Taxonomy and Imaging Manifestations of Systemic Amyloidosis

Naoki Takahashi, MD[a,*], James Glockner, MD, PhD[a], Benjamin M. Howe, MD[a], Robert P. Hartman, MD[a], Akira Kawashima, MD, PhD[b]

KEYWORDS

• Amyloidosis Heart Lung Urinary tract Joint Computed tomography MR imaging

KEY POINTS

- Amyloid light-chain amyloidosis is the most common type of amyloidosis, and cardiac involvement is often a major determinant of prognosis.
- Global subendocardial to transmural cardiac wall enhancement is the most common pattern of cardiac amyloidosis on late gadolinium enhancement on MR images.
- The localized form of amyloidosis most commonly involves urinary tract or respiratory tract, and usually has a benign clinical course.
- Amyloid arthropathy is most commonly owing to Ab2M (dialysis-related) amyloid deposition.
- Amyloid deposits commonly exhibit decreased T1- and T2-weighted signal on MR images.

INTRODUCTION

Amyloidosis is a heterogeneous group of multisystem disorders that are characterized by extracellular deposition of amyloid fibrils in b-pleated sheets resulting in organ dysfunction. Although approximately 25 different amyloid proteins have been identified, 5 types of amyloidosis account for 99% of all amyloidosis. Amyloid of all types shares the same physical properties: apple-green birefringence after Congo red staining. Amyloid deposits produce diverse clinical syndromes depending on their type, location, and the amount of deposition.

AMYLOID TYPES AND MANAGEMENT

There are several forms of amyloidosis. The 2 most common types of amyloidosis are amyloid light-chain (AL) amyloidosis (previously referred to as primary amyloidosis) and amyloid A (AA) amyloidosis (previously referred to as secondary amyloidosis).[1] AL amyloidosis is owing to deposition of protein derived from immunoglobulin light chain fragments. Patients with AL amyloidosis have monoclonal B-cell dyscrasia, which generally has low-level activity. However, 10% to 50% of patients are associated with multiple myeloma or other plasma cell neoplasia, such as B-cell lymphoma and Waldenstro¨ m macroglobulinemia.[2] Similar to other plasma cell dyscrasias, AL amyloidosis is a disease of older adults with a median age at diagnosis of 65 years old. AL amyloidosis is mostly a systemic disorder that can present with a variety of symptoms or signs depending on the predominant sites of involvement. Nonspecific systemic symptoms include fatigue and weight loss. Other common clinical presentations of AL amyloidosis include proteinuria or nephrotic syndrome, heart failure, hepatosplenomegaly, and neuropathy. Without treatment, systemic AL amyloidosis is a fatal disease owing to uncontrolled organ damage. Treatment is aimed at control of plasma cell

[a] Department of Radiology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA; [b] Department of Radiology, Mayo Clinic, Scottsdale, Az, USA
* Corresponding author.
E-mail address: takahashi.naoki@mayo.edu

Radiol Clin N Am 54 (2016) 597–612
http://dx.doi.org/10.1016/j.rcl.2015.12.012
0033-8389/16/$ – see front matter

dyscrasia in the form of chemotherapy and/or hematopoietic stem cell transplantation.

In AL amyloidosis, amyloid deposition can be isolated to a single organ resulting in specific syndromes. Localized amyloidosis is attributed to a local immunocyte dyscrasia and resulting in deposition of immunoglobulin light chain. The location of the amyloid deposits can be a clue to its localized nature. Respiratory tract, skin, and urinary tract are common sites of localized amyloidosis. Pa- tients with localized amyloidosis do not have mono- clonal protein in the serum or urine or bone marrow plasmacytosis. Patients with localized amyloidosis do not require systemic therapy, and surgical excision may be the only treatment needed.

AA amyloidosis is a result of chronic inflammatory conditions such as rheumatoid arthritis, Crohn's disease, tuberculosis, bronchiectasis, and chronic osteomyelitis. It may occur in associ- ation with other causes, including neoplasms (renal cell carcinoma and Hodgkin's disease). Am- yloid is composed of fragments of the acute phase protein, serum AA. The most common organ involved is the kidney, leading to nephrotic syn- drome. If untreated, secondary amyloidosis may be fatal owing to end-stage renal disease, infec- tion, or heart failure. Treatment is aimed at control of the underlying inflammatory or infectious pro- cess. AA amyloidosis is more common in underde- veloped countries, whereas AL amyloidosis is the most common type of amyloidosis in the devel- oped countries.

