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Multimodality imaging approach to cardiac amyloidosis: part 2

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Abstract
With recent advances in cardiac imaging, genetics, and treatment options, cardiac amyloidosis (CA) is now recognized as an important and under diagnosed condition contributing to cardiovascular morbidity and mortality. Although still considered a rare disease, CA is now recognized as an important contributor to heart failure with preserved ejection fraction (HFPEF) and low gradient aortic stenosis, two important conditions commonly faced in clinical practice. This review uses clinical scenarios to highlight the complementary role of traditional imaging tools such as electrocardiogram (ECG) and echocardiography (echo) in conjunction with advanced cardiac imaging with cardiac magnetic resonance (CMR) and nuclear cardiac scintigraphy using bone avid tracers in the comprehensive workup of CA. We also highlight the importance of workup of light chain disease as part of integration of imaging findings and discuss the key aspects of various imaging modalities. Finally, an algorithm integrating clinical suspicion, laboratory testing, and imaging in the workup of CA is presented.

Keywords Cardiac amyloidosis · Light chain cardiac amyloidosis · Transthyretin cardiac amyloidosis · Electrocardiogram · Echocardiogram · Cardiac magnetic resonance · Technetium-99 m pyrophosphate · Multimodality imaging

Introduction

Cardiac amyloidosis (CA) is a rare restrictive infiltrative cardiomyopathy characterized by extracellular amyloid fibril infiltration leading to thickening of ventricular walls, increased ventricular stiffness, and consequently high ventricular filling pressures. Various forms of CA have been identified, with AL-cardiac amyloidosis (AL-CA) and transthyretin cardiac amyloidosis (ATTR-CA) being the most clinically relevant. Evaluation of CA requires heightened suspicion of CA's unique clinical manifestations in addition to understanding the electrocardiography (EKG), echocardiographic (echo), and radionuclide as well as cardiac magnetic resonance (CMR) imaging nuances. Apart from imaging, cardiac biomarkers, genetic analysis, and histopathological confirmation with tissue sampling play a key role for solidifying the diagnosis as well as for staging and management. For the purposes of this manuscript, cardiac nuclear scintigraphy will primarily focus on Technetium-99m pyrophosphate imaging (PYP) as other bone avid tracers are not available for clinical use in the USA.

AL-CA vs ATTR-CA

Morbidity and mortality related to CA is significant if diagnosis is delayed. This is partially due to large lag time between suspicion and diagnosis and in many cases misdiagnosis. Untreated, the median survival from onset of AL amyloidosis to congestive heart failure (CHF) is approximately 6 months [1], but modern therapies have extended that to 5 years, with increasing survival beyond 10 years [2]. The median survival of ATTR-CA is about 3–5 years in untreated individuals [3]. The ATTR staging system from the U.K. National Amyloidosis Center which included both wild type (wt-ATTR-CM) and hereditary (mtATTR) used N-terminal pro–B-type natriuretic peptide threshold of > 3,000 pg/ml) and estimated glomerular filtration rate (< 45 ml/min/1.73 m^2) and reported a median survival for stage II wtATTR patients of 49 months and a survival of 29 months in patients with mtATTR (Val122Ile mutation only) [4]. Clinical observations have suggested that the severity of heart failure in AL-CA is more severe than in ATTR-CA, despite higher left ventricular (LV) mass in ATTR [5]. This is likely related to

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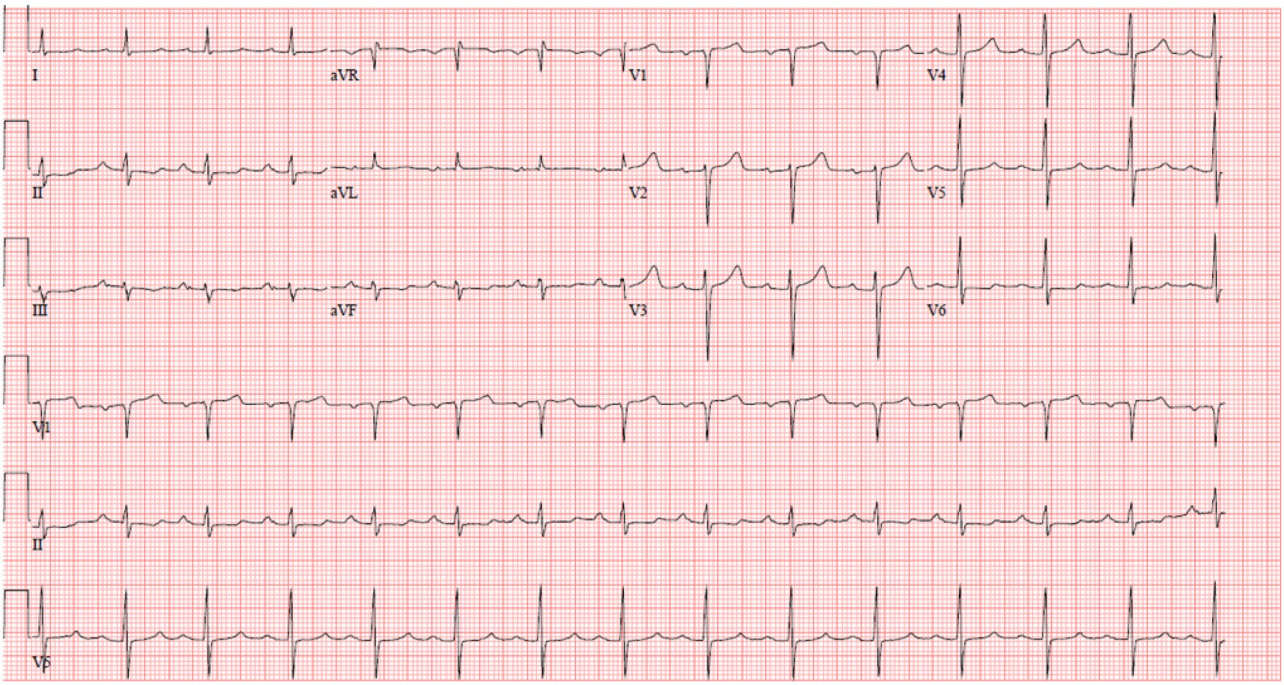

Fig. 1 A relatively benign appearing ECG in a patient with wtATTR-CA with normal precordial voltage

direct light chain toxicity and non-inflammatory edema in addition to interstitial infiltration [6].

This section discusses the integral role of multimodality imaging in the diagnosis of CA by illustrating 3 clinical scenarios of patients diagnosed with CA in our Amyloid Clinic with multimodality imaging. Each case illustrates a teaching point. The cases are used to discuss key aspects of various imaging modalities and how they are integrated towards diagnosis of CA. We summarize by providing a diagnostic algorithm our institution uses in the workup of CA.

