines, lymph nodes, liver, spleen, pleura, lungs, joints) in 22 of 23 patients with known or suspected amyloidosis [25]. Biopsy or autopsy evaluations were available for 20 of the 90 detected localizations and confirmed the presence of amyloid deposits [25]. Asymptomatic uptake accounted for approximately 50% of detected lesions and, notably, in five patients, preceded clinical symptoms [25]. In a more recent retrospective study, involving 18 patients with biopsy-proven amyloidosis and 17 controls, Han et al. showed myocardial uptake of $^{99m}$Tc-aprotinin in all the five patients who had amyloid cardiac involvement as assessed by clinical, echocardiographic, and magnetic resonance criteria [26]. Four of these five patients eventually died due to cardiac amyloidosis [26]. In none of the other 30 patients, who had no signs of cardiac involvement, thoracic uptake of $^{99m}$Tc-aprotinin was detected [26]. The available data indicate that $^{99m}$Tc-aprotinin is a very promising radiotracer for cardiac amyloidosis, with high sensitivity and specificity and able to detect early cardiac involvement before it becomes detectable by echocardiography.
Scintigraphy with $^{99m}$Tc-Labeled Phosphate Derivatives

Radiolabeled phosphate derivates were developed as bone tracers and they are believed to localize to amyloid deposits because of their relevant calcium content. In 1977 Kula et al. visualized calcifications in amyloid deposits with $^{99m}$Tc-diphosphonate [27]. Since then, several phosphate derivatives have been tested in cardiac amyloidosis, including $^{99m}$Tc-pyrophosphate ($^{99m}$Tc-PYP) [27–32], $^{99m}$Tc-(hydroxy)methylene diphosphonate ($^{99m}$Tc-MDP or $^{99m}$Tc-HMDP) [33], and $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD) [34, 35]. The latter was also shown to help in differentiating AL- and ATTR-type cardiac amyloidosis, suggesting a role of $^{99m}$Tc-DPD scintigraphy in the evaluation of cardiac amyloidosis etiology [34].

Overall, although $^{99m}$Tc-labeled phosphate myocardial scanning seems to be a sensitive test for the diagnosis of cardiac amyloidosis in patients with congestive heart failure, it does not appear to be of value for the early detection of cardiac involvement in patients with known amyloidosis. Differently from aprotinin scintigraphy, positive phosphate scanning seems to correlate with high amounts of amyloid fibrils in the heart, but this occurs at an advanced stage of the disease, when clinical symptoms of cardiomyopathy are already apparent. Thus, the clinical relevance of $^{99m}$Tc-labeled phosphate myocardial scintigraphy remains uncertain, and according to Eriksson et al., a high threshold amount of amyloid is probably required to produce an abnormal scintigram, although lesions with less amyloid can evidently be identified by echocardiography [36], a finding that was confirmed by Lee et al. [37]. In the same line, Hartmann et al. showed that $^{99m}$Tc-PYP scintigraphy is not useful in screening patients for cardiac involvement in amyloidosis, but that first-pass studies yield valuable information about diastolic function impairment [38].

Beyond being used to image cardiac amyloidosis, radiolabeled phosphate derivatives have also been reported to localize in extracardiac amyloid deposits, such as amyloid deposits in the bronchi [39], soft tissues [40], testicles [41], liver [42], and lungs [43]. In patients with amyloidosis localized to the airways, SPECT and PET techniques with radiolabeled phosphate derivates can provide accurate anatomical localization [44, 45].

Assessment of Cardiac Innervation with $^{123}$I-Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG), a structural analogue of the “false” neurotransmitter guanethidine, shares noradrenaline uptake and storage mechanisms in the sympathetic nerve endings, allowing to visualize cardiac innervation when labeled with $^{123}$I. The use of $^{123}$I-MIBG in patients with amyloidosis was reported for the first time by Nakata et al. in 1995 [46], who found decreased myocardial activity of $^{123}$I-MIBG in all cardiac regions in a patient with severe peripheral neuropathy due to a TTR-related familial amyloidotic polyneuropathy. Subsequently, a high incidence of myocardial denervation by $^{123}$I-MIBG imaging, even in the presence of normal LV wall thickness and systolic function, was shown in ATTR patients [47, 48]. Similar findings were reported in patients with AL amyloidosis, who show signs ranging from presynaptic sympathetic dysfunction to overt myocardial denervation according to the degree of congestive heart failure and cardiac autonomic dysfunction [49].