Two other major forms of amyloidosis are transthyretin-related amyloidosis (ATTR) and Ab2M amyloidosis. ATTR amyloidosis is owing to deposition of wild-type transthyretin (TTR) or mutant TTR. Wild-type ATTR amyloidosis is commonly referred to as age-related or senile amyloidosis. The predominant site of involvement is heart and it almost exclusively affects older men; most patients are older than 70 years at diag- nosis, with a 10-fold greater incidence in men. Au- topsy series suggests asymptomatic amyloid deposition is common in heart and gastrointestinal tract.[3,4] Mutant ATTR amyloidosis is a hereditary disease, and commonly referred to as familial am- yloid polyneuropathy. It has predilection for involvement of the peripheral and autonomic nerves. Inheritance is autosomal dominant with variable penetrance, and at least 120 point muta- tions of the TTR gene have been described. Ab2M amyloidosis (dialysis related) occurs in pa- tients undergoing long-term hemodialysis owing to deposition of b2 microalbumin. It has a predilection for deposition in the bones and joints.

Although amyloidosis may be suggested by the history and clinical manifestations (eg, nephrotic syndrome in patients with myeloma), tissue biopsy is often necessary to confirm the diagnosis. Biopsies can be obtained from either clinically uninvolved site, such as subcutaneous fat, or from dysfunctional organs. Abdominal fat pad biopsy is preferred in patients with suspected systemic amyloidosis because it is less invasive. Biopsy of an involved organ is often necessary when a limited number of organs is affected, such as in localized amyloidosis.

GENERAL IMAGING FEATURES OF AMYLOID DEPOSITION

On computed tomography (CT), amyloid deposition is commonly associated with calcification, and it is attributed to an affinity of amyloid fibrils for calcium.[5] On CT and MR imaging, the enhancement of the affected organs is often decreased in the parenchymal phase and increased in the delayed phase. This enhancement pattern is considered owing to expansion of the extracellular space by amyloid deposition causing delayed inflow and washout of contrast material.[6,7] Amyloid deposits often shows decreased T1 signal (T1 prolongation) and decreased T2 signal (T2 shortening) on MR imaging likely related to physical properties of amyloid fibrils, but the exact cause of these signal changes are unknown.[8]

HEART

Amyloid Variants Affecting the Heart

The heart can be affected by several amyloid types, and cardiac involvement is often a major determinant of prognosis. The 2 most common forms of cardiac amyloidosis are the AL and ATTR types. AL amyloid is the most commonly diagnosed form of cardiac amyloidosis. It may involve almost any organ in the body, with cardiac disease seen in 50% to 70% of patients.[9] The prevalence of wild-type ATTR amyloidosis is uncertain; although fewer cases are diagnosed annually in comparison with AL amyloidosis, autopsy series have noted ATTR deposits in up to 25% of individuals greater than 80 years of age in the heart,[3] suggesting that the disease is underdiagnosed, or that perhaps there is a spectrum of disease including asymptomatic or minimally symptomatic disease. Cardiac involvement is the predominant clinical feature of wild-type ATTR amyloidosis, although carpal tunnel syndrome is common and may precede development of cardiac symptoms by 10 to 15 years. Isolated atrial amyloidosis occurs when atrial natriuretic peptide serves as the precursor protein for amyloid

formation and deposition into the atrial walls. Isolated atrial amyloidosis typically occurs in elderly women, with prevalence increasing with advancing age; 1 autopsy study found 95% of subjects aged 81 to 90 years had atrial amyloid deposits.[10] Isolated atrial amyloidosis is almost always asymptomatic and an incidental diagnosis, although some authors have suggested a role in the development of atrial conduction defects.