Case 1: Role of multimodality imaging in clarifying etiology of hypertrophied ventricle

Seventy-seven-year-old male initially diagnosed as hypertrophic cardiomyopathy (HCM) based on CMR and echo with history of atrial fibrillation on Eliquis. Serial echo during follow-up showed new left ventricular dysfunction prompting repeat cardiac MRI which showed abnormal diffuse gadolinium enhancement of the myocardium more suggestive of an infiltrative process like amyloidosis. Parametric mapping techniques were not available at our institution at time of this MRI. Monoclonal protein screen and serum urine electrophoresis/immunofixation were negative for light chain disease. Endomyocardial biopsy (EMB) was attempted given the conflicting prior diagnosis of HCM, but the patient developed transient complete heart block and biopsy was aborted. He subsequently underwent an abdominal fat pad biopsy, which was reported as negative. Ultimately, a PYP scan was done with strongly positive myocardial uptake with H/CL ratio of 2.4 and grade 3 visual uptake with diffuse myocardial uptake on SPECT which helped confirm diagnosis of ATTR-CA. TTR DNA sequencing was negative for mutations. Therefore, a diagnosis of wtATTR was made. The patient is currently on Tafamidis.

Teaching point

CA should be considered in the differential of hypertrophied ventricles. Specifically, CA should be considered when a new diagnosis of hypertrophic cardiomyopathy is considered in the middle to older age patient.

Patient 2: Multimodality imaging in a patient with elevated light chains

Seventy-six-year-old male with CAD with prior percutaneous interventions, peripheral arterial disease, and atrial fibrillation with prior normal ejection fraction (EF) of 55% presents with new decline in EF to 40%. Patient relevant past history included bilateral carpel tunnel syndrome, lumbar spinal stenosis, and rotator cuff tear apart from other medical co-morbidities. CMR was ordered showing diffuse increased LV wall thickness, diffuse myocardial

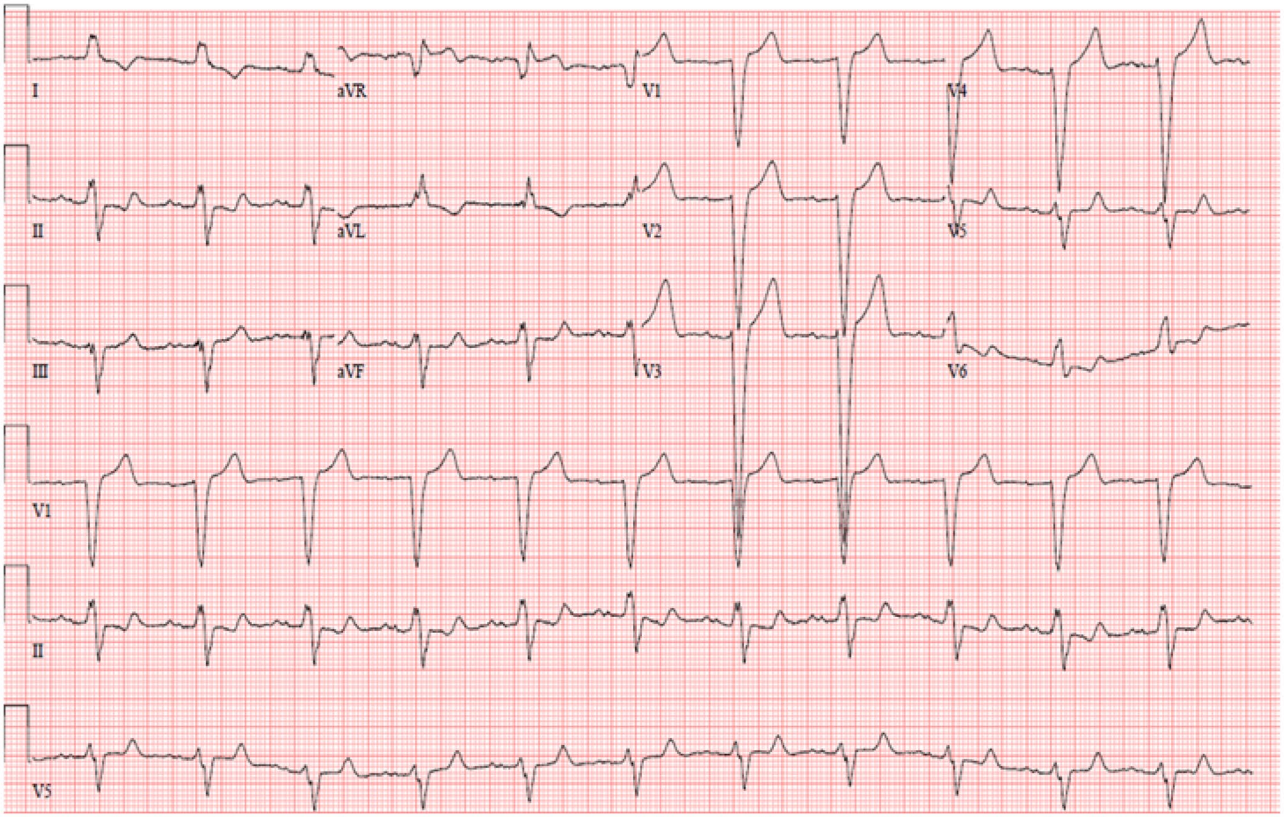

Fig. 2 ECG in patient 1 with wtATTR-CA showing left bundle branch block and voltage criteria for left ventricular hypertrophy. Another example of absence of low voltage in ATTR

delayed enhancement along with elevated native T1 relaxation times, and markedly increased myocardial extracellular volume all suggestive of CA. Workup for light chain disease was abnormal. He underwent hematological evaluation as well as bone marrow biopsy. Congo red stain was positive for amyloid deposits. Liquid chromatography tandem mass spectrometry was performed on the Congo red positive microdissected areas of paraffin embedded specimens (Mayo Clinic laboratories) and a peptide sequence consistent with ATTR amyloid protein deposition was noted. Subsequent amino acid sequencing was negative for mtATTR and hence a final diagnosis of wtATTR was established. PYP scintigraphy showed a H/CL ratio of 1.6 and grade 3 visual uptake with diffuse myocardial uptake on SPECT. Salivary genetics was negative for mtATTR. A multidisciplinary review of the case with hematology and cardiology was done. Based on above findings, an endomyocardial biopsy was deemed not necessary. A final diagnosis of wtATTR with coexistent monoclonal gammopathy of unknown significance (MGUS) was made. The patient is currently on Tafamidis. His most recent office visit 6 months post Tafamidis showed primarily progression of cervical spinal canal narrowing needing neurosurgical intervention with stable cardiac status and no active cardiac symptoms.

Teaching point

Comprehensive workup is needed to evaluate light chain disease prior to diagnosing ATTR-CA. MGUS can coexist with ATTR-CA.