$^{99m}$Tc Pentavalent Dimercaptosuccinic Acid Scintigraphy

$^{99m}$Tc pentavalent dimercaptosuccinic acid ($^{99m}$Tc-(V)-DMSA) is a tumor tracer used in medullary thyroid cancer and soft tissues tumors, which is taken up by cancer cells...
probably due to the structural similarity with the phosphate ion. Initially, the possibility of imaging plasmacitomas associated with localized AL amyloid deposits with this tracer has been reported and could be explained by uptake by plasma cells [50]. However, in a patient with systemic AL amyloidosis, $^{99m}$Tc-(V)-DMSA uptake was observed in the heart, kidney, liver, spleen, and thyroid and correlated with autopsy findings [51]. Moreover, cases of myocardial uptake of $^{99m}$Tc-(V)-DMSA in patients with systemic amyloidosis and heart involvement have been described [52]. However, the possibility to image myocardium with $^{99m}$Tc-(V)-DMSA is hampered by a strong signal from the blood pool.

**Radiolabeled $\beta_2$-Microglobulin**

Since conventional techniques, such as joint ultrasonography, X-ray, CT, or MRI, lack specificity in evaluating lesions caused by dialysis-related amyloidosis (A$\beta_2$m), imaging of $\beta_2$-microglobulin deposits has been attempted using $\beta_2$-microglobulin labeled with $^{131}$I as a radiotracer [53–55]. Tracer accumulations correspond to the typical distribution pattern of A$\beta_2$m deposits [53, 54]. $^{111}$In (indium)–$\beta_2$-microglobulin reduces the radiation exposure and improves the optical resolution of this scan [53, 54, 56]. Recombinant $\beta_2$-microglobulin has been produced for use as a radiotracer [53, 54, 56]. A limitation of $\beta_2$-microglobulin scintigraphy is that it cannot be performed in case of residual renal function, because the tracer is rapidly cleared in the urine.

$\beta_2$-Microglobulin amyloid deposits can be also imaged by $^{201}$Tl (thallium) and $^{67}$Ga (gallium) scintigraphy [57].

**Radioimaging with Fibril-Reactive Monoclonal Antibodies**

Researchers at the University of Tennessee observed that certain murine anti-human light chain antibodies recognize a conformational epitope common to fibrils formed from light chain as well as other amyloidogenic precursors such as SAA, TTR, and ApoAI [58]. Hence, the same group developed a radiolabeled fibril-reactive monoclonal antibody (mAb), conjugated with $^{125}$I or $^{124}$I, that was tested in mice. In an amyloidoma mouse model the radioiodinated mAb localized predominantly in the tumor and could be accurately imaged by SPECT and PET [59]. Combination of high-resolution SPECT with the radioiodinated mAb and I-SAP with computed tomography allows accurate anatomical localization of amyloid deposits in AL and AA mouse models [59].

**Other Scintigraphic Tracers**

$^{67}$Ga (gallium) has been proposed to image cardiac involvement in systemic amyloidosis, but it proved less sensitive than $^{99m}$Tc-PYP in this setting [60, 61]. $^{111}$In (indium)-labeled antimonyosin antibodies that bind specifically to areas of myocardial necrosis were used to image cardiac amyloid deposits [62, 63].

**Ultrasound Imaging**

The echocardiographic features of advanced cardiac amyloidosis are distinctive, with non-dilated ventricles showing marked thickening of the left and right ventricular walls, as well as of the interventricular and interatrial septa. Amyloid infiltration gives a characteristic aspect to the myocardial texture, which has been described as “granular sparkling” [64–68], due to the granular appearance of the myocardium.
In the attempt of quantifying the subjective evaluation of increased myocardial echoreflectivity, tissue characterization can be achieved by cycle-dependent variation of myocardial integrated backscatter, a measure that has been shown to have a prognostic potential [69].

