The evolving landscape of nuclear imaging in cardiac amyloidosis

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BACKGROUND

Amyloidosis is an infiltrative disease characterized by the extracellular deposition of abnormal protein fibrils in various organ systems, including the heart. While there are multiple proteins which can form amyloid fibrils, the vast majority of patients with cardiac amyloidosis (CA) have one of two types: immunoglobulin light chain-associated amyloid (AL) or transthyretin amyloid (ATTR). ATTR amyloid is further subdivided into a hereditary form associated with a pathogenic transthyretin mutation (''mutant'' TTR, or TTR-m) and a ''wild-type'' form (TTR-wt) in which a mutation is not identified and which tends to present later in life.

AL CA is a relatively rare condition, with approximately 3000 new cases per year in the United States;[1] of these, 30%-50% have symptomatic cardiac involvement. By contrast, ATTR CA is being increasingly recognized as a more common cause of heart failure with preserved ejection fraction (HFpEF), with transthyretin amyloid deposits found at autopsy in over 30% of patients over the age of 75 with HFpEF.[2]

While the age of presentation and associated organ involvement can provide clues as to the type of amyloid present, cardiac involvement in both AL CA and ATTR CA can manifest similarly clinically (typically progressive heart failure, occasionally with arrhythmias or conduction disease, and rarely with chest pain) and on cardiac imaging. However, distinguishing between the different types of CA is absolutely crucial; treatment is entirely dependent on the amyloid type, and the prognosis of AL CA differs substantially from that of ATTR CA.

While treatment of AL CA, including autologous stem cell transplantation, chemotherapy, and cardiac transplantation in highly selected cases, has improved over the past decade, it is generally associated with a poor prognosis, with 12-month mortality remaining high at 24% in recent years.[1] Patients with more advanced cardiac disease have worse survival, highlighting the importance of early diagnosis.

In patients with ATTR CA, survival is measured in years rather than months but does still result in reduced life expectancy and can have a significant impact on quality of life.[1] Liver and/or cardiac transplantation for patients with ATTR-m is well studied and reported, but pharmacological therapies have generally remained limited until recently. Emerging therapies currently undergoing clinical trials include transtheyretin stabilizers, such as difunisal and tafamidis, as well as microRNA inhibitors that interrupt the production of amyloid proteins, which may shape the management of ATTR amyloid in the near future.[1]

With improving therapies for AL amyloid and promising new treatment options for ATTR amyloid on the horizon, the need for early and accurate diagnosis of CA, including the ability to distinguish between AL CA and ATTR CA, is becoming paramount.

NONINVASIVE IMAGING ASSESSMENT

Echocardiography is usually the initial screening tool for CA in patients with heart failure and increased ventricular wall thickness. Characteristic findings of CA include biventricular wall thickening, valvular thickening, pericardial effusion, and biatrial enlargement. Diastolic dysfunction is one of the earliest echocardiographic findings in CA and may occur prior to the development of overt heart failure symptoms,[1] but it is a nonspecific finding. The characteristic global

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longitudinal strain pattern with apical sparing is more specific for CA but does not allow differentiation among subtypes. Classic cardiac magnetic resonance imaging (CMR) findings include late gadolinium enhancement (LGE), typically of the subendocardium initially and atria with subsequent progression into all layers of myocardium, difficulty nulling the myocardium, and extracellular volume expansion on T1 mapping. LGE has good sensitivity (80%) and specificity (94%) for detection of cardiac amyloidosis compared to endomyocardial biopsy (EMB),[3] with both more extensive LGE and RV free wall LGE more suggestive of ATTR CA than AL CA; however, sufficient pattern overlap precludes accurate differentiation between types. EMB is generally considered the gold standard for confirmation of CA. However, it is associated with procedural risks, requires expertise that can introduce diagnostic delay,[4] and does not provide information about the extent of disease, progression, prognosis, or response to treatment.[5]