Patient 3: Multimodality imaging in diagnosis of hereditary amyloid neuropathy with mixed phenotype including cardiomyopathy

Fifty-year-old male with bilateral carpal tunnel, syncope, severe orthostatic hypotension, PVCs, chronic diarrhea, and bilateral leg numbness requiring a cane for walking was evaluated for CA. Echo indicated thickened LV walls, which raised suspicion for HCM versus amyloidosis. Cardiac MRI with gadolinium showed diffuse LGE more consistent with CA. Serum urine immunofixation and monoclonal protein

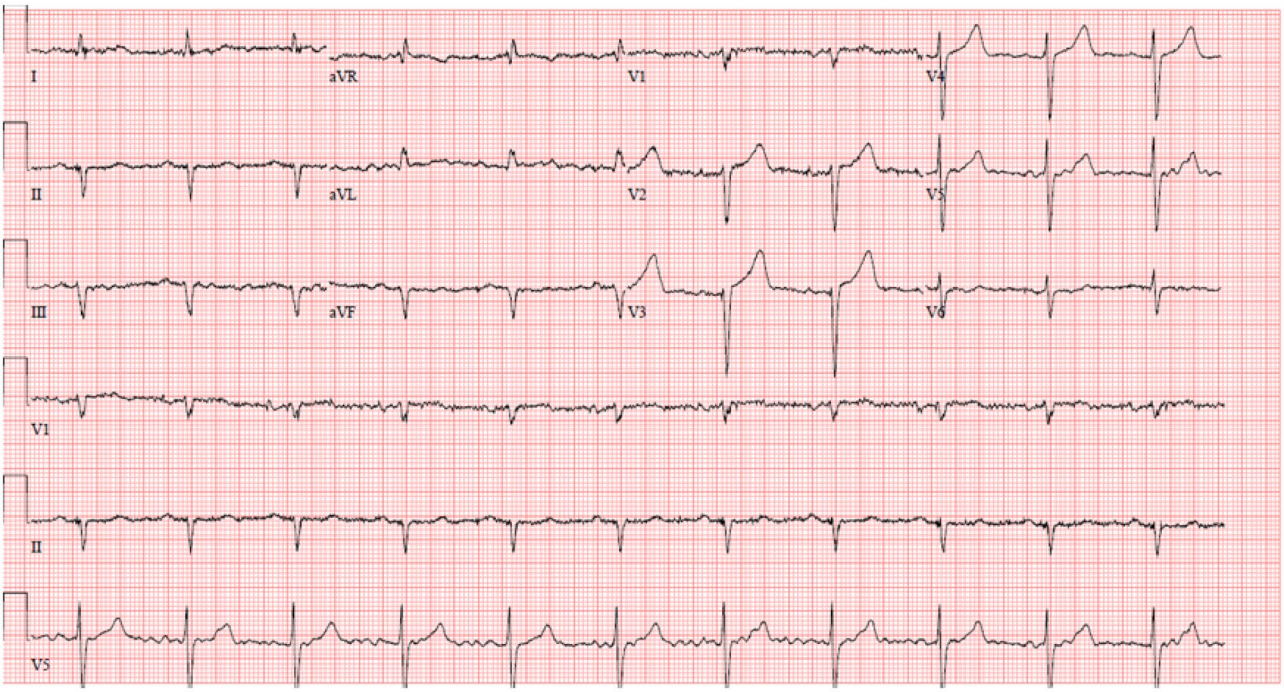

Fig. 3 ECG in mtATTR (patient 3). Pseudo-infarct pattern is present. Patient has no history of CAD. Again, note the relatively preserved precordial voltage

screen were negative for light chain disease. Fat pad biopsy was positive for Congo red positive amyloid fibrils and confirmed with mass spectroscopy to be ATTR. PYP scintigraphy was also consistent with ATTR cardiac amyloidosis with H/CL ratio 1.9 and diffuse myocardial SPECT uptake. Salivary genetic analysis was positive for T60A mutation. Neurological evaluation and workup confirmed Familial Amyloid Polyneuropathy (FAP) with severe disabling autonomic symptoms in addition to ATTR-CA. He was initiated on midodrine and patisiran for FAP given disabling neurological symptoms. Given concomitant cardiac involvement, he is also currently under evaluation for addition of Tafamidis.

Teaching point

Amyloidosis can present with neuropathic symptoms in addition to cardiomyopathy. Genetic analysis is integral in defining treatment options for FAP.

Table 1 Differential diagnosis of increased left ventricular wall thickness

Hypertrophic cardiomyopathy
Hypertensive heart disease
Fabry's disease
Amyloidosis
Athlete heart
Glycogen storage diseases

The case for non-biopsy diagnosis of amyloidosis with multimodality imaging

The gold standard for diagnosis of cardiac amyloidosis remains EMB from > 4 sites. A 2011 review of EMB from Mayo Clinic found the complication rates to be less than 6%

Fig. 4 Apical 4-chamber view showing severe left and right ventricular hypertrophy as well as granular sparkling appearance in patient 1 with wtATTR but s initially suspected as having HCM