Also valve leaflets are often thickened showing increased echogenicity. Concentric left ventricular geometry is almost invariably present [70] due to increased wall thickness with normal or reduced ventricular diameters, with normal or near-normal global left ventricular function as assessed by ejection fraction. In the many patients with reduced end-diastolic diameters and volumes, this leads to reduced stroke volume that is often associated with increased heart rate to maintain cardiac output. Wall thickening is disproportionate to the degree of current or prior arterial hypertension or valve disease, due to myocardial infiltration rather than to cardiomyocyte hypertrophy (Fig. 2-2). As a consequence, the ECG limb lead voltages tend to decrease as the ventricle wall thickens, resulting in a decreased ratio of voltage to echo-derived left ventricular mass, a finding that strongly suggests an infiltrative cardiomyopathy [68]. Indeed, a low-voltage pattern (defined as all limb lead voltage <5 mm) is found in a high proportion of patients.

In a minority of patients (that has been estimated around 5%), the echocardiographic aspect may mimic hypertrophic cardiomyopathy [71–75], with normal or even mildly hyperdynamic left ventricular function and normal voltages on the 12-lead ECG. However, at variance with “true” hypertrophic cardiomyopathy, mitral valve systolic anterior motion is very uncommon and ECG limb lead voltages are not in the ventricular hypertrophy range.

Diastolic function is abnormal in both myocardial relaxation and ventricular compliance, with Doppler transmitral velocity profile ranging from an impaired distensibility to a clear-cut restrictive pattern, and Doppler serial studies demonstrate a progression of diastolic dysfunction as myocardial infiltration progresses [66]. In advanced disease, left ventricular filling restrictive physiology can be identified by

![Fig. 2-2. Two-dimensional directed M-mode imaging of the right and left ventricular cavities in a patient with cardiac AL amyloidosis. RVEDD: right ventricular end-diastolic diameter; IVS: end-diastolic interventricular septum thickness; LVEDD: left ventricular end-diastolic diameter; PW: end-diastolic posterior wall thickness; LVESD: left ventricular end-systolic diameter.](image-url)
combined Doppler studies evaluating transmural and pulmonary venous flow velocities. Such a profound alteration in filling dynamics is caused by the association of left ventricular diastolic dysfunction and impaired atrial contraction, both due to myocardial amyloid infiltration [64, 76–83]. As a consequence, the Doppler transmural flow velocity profile shows increased peak early (E) to peak atrial (A) velocity ratio, reduced E-wave deceleration time, and low-velocity A wave.

Beyond allowing further insights into cardiac diastolic dysfunction in cardiac amyloidosis, pulsed tissue Doppler imaging can demonstrate the presence of longitudinal systolic impairment before the ejection fraction becomes abnormal [84–86]. Moreover, myocardial velocity tissue Doppler indices proved helpful in differentiating from control subjects patients with biopsy-proven cardiac amyloidosis with borderline conventional echocardiographic features and non-restrictive LV filling pattern [87]. Also the ratio of early transmitral flow velocity to early diastolic mitral annular velocity ($E/E_m$) has been suggested as a useful index of elevated LV filling pressure in cardiac amyloidosis [88]. Long-axis dysfunction might also be demonstrated by M-mode echocardiography in both the left [89] and the right ventricles [90], as well as by strain and strain rate imaging, that may also have potential for evaluating the prognosis in AL amyloidosis [75, 84, 85, 90–92]. Combined pulsed tissue Doppler and strain imaging may disclose early signs of infiltrative cardiac disease in both ventricles, even in the absence of myocardial wall thickening [93]. Moreover, the evaluation of systolic mechanical deformation by two-dimensional strain imaging via the speckle-tracking technique has been recently shown to differentiate cardiac amyloidosis from both asymmetric hypertrophic cardiomyopathy and secondary LV hypertrophy [75].