EMERGING NUCLEAR TECHNIQUES

Nuclear scintigraphy offers an additional noninvasive imaging modality in the assessment of suspected CA with a growing body of evidence suggesting potential for earlier diagnosis of CA relative to echocardiography and CMR,[6] better diagnostic accuracy than CMR,[7] and ability to quantify amyloid burden,[7,8] distinguish between CA types,[8–11] and provide prognostic data.[6,12,13]

Several bone-seeking tracers, including ^{99m}Technetium-labeled pyrophosphate (^{99m}Tc-PYP), 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and hydroxymethylene diphosphonate (^{99m}Tc-HMDP) have all demonstrated utility in identification of ATTR CA. While the exact mechanism by which these tracers bind to amyloid is somewhat unclear, the presence of any cardiac uptake has $> 99\%$ sensitivity and 86% specificity for ATTR CA, with the majority of false positive test results for ATTR CA related to lower-intensity uptake in patients who in fact had AL CA, typically along with evidence of a monoclonal protein in serum and urine;[9] the presence of cardiac uptake equal to or greater than that of bone uptake combined with the absence of a monoclonal protein in serum or urine has a specificity and positive predictive value of 100% for ATTR CA in patients with symptoms and an echocardiogram or CMR suggestive of possible amyloidosis. This impressive capacity to identify ATTR CA with nuclear scintigraphy has led to a change in diagnostic criteria such that a positive biopsy is no longer required (although should still be followed by genotyping to differentiate between ATTR-m and ATTR-wt).

Unfortunately, these tracers, which have been used in planar and single photon emission computed tomography (SPECT) imaging, are far less reliable in the diagnosis of AL amyloid, which tends to be associated with no or mild myocardial uptake; in the same study, myocardial uptake was seen in less than half of patients with EMB-proven AL CA.[9] ^{99m}Tc-labeled aprotinin, a protease inhibitor, has been studied predominantly in AL patients but only in small numbers. With myocardial uptake seen in only 25%-40% of patients with AL CA,[14] insufficient evidence for use in ATTR CA, and concerns about safety,[15] its use has fallen out of favour. Additionally, SPECT imaging provides limited ability to quantify uptake at affected sites and thus can not be easily used for assessment of disease burden and response to therapy.[16]

However, other radiotracers used in positron emission tomography (PET) scanning, such as Pittsburgh compound B (^{11}C-PIB), initially used for imaging β-amyloid in Alzheimer's disease, and ^{18}F-florbetapir, have shown more promise. Both radiotracers bind to amyloid deposits and allow direct imaging of amyloid fibrils. Theoretically, direct imaging of amyloid deposits may allow for quantification of amyloid burden and potentially identify early CA involvement before overt structural changes are present.[6] In a study by Lee et al, 13 out of 15 patients with EMB-proven AL CA had a positive scan result, providing better diagnostic accuracy than concomitant CMR in the same patient population.[7] Further, ^{11}C-PIB was present but significantly reduced in the 5 patients with AL CA who had previously undergone chemotherapy, suggesting a possibility of using ^{11}C-PIB to assess disease burden/activity as well by quantifying the maximum standard uptake value (SUV) of the myocardium relative to the blood cavity. ^{18}F-florbetapir also shows promise in quantifying disease activity. In a small pilot study, increased myocardial uptake of ^{18}F-florbetapir was seen in all nine patients with CA and in none of the five controls. Further, in this small population, the ^{18}F-florbetapir myocardial retention index displayed a near-significant trend towards higher values in the 5 patients with AL CA compared to the 4 patients with ATTR CA ($P = 0.057$);[8] additional studies have also demonstrated increased ^{18}F-florbetapir uptake in patients with AL CA relative to patients with ATTR CA,[10,11] lending further support to the concept that ^{18}F-florbetapir may preferentially bind AL fibrils and that measures of ^{18}F-florbetapir uptake may have the capacity to differentiate between AL CA and ATTR CA.

PROGNOSIS

We are now getting closer and closer to accurately identifying not just the presence of CA but also specific subtypes with noninvasive nuclear imaging. The next logical question to ask is, for a given patient with a new diagnosis of CA, what additional information can these test results provide to help shape individualized management decisions?