Clinical Features and Pathophysiology

Cardiac amyloidosis represents the classic prototype of restrictive cardiomyopathy, and is characterized initially by diastolic dysfunction with symptoms of exercise intolerance, fatigue, and shortness of breath. Myocardial deposition of amyloid results in progressive thickening of ventricular walls, thereby increasing myocardial stiffness and ventricular filling pressures. Chronic elevation of ventricular filling pressures leads to atrial enlargement and subsequent paroxysmal or persistent atrial fibrillation—atrial thrombi are relatively common in cardiac amyloidosis[11] and can cause systemic embolic events. Pericardial effusions are found in 40% to 60% of patients and are thought to occur because of increased right atrial pressures as well as pericardial amyloid infiltration. Valve thickening and subsequent regurgitation is a common finding, although the level of dysfunction is typically mild. The most common causes of death in cardiac amyloidosis are progressive heart failure and sudden cardiac death.[12]

Laboratory and Electrocardiographic Findings

The presence of low-voltage QRS complexes in a patient with increased left ventricular wall thickness is a classic finding in cardiac amyloidosis; however, the sensitivity of this finding is probably not high, and low-voltage QRS complexes are less frequent in patients with ATTR amyloid. On the other hand, conduction system abnormalities are relatively common in ATTR amyloid and are infrequent in patients with AL amyloidosis. The combination of elevated serum *N*-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T is associated with a poor prognosis, and is the basis of the Mayo Clinic staging system widely used in clinical practice.

Prognosis

The prognosis for patients with cardiac amyloidosis is generally poor; however, innovative treatment strategies have led to improved survival in patients with cardiac amyloidosis. AL cardiac amyloidosis has the worst prognosis, with greater than 50% mortality within 6 months of the initial diagnosis and an overall survival of 33% at 4 years from diagnosis.[13] ATTR cardiac amyloid has a more favorable prognosis of 3 to 5 years, with nearly 100% survival at 2 years.[14]

Echocardiography

Echocardiography is usually the first imaging study performed in patients with cardiac amyloid- osis, and can often suggest the diagnosis, partic- ularly in patients with advanced disease. The classic appearance of amyloid includes concentric thickening of the left ventricular walls (>12 mm at end diastole) with a normal or small left ventricular cavity and preserved left ventricular ejection fraction (>50%; Fig. 1). The right ventricle may also be thickened. The myocardium in cardiac amyloidosis has been described as having a brilliant speckled appearance, although the sensitivity and specificity of this sign are probably low. Dia- stolic dysfunction is indicated by an abnormal mitral filling pattern and associated atrial enlarge- ment. Thickening of valve leaflets, thickening of the interatrial septum, and small pericardial and pleural effusions are also common findings.

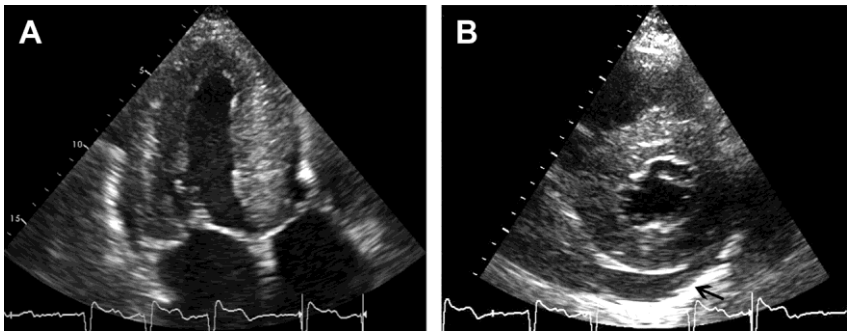

Fig. 1. Horizontal long axis (*A*) and midventricular short axis (*B*) images in a patient with cardiac amyloidosis demonstrate diffuse thickening of the left ventricle, biatrial enlargement, and a small pericardial effusion (*arrow* in *B*).

Myocardial strain imaging has recently emerged as an important technique in assessing patients with known or suspected cardiac amyloid. Speckle tracking echocardiography uses auto- matic frame by frame tracking of natural acoustic markers to track myocardial deformation over the cardiac cycle. A recent study of 200 patients with AL cardiac amyloid showed that longitudinal strain was strongly correlated with NT-proBNP levels, and that longitudinal strain was independently correlated with survival.[15] An apical sparing pattern of longitudinal strain has been noted in car- diac amyloid,[16] which can be very helpful in distinguishing amyloidosis from other causes of myocardial thickening, such as hypertrophic cardiomyopathy and hypertensive cardiomyopathy (Fig. 2).