Also the myocardial velocity profile, derived from color-coded tissue Doppler imaging (TDI), can identify transmural heterogeneity, possibly differentiating cardiac amyloidosis from other causes of left ventricular hypertrophy. At comparable left ventricular wall thickness, myocardial velocity gradient during systole and early diastole is in fact depressed in cardiac amyloidosis when compared with hypertensive heart disease and hypertrophic cardiomyopathy [94]. Contrast echocardiography can also be used to recognize microvascular dysfunction in patients with cardiac amyloidosis [95], relying on the ultrasound detection of microbubble contrast agents that are confined to the intravascular space.

While echocardiography is an irreplaceable tool for the diagnosis and evaluation of cardiac amyloid disease, only a few reports describe the use of ultrasound scan for imaging amyloid deposits localized outside the heart, such as enlargement and increased echogenicity of the thyroid gland in patients with amyloid goiter [96] or hypoechoic nodular plicae in the bowel of patients with gastrointestinal amyloidosis [97]. Ultrasonography has been used to study periarticular changes in patients with dialysis-related amyloidosis. It has been shown that patients with β2-microglobulin amyloidosis have increased diameter of supraspinatus tendon, greater cross-sectional area of the long head of biceps tendon, and increased thickness of the rotator cuffs and may present echogenic pads between the muscle groups of the rotator cuffs [98, 99]. These findings indicate that shoulder ultrasound might have a role in the diagnosis and, possibly, in the follow-up of patients with dialysis-related amyloidosis.

**Computed Tomography**

Computed tomography (CT) imaging is of limited value in systemic amyloidosis mainly because of low specificity. Computed tomography was used to evaluate soft
tissue [100], intestinal [97], and lymph node involvement [101]. The clinical usefulness of CT imaging is probably higher in localized amyloidosis. Several cases of orbital amyloidosis detected by CT scans were reported [102]. Localizations to the nasopharynx [103] and larynx [104, 105] have also been identified by CT. However, these findings were not specific and the final biopsy results were often unforeseen at the time of the CT scan. Nevertheless, CT imaging can be useful in the follow-up of localized amyloidosis.

One of the most important applications of CT in amyloidosis is the imaging of amyloid localized to the lungs and airways. In patients with respiratory tract amyloidosis standard chest radiography findings are usually non-specific and consist of a reticular pattern due to interlobular septal thickening, nodules, or post-obstructive features such as atelectasias and consolidation [106]. Reticular patterns are consistent with systemic involvement. Pleural effusions are common in systemic amyloidosis, but are usually secondary to heart failure and nephrotic syndrome due to cardiac and renal involvement. However, pleural amyloid infiltration can be responsible for persistent effusion. Computed tomography recognizes three distinct patterns of localizations to the respiratory system: (1) tracheobronchial amyloidosis, (2) nodular parenchymal amyloidosis, and (3) diffuse alveolar septal amyloidosis. Tracheobronchial amyloidosis appears as focal or diffuse submucosal deposits resulting in nodules, plaques, or circumferential thickening often with luminal narrowing [106, 107]. Localization to segmental airways can result in collapse, consolidation, bronchiectasias, and hyperinflation [106]. In nodular parenchymal amyloidosis (Fig. 2-3), nodules are well defined, can be single or multiple with an extremely variable diameter, are usually subpleural in distribution, and often contain calcifications [108–110]. Due to non-specific appearance, amyloid pulmonary nodules are often interpreted as neoplasia [109]. Diffuse alveolar septal amyloidosis is a less common form of pulmonary involvement, but it is often associated with systemic amyloidosis. It manifests with widespread amyloid deposition involving small vessels and

![CT appearance of AL nodular pulmonary amyloidosis, with multiple bilateral calcified amyloid nodules of variable diameter.](image)
the interstitium, with reticular opacities, interlobular septal thickening, micronodules, and, less frequently, ground-glass opacification, traction bronchiectasias, and honey-combing at high-resolution CT [109]. Diffuse amyloidosis is sometimes accompanied by mediastinal lymphadenopathy [108].