Findings on other imaging modalities, such as abnormal global longitudinal strain on echocardiography and diffuse or transmural LGE on CMR, are independently associated with worse survival.[17,18] Regarding the bone-seeking tracers, increased ^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMDP have all been shown to be associated with worse freedom from major adverse cardiac events and/or increased mortality.[6,12,13] Data is currently lacking with respect to the association of PET tracers with adverse clinical events. ^{11}C-PIB has been shown to provide useful prognostic data in Alzheimer's patients,[19] and the question remains as to whether it can do the same in patients with CA.

In the current issue of *Journal of Nuclear Cardiology*, Minamimoto et al propose that ^{11}C-PIB may have this prognostic capacity. The authors evaluated nine patients with suspected CA who underwent both ^{11}C-PIB PET/CT and ^{99m}Tc-aprotinin scintigraphy and the results were correlated with additional diagnostic testing and clinical endpoints. Interestingly, 3 of the 9 patients had positive ^{11}C-PIB imaging (defined in this study as ^{11}C-PIB uptake in the myocardium above that of the blood pool) and all 3 had positive endomyocardial biopsies demonstrating AL amyloid and demonstrated progressive worsening of cardiac function or death attributed to heart failure in follow-up. There were 5 additional patients who had ^{99m}Tc-aprotinin uptake in the myocardium but no significant ^{11}C-PIB uptake, and these 5 patients remained stable from a cardiovascular perspective over the follow-up period. From this, the authors concluded that ^{11}C-PIB uptake may identify a subset of patients with CA who have a poor prognosis.[20] While this study does have limitations, including the small patient population and the potential for false positive ^{99m}Tc-aprotinin studies given that not all patients underwent biopsy or had definitive amyloidosis identified, the results are certainly provocative and represent early efforts to identify PET imaging techniques that offer prognostic data in patients with CA and thus the ability to potentially guide management decisions.

There are some limitations to using ^{11}C-PIB more widely, due to its short half-life and the need to have a cyclotron on site for production. However, ^{18}F-florbetapir is an emerging PET tracer which may circumvent some of these limitations as it has a longer half-life and is already clinically available as an FDA-approved brain-imaging agent.

FUTURE DIRECTIONS

More and more, we are beginning to appreciate the true prevalence of CA in patients with HFpEF, and this prevalence will only increase, particularly with respect to ATTR-wt CA, as the general population ages. With more effective treatment options for both AL and ATTR CA becoming more readily available, no longer are we at a stage of resignation and acceptance of a poor outcome upon diagnosis. Survival in both AL and ATTR CA has been improving, and early diagnosis along with subtype identification is critical in order to help improve survival further. It is in this capacity of subtype differentiation that nuclear imaging excels above other imaging modalities such as echocardiography and CMR; ATTR CA can now be readily diagnosed noninvasively with bone-seeking tracers in the absence of a monoclonal protein, and newer PET tracers show some promise in identifying AL CA with better success as well as distinguishing AL CA from both ATTR CA and non-CA conditions. It is possible that in the future, the need for invasive endomyocardial biopsy will be limited even further to rare exceptions. Figure 1 demonstrates a practical algorithm for the diagnosis of CA with the increased reliance on nuclear imaging to aid in diagnosis. This simple approach allows for ease of use in the work-up of the patient population with suspected CA. Of course, each patient must be assessed individually, as no diagnostic test is perfect. If clinical suspicion for CA remains high, despite negative or contradictory testing, complementary investigations are warranted. Special attention in particular may be necessary for patients with mild myocardial uptake on ^{99m}Tc-PYP/DPD/HMDP nuclear imaging in the absence of a monoclonal protein, and these patients may require ancillary testing or close follow-up. If ^{18}F-florbetapir or an alternative tracer is ultimately confirmed to adequately distinguish AL CA from ATTR CA and from patients without CA, or if a nuclear tracer specific for AL amyloid is identified, the niche for nuclear imaging in making a diagnosis of CA will likely increase even further.