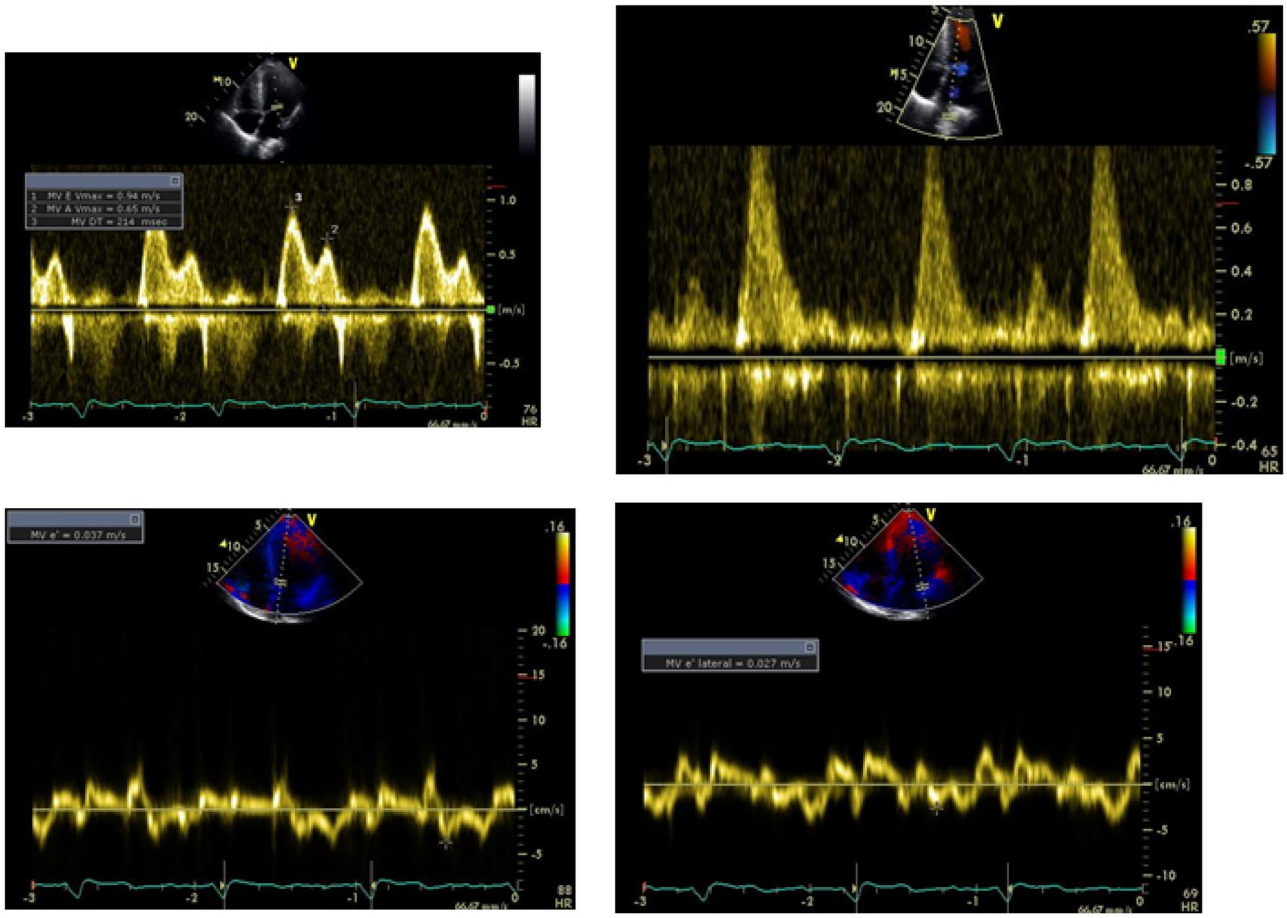

Fig. 5 Restrictive mitral flow pattern, right upper pulmonary vein pulse Doppler showing systolic blunting consistent with restrictive inflow, tissue Doppler imaging of the medial and lateral mitral annulus with very low systolic, and e' velocities in patient 1 with wtATTR

in most case series. Reported complications include access site hematoma, transient right bundle branch block, transient arrhythmias, tricuspid regurgitation, and occult pulmonary embolism. Right ventricular perforation was reported in less than 1% of patients in recent reports [7]. As mentioned in above, patient 1 developed a complete heart block during his EMB which required atropine and dopamine. Thus, EMB should ideally be reserved as the final step when comprehensive laboratory and imaging workup still remain inconclusive. Extra-cardiac sites for biopsy diagnosis have met with variable success. In a large study of 286 ATTR-CA patients by Fine and colleagues, non-cardiac organ biopsy or fat aspiration was positive nearly ¾ of the time. Overall, 210 patients had positive results on non-cardiac sampling. Nearly all patients (*n*-175/186, 94%) with mtATTR had positive histologic findings on non-cardiac tissue sampling (either fat aspiration or bone marrow biopsy), whereas only 35% (35/100) of the patients with wtATTR had positive results [8]. Endomyocardial biopsy which was performed in 46% of study population was 100% positive. Hence, although not unreasonable to consider extra-cardiac tissue sampling, it is important to be aware that the positivity rate, particularly for wtATTR amyloidosis, can be fairly low. Patient 1 with wtATTR-CA had a negative fat pad biopsy and patient 3 with mtATTR-CA (T60A mutation) had positive fat pad biopsy reiterating above study findings.

Given the challenges of biopsy, the current diagnostic approach for CA involves multimodality imaging in conjunction with assessment of a plasma-cell dyscrasia. Serum and urine immunofixation and the measurement of serum free light chains (FLCs) are necessary for the diagnosis of AL amyloidosis. The sensitivity of serum plasma electrophoresis for AL amyloidosis is ~ 70%, whereas the sensitivity of serum IFE is > 90% [9]. Together, measurement of serum IFE, urine IFE, and serum free light chain is > 99% sensitive for AL amyloidosis [10, 11]. This is key as missing a diagnosis of AL amyloidosis can be disastrous for patients given the high mortality and only depending on imaging may result in unacceptable false positive rates for ATTR amyloidosis. In the cases illustrated, patients 1 and 3 had AL excluded

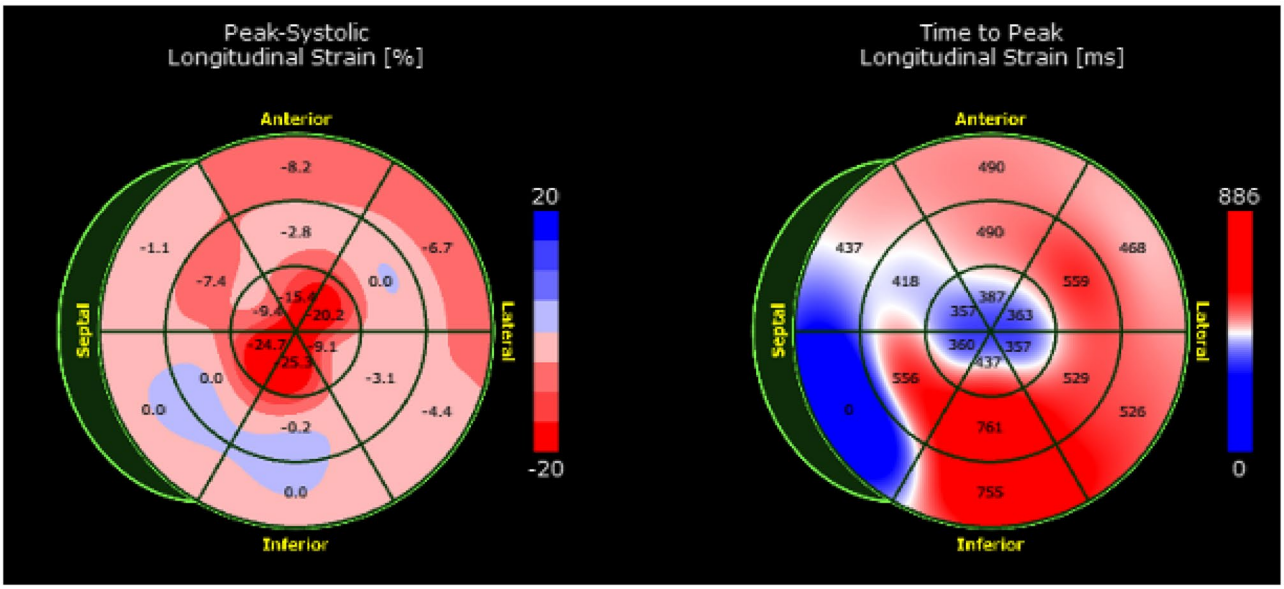

Fig. 6 Classic example of reduced global longitudinal strain with apical sparing aka "cherry on top" in a patient with wtATTR-CA. GLS was − 7%

by normal SPEP, UPEP, immunofixation, and monoclonal protein screening. Patient 2's workup for light chains was abnormal. He underwent hematological evaluation as well as bone marrow biopsy and was found to have coexisting MGUS with concomitant multimodality imaging confirming ATTR-CA.