MR Imaging

Cardiac MR imaging is one of the most useful and comprehensive techniques available for assessing cardiac amyloidosis. Demonstration of left and right ventricular myocardial thickening, increased myocardial mass, atrial enlargement, and pleural and pericardial effusions can all be accomplished with standard electrocardiograph-gated cine steady-state free precession images (Fig. 3). These series can also be used to quantify chamber size and ventricular function, with greater accuracy and reproducibility in comparison to echocardiography.

Postgadolinium images are often strikingly abnormal in cardiac amyloid patients. Late gadolinium enhancement (LGE) images are typically obtained 10 to 20 minutes after gadolinium injection using electrocardiograph-gated inversion recovery spoiled gradient echo T1-weighted pulse sequences. The marked expansion of the extracellular myocardial space caused by amyloid deposition leads to slower washout of gadolinium, with corresponding extensive myocardial enhancement (in contrast with the usual dark signal of normal myocardium; Fig. 4). Global subendocardial to transmural enhancement is the most commonly described pattern; however, enhancement can be patchy, usually predominant in the basal left ventricle.[7,17,18] A recent study showed that LGE had a sensitivity and specificity of 88% and 95% for detecting cardiac amyloidosis, respectively.[19] Right ventricular enhancement is often seen, and its presence can help to distinguish amyloid from other nonischemic cardiomyopathies. Diffuse atrial wall enhancement and thickening may also be noted.

Gadolinium contrast agents often are cleared from the blood pool more quickly in amyloidosis patients, with the blood pool often appearing dark on LGE images, and the altered kinetics of both myocardium and blood pool cause difficulties in determining the correct inversion time (TI) for LGE acquisitions. This general observation has been termed abnormal myocardial nulling. A more specific finding is myocardium reaching its null point before the blood pool on a cine inversion recovery spoiled gradient recalled echo acquisition used to select the optimal TI for LGE imaging, where each successive cardiac phase has an incrementally longer TI (Fig. 5).[18,20]

The abnormal nulling phenomenon is a reflection of the reduced myocardial T1 owing to retention of gadolinium, which in turn results from expansion of the extracellular space by amyloid deposition. T1 mapping offers an attractive means of quantifying the extent of myocardial disease in comparison to LGE imaging, in which the amount of apparent enhancement depends on the choice of TI. T1 mapping is typically performed with a shortened modified Look Locker inversion recovery sequence. Measurement of myocardial and

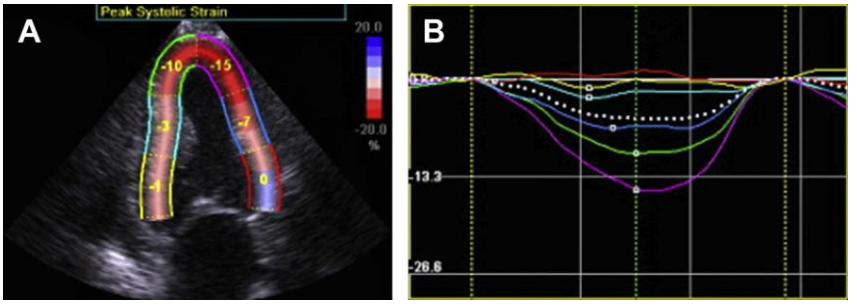

Fig. 2. Echocardiographic longitudinal strain measurements in a patient with cardiac amyloidosis. Parametric image of longitudinal strain superimposed over a long axis echocardiography view (*A*) reveals reduced longitudinal strain values (normal, less than -16), with relative sparing of apical segments. Two-dimensional plot of strain in color-coded cardiac segments (*B*) again demonstrates markedly reduced strain in basal segments with preserved strain in apical segments.