However, the ideal test should not just provide a means of early and accurate diagnoses but also allow for prognostication and monitoring of disease progression. While SPECT imaging with bone-seeking tracers does provide some prognostic information, the ability to potentially quantify disease burden and activity with PET imaging could help identify which patients might benefit from therapy, guide treatment strategy, and

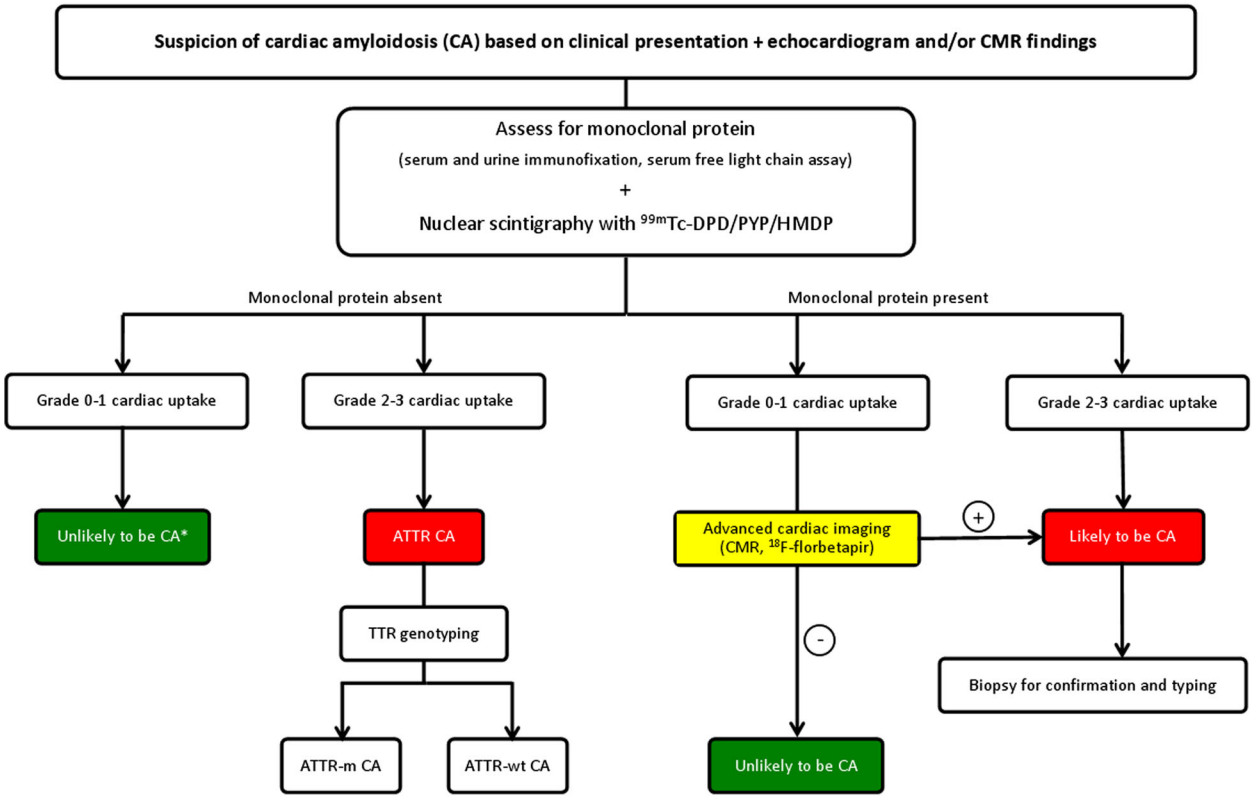

Figure 1. Diagnostic algorithm for patients with suspected cardiac amyloidosis. Grade 0-1, absent or mild (less than bone) cardiac uptake; Grade 2-3, moderate-to-high cardiac uptake (equal to or greater than that of bone); *, patients with Grade 1 uptake in the absence of a monoclonal protein may require ancillary testing or close follow-up.

provide a mechanism by which treatment response can be followed over time. In this respect, by identifying patients with poor prognosis using ^{11}C-PIB PET imaging, Minamimoto and colleagues are clearly leading the charge.

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