Role of multimodality imaging

The use of multimodality cardiac imaging either directly identifies the presence of amyloid fibrils or indirectly images the effects of that infiltration on the myocardium: increased tissue calcium, interstitial expansion, and inflammation and

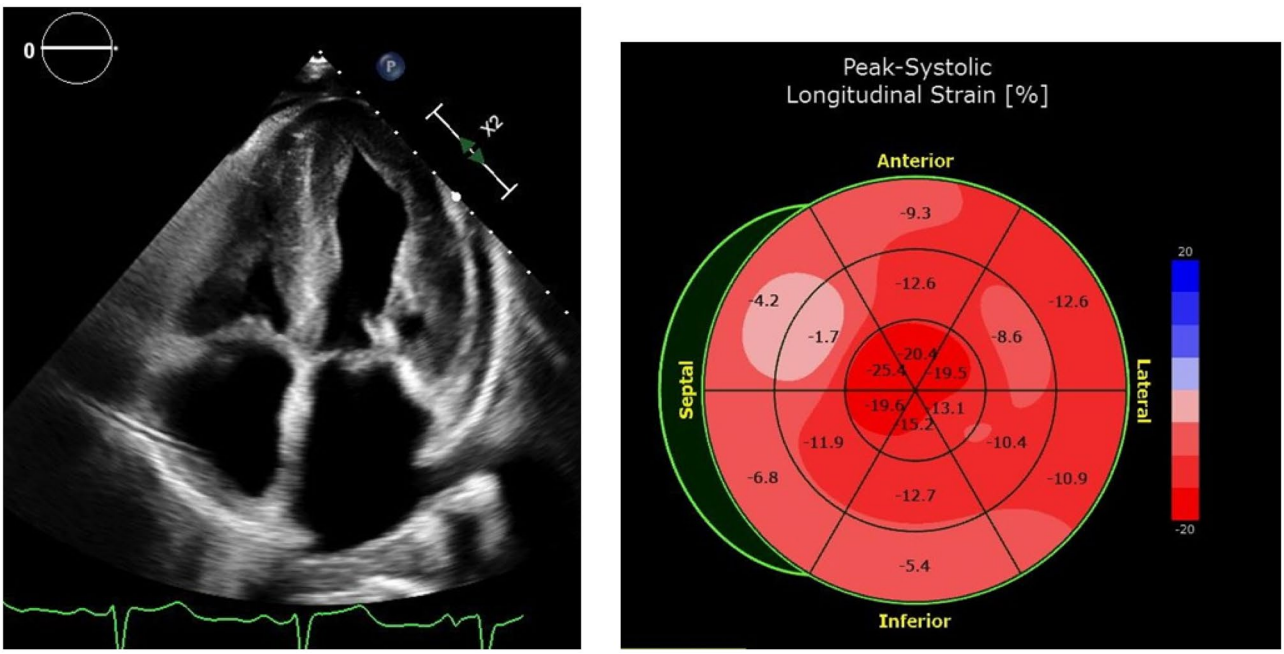

Fig. 7 Apical 4-chamber view showing biventricular increased wall thickness, thickening of mitral and tricuspid valve, and atrial enlargement. Speckle-tracking LV strain assessment bullseye image with diffuse reduction in strain but with relative apical sparing global longitudinal strain in patient 3 with T60A positive hATTR, with a mixed neuropathic and cardiomyopathic form of amyloidosis

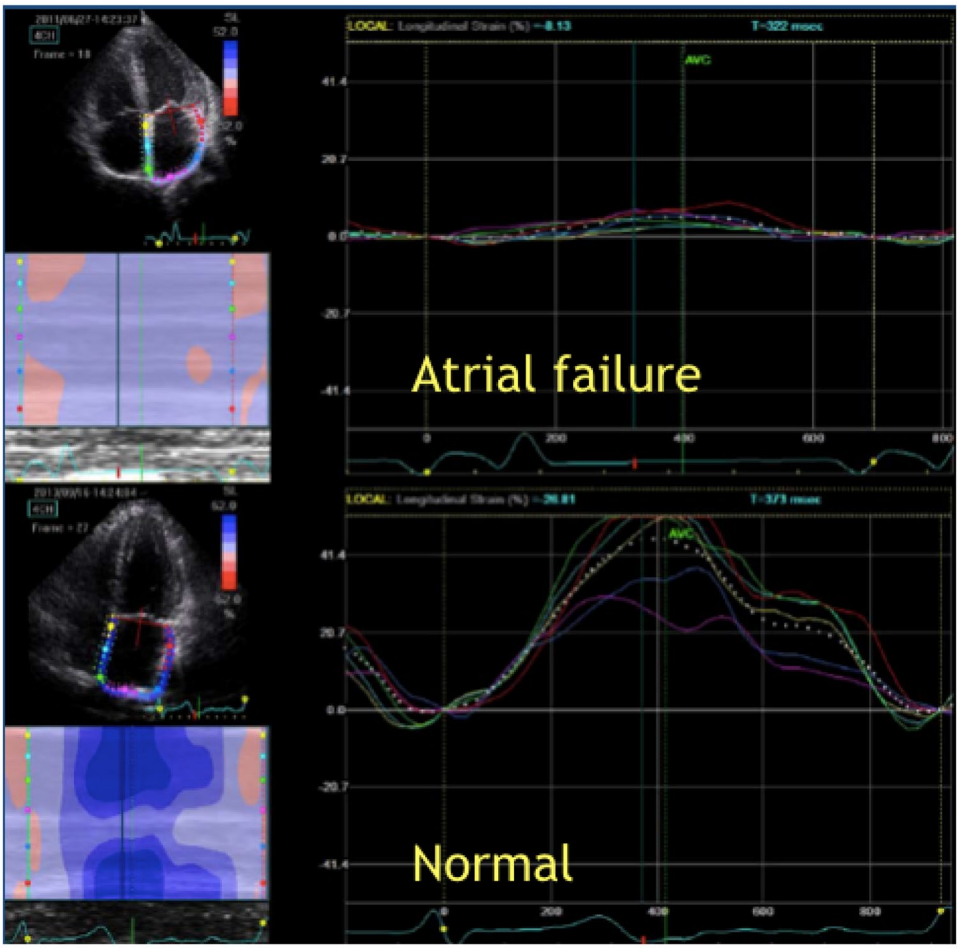

Fig. 8 Normal left atrial strain and abnormal left atrial strain in a patient with known wtATTR showing the markedly reduced left atrial reservoir strain

edema. In order for multimodality imaging to be cost effective, the initial clinical suspicion of CA should be correlated with the patient's presentation of heart failure, arrhythmias, and/or systemic autonomic and neurological symptoms as well as electrocardiography (ECG) and echocardiography (as discussed in clinical clues table of epidemiology section).