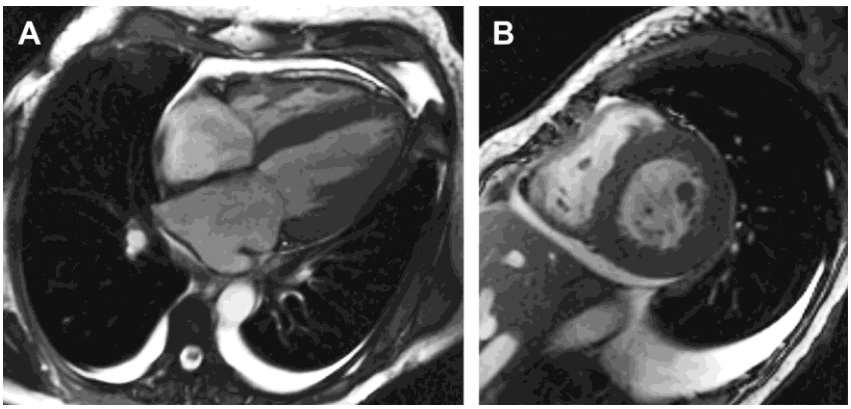

Fig. 3. Horizontal long axis (*A*) and midventricular short axis (*B*) electrocardiographic-gated cine steady state free precession MR images in a patient with cardiac amyloidosis demonstrate mild diffuse left ventricular thickening, biatrial enlargement, and small pericardial and pleural effusions.

blood pool T1 before and after gadolinium administration along with knowledge of the hematocrit allows calculation of the myocardial extracellular volume. A recent investigation found that an increased extracellular volume was associated with an increased hazard ratio for death.[21] An additional important result of this research is that T1 mapping of native myocardium (ie, without gadolinium contrast) is also strongly predictive of the presence of amyloid, with increasing T1 values associated with a larger amyloid burden and predictive of increased mortality.[21,22] Because many patients with AL amyloid also have renal involvement and reduced renal function, the ability to perform a quantitative assessment of disease burden without using gadolinium contrast agents is very attractive.

Nuclear Medicine

Radiolabeled serum amyloid P component scintigraphy is useful for evaluating the whole-body amyloid burden; however, it cannot assess cardiac involvement owing to blood pool uptake.[23] There has been much recent interest in off-label use of the bone scintigraphy tracers technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) and technetium pyrophosphate (^{99m}Tc-PYP) for diagnosis of cardiac ATTR amyloidosis.[24–26] The ^{99m}Tc phosphate derivatives can bind to TTR in the myocardium, but not to immunoglobulin light chains, and therefore a positive scan provides strong evidence for ATTR cardiac amyloidosis (Fig. 6). Both ^{99m}Tc-DPD and ^{99m}Tc-PYP seem to be very sensitive for the detection of ATTR amyloid deposits, and have identified presymptomatic disease.

Computed Tomography

CT has played a limited role in diagnosis of cardiac amyloidosis, and has generally been used in our practice as an alternative technique in patients who are not candidates for MR imaging. CT can

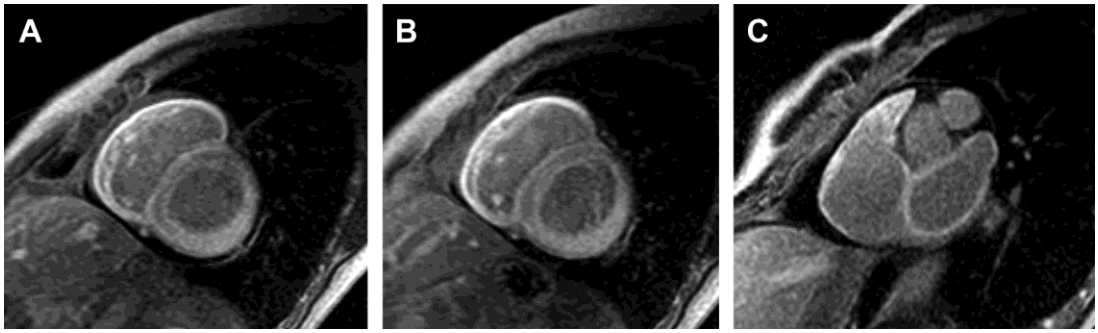

Fig. 4. Short axis late gadolinium enhancement MR images in a patient with cardiac amyloidosis. Midventricular short axis images (*A*, *B*) reveal marked diffuse enhancement of the right ventricular free wall as well as patchy near transmural enhancement of the lateral and inferior left ventricular walls. Short axis image through the atria (*C*) demonstrates diffuse enhancement and mild thickening of right and left atrial walls.