In β2-microglobulin amyloidosis, destructive arthropathy, spondylarthropathy, and periarticular cystic bone lesions can be demonstrated by plain X-ray and CT [111].

As to cardiac amyloidosis, ECG-gated enhanced multislice computed tomography can visualize wall thickening with partial fibrotic changes [112].

**Magnetic Resonance Imaging**

In systemic amyloidoses, magnetic resonance imaging (MRI) is mainly used in evaluating cardiac morphology and function (Fig. 2-4). Cardiac MRI in patients with advanced cardiac amyloidosis shows an unusual pattern characterized by global subendocardial late gadolinium enhancement and associated abnormal myocardial and blood pool gadolinium kinetics [113–117]. These abnormalities are common but not universally present in cardiac amyloidosis, probably due to expansion of infiltrated myocardial interstitium in association with impaired segmental and global

![Cardiac magnetic resonance imaging from a patient with cardiac AL amyloidosis. Transverse sections of the right and left ventricular cavities showing increased wall thickness and global subendocardial late gadolinium enhancement.](image)
contractility [116]. Amyloid and collagenous fiber deposition was correlated with late enhancement that was shown to be associated with fibrosis due to ischemia of cardiomyocytes by small vessel amyloid deposition [118]. In patients with endomyocardial biopsy-proven cardiac amyloidosis, late gadolinium enhancement shows good sensitivity (80%) and excellent specificity (94%) [119], being strongly correlated with heart failure severity as assessed by brain natriuretic peptide [120]. Magnetic resonance relaxometry, measuring T₁ and T₂ relaxation times of the left ventricular myocardium, might improve the diagnostic reliability of this technique [121], and tissue characterization of the myocardium by T₁ quantification predicts survival [122].

A few reports describe the clinical use of magnetic resonance in imaging extracardiac localizations in systemic amyloidosis. In β₂-microglobulin amyloidosis MRI can show increased thickness of the supraspinatus tendon, capsular thickening at the hip, and osseous lesions [111, 123]. It has been suggested that MRI can detect early lesions in asymptomatic patients with dialysis-related amyloidosis [123]. In a patient with AL amyloidosis and liver involvement, who underwent MRI with an oral manganese-containing contrast agent, focal areas without contrast uptake and no bile excretion were detected [124]. These observations correlated with liver biopsy findings, such as atrophy of the hepatocytes, amyloid deposits in the portal veins, and compression of bile ducts [124]. Magnetic resonance imaging proved useful in detecting localized amyloid deposits in the nasopharynx [103], spine [125], larynx [105], urethra [126], and seminal vesicles [127]. Enhanced T₂ relaxation and hypointensity on T₂-weighted MR are considered peculiar characteristics of amyloid masses.

### Conclusion

A wide armamentarium of imaging techniques has been developed for amyloidosis. Clinical practice will select those tools that will prove helpful in the management of this disease based on efficacy and availability.

Imaging techniques can provide not only anatomical but also functional information, particularly in evaluating cardiac amyloidosis. Functional imaging of cardiac involvement can now be combined with biochemical assessment of heart dysfunction with cardiac troponins and natriuretic peptides [128, 129]. This is very relevant since cardiac involvement predicts prognosis and affects treatment strategy.

Moreover, the imaging of amyloid deposits and the biochemical assessment of organ dysfunction can now be correlated with reliable measurement of the circulating precursors, such as FLC in AL and SAA in AA amyloidosis. This has the potential of answering questions on the pathogenesis of amyloidosis. One of the most important and still open issues in the field of amyloidosis is the mechanism of organ damage. Observations with SAP scintigraphy demonstrated that amyloid load is not always proportional to organ dysfunction [11]. Subsequent clinical observations suggested that the concentration of the amyloid precursor has a direct impact on biochemical indices of cardiac dysfunction and prognosis, independently from amyloid load [130]. Studies are warranted in correlating the extent of disease activity, amyloid load, biomarkers, and indices of myocardial function that can be derived from several functional imaging techniques.

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