Electrocardiography and echocardiography

The presence of low voltage on ECG is a well-known and sought after finding in the diagnosis of CA. However, the absence of low voltage should not be used to exclude CA as in Fig. 1. Although AL-CA can cause low voltage in up to 60% of cases, low voltage EKG in ATTR-CA is highly variable and seen in only 20% with mtATTR and up to 40% wild type ATTR-CA [12]. Bundle branch block and voltage criteria for LVH may in fact be seen in patients with CA as noted in patient 1, Fig. 2 [13]. Patients 2 and 3 both had normal precordial voltage. The ECG for patient 3 showed inferior Q waves with no coronary artery disease (pseudo-infarct pattern), Fig. 3. Thus, ECG can sometimes provide clues, but additional imaging plays a key role in solidifying suspicion for CA.

Echocardiography (echo) is often the initial imaging study in evaluating patients suspected of CA due to ease, availability, portability, and ability to identify morphological and pathological consequences of amyloid deposition. The presence of left ventricle wall thickness > 1.2 cm [14] particularly in patients with controlled hypertension and heart failure with preserved ejection fraction should raise

Table 2 Key echo findings in cardiac amyloidosis

Increased left ventricular thickness
Speckled appearance of myocardium
Thickened valves
Thickened atrial septum
Pericardial effusions
Atrial dilation
Diastolic dysfunction
Abnormal global strain
Apical sparing pattern on strain

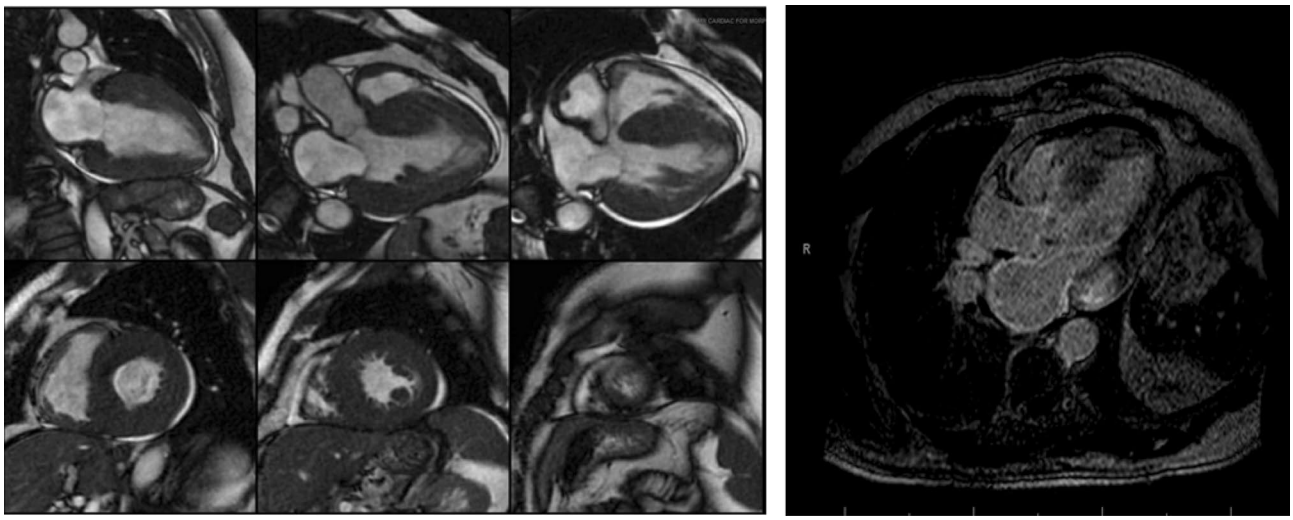

Fig. 9 CMR composite with increased myocardial wall thickening as well as 3-chamber post-contrast image showing extensive LV enhancement as well as left atrial LGE in a patient with wtATTR

the differential of CA amongst other causes (Table 1). The suspicion is strengthened by the discordance between ECG voltage and wall thickness and the echo LV mass/ECG voltage ratio has been shown to carry more diagnostic value than ECG voltage alone [15]. As illustrated in patient case 1, ATTR-CA can mimic HCM, Fig. 4. The initial echo for this patient showed massive asymmetric septal hypertrophy and increased LV and RV wall thickness and was initially treated as non-obstructive HCM. Asymmetric septal hypertrophy and reversed septal curvature mimicking HCM can be seen in up to 70% and 30% of CA patients, respectively [16]. Intraventricular dynamic obstructive physiology mimicking HCM can also be seen [17]. A granular sparkling appearance of the myocardial walls may be appreciated as in patient case 1 (Fig. 4), but it is not considered highly specific and has been reported in hypertensive as well as end-stage renal disease patients [18].

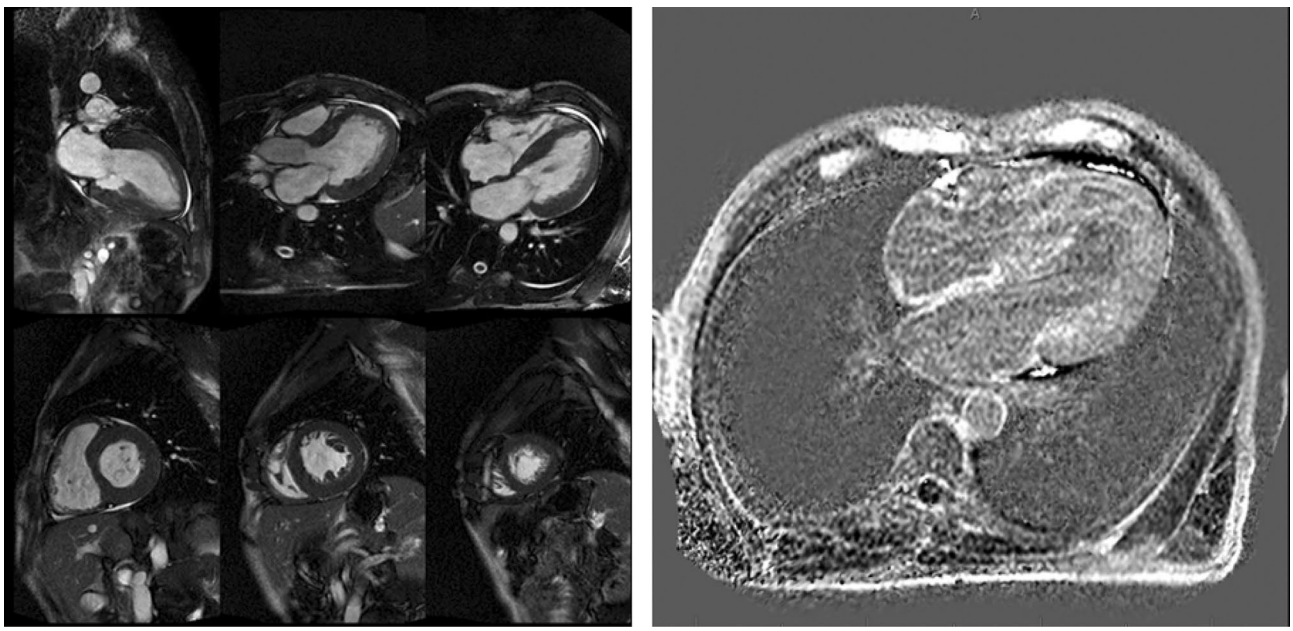

Fig. 10 CMR composite showing extensive LV wall thickness and diffuse biatrial and biventricular delayed myocardial enhancement in patient 3 with mtATTR

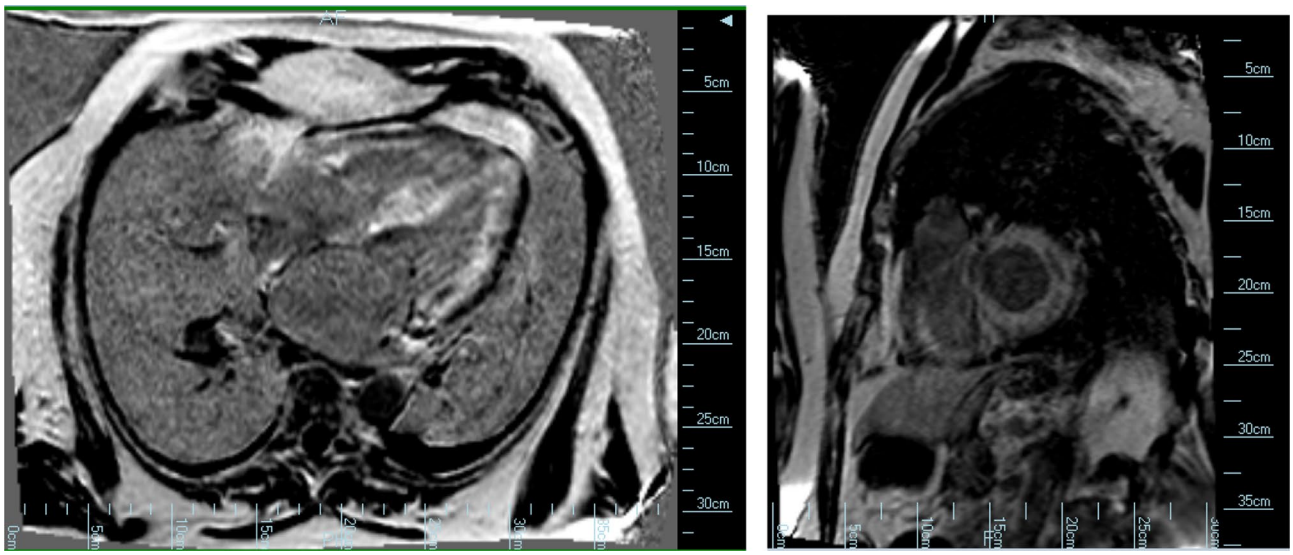

Fig. 11 Post-gadolinium 4-chamber and short-axis images in patient 2 with MGUS and wtATTR showing diffuse myocardial LV enhancement and RV enhancement

Tissue Doppler imaging (TDI) and speckle-tracking echocardiography permit a non-invasive evaluation of this pathological change secondary to infiltration of amyloid fibrils. TDI will show reduced myocardial systolic (S') and diastolic (e') and longitudinal velocities as shown for patient 1 in Fig. 5. The degree of TDI dysfunction is usually worse in CA than HCM [19]. Reduced longitudinal shortening with preserved LV ejection fraction (due to preserved radial shortening) is seen in earlier phases of CA although stroke volume may be low. Both AL- and ATTR-CA patients demonstrate a typical pattern of distribution of speckle-tracking echo-derived global longitudinal strain (GLS) in which basal LV segments are severely impaired while apical segments are relatively spared popularly referred to as "apical sparing" or cherry on top appearance [20, 21] as seen in the echos of patients 2 and 3, Figs. 6 and 7. However, an important caveat in using echocardiographic strain imaging is that "apical sparing" pattern is not specific for CA as this pattern has also been

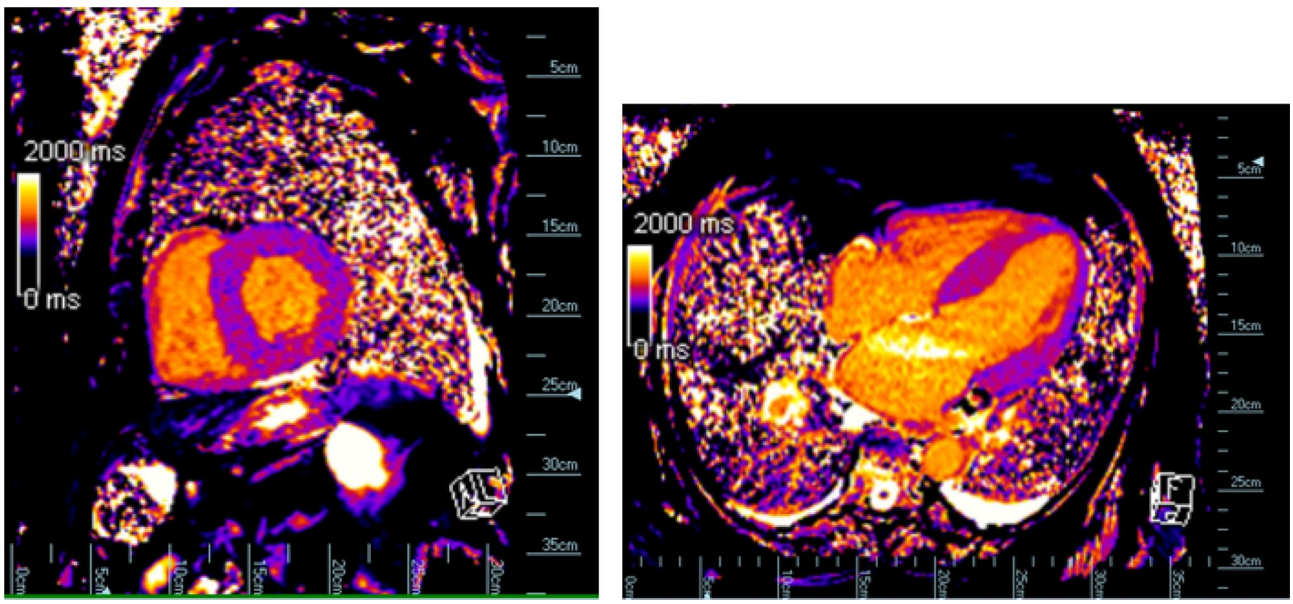

Fig. 12 Native T1 maps of short-axis and 4-chamber slices before gadolinium administration (1.5 T), in patient 2 with confirmed MGUS and wtATTR. The native septal T1 was 1115 ms, while the septal post-contrast T1 was 340 ms, resulting in a markedly elevated ECV of 54.7% (normal 23–29%)

reported in hypertensive heart disease and end-stage renal disease [22]. Hence, in the right clinical setting, echo findings can definitely raise the suspicion for CA which then requires confirmation with laboratory testing, bone marrow biopsy, advanced cardiac imaging, and if needed EMB. The ratio of LVEF to global longitudinal strain (EF/GLS) can also be used to differentiate amyloidosis from other forms of cardiac hypertrophy with preserved ejection fraction and a ratio of EF/GLS > 4 was the most accurate predictor of CA, performing better than other traditional deformation parameters especially in challenging cases of CA with only mild increased LV wall thickness [23]. The degree of reduction in GLS has been shown to correlate with MRI fibrosis and the lower the GLS correlateing with lower EF. Left atrial strain by speckle-tracking echocardiography is another emerging echocardiographic tool to further delineate cardiac dysfunction and extent of CA infiltration. Figure 8 shows marked atrial dysfunction in a patient with advanced CA compared to a normal atrial strain pattern in a control.

The key echocardiographic findings of CA are summarized in Table 2 [12, 20, 24–26].

CMR

While echocardiography is often the initial test in evaluation of CA, the ability of CMR to provide tissue characterization in addition to high-resolution morphologic and functional assessment makes CMR an excellent modality after

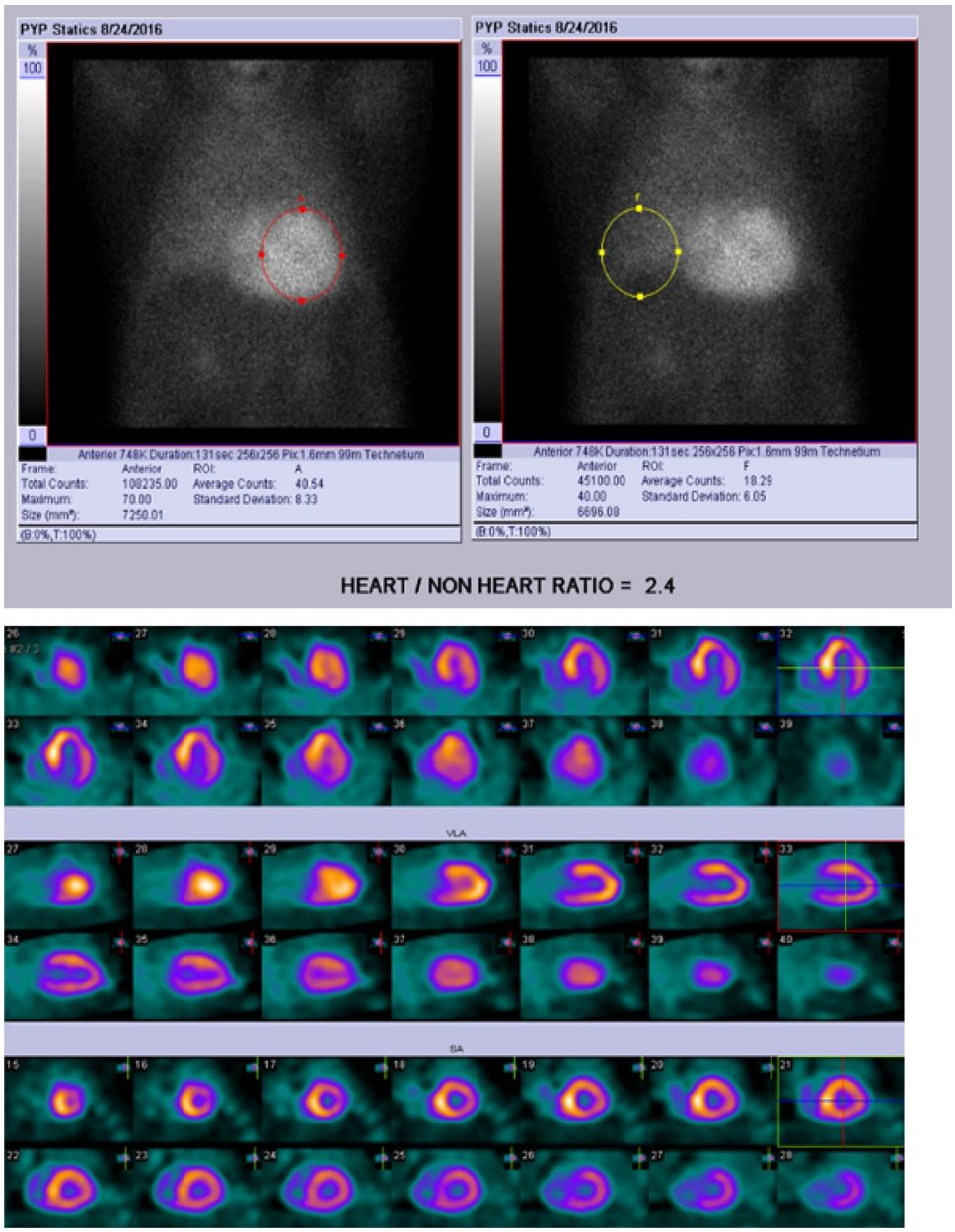

Fig. 13 **A** and **B** H/CL (heart/contralateral lung) lung-ratio methodology with measurement of mean counts per pixel for target (heart) and background (contralateral chest) ratio at 1 h (> 1.5 suggestive of ATTR-CA). SPECT images confirm diffuse pyrophosphate radio-tracer uptake in the myocardium, differentiating myocardial uptake from blood pool or overlying bone uptake

abnormal echo or to evaluate patients with systemic amyloidosis for early manifestations of cardiac amyloid. More importantly when evaluating for different causes of cardiomyopathy, CMR offers unparalleled morphologic and tissue characterization information. CMR for amyloidosis includes cine imaging, evaluation of native T1 signal (assessed on non-contrast T1 mapping prior to gadolinium infusion), assessment of late gadolinium enhancement using phase sensitive inversion recovery (PSIR), and extracellular volume (ECV) measurement. Gadolinium is a purely extracellular agent, and thus in CA, its volume of distribution is proportional to the interstitial expansion secondary to amyloid deposition [27]. Early CMR studies in cardiac amyloidosis described altered gadolinium kinetics, difficulty nulling the myocardium, and a global subendocardial pattern of late gadolinium enhancement (LGE) [28].

Multiple LGE distributions have been described in both ATTR- and AL-CA and studies have shown the extent of LGE in MRI has implications for adverse outcomes in CA. In a prospective study by Fontana et al., 250 patients (119 with AL, 122 with ATTR, and 9 asymptomatic mutation carriers) were studied with MRI with and without PSIR for LGE imaging. PSIR-based LGE assessment was superior and the patterns of LGE from none, to subendocardial, and finally to transmural enhancement were correlated with progressive increase in ECV. Overall, this study showed that a pattern of transmural enhancement was an independent predictor of adverse outcomes [29]. This differs from the pattern of LGE seen in HCM. LGE in HCM is often heterogeneous and patchy throughout the areas of hypertrophy and along the superior and inferior RV insertion sites [30, 31].

Both patients 1 and 3 were initially suspected of having HCM secondary to increased LV wall thickness, CMR was crucial in clarifying the etiology of hypertrophy, and given the extent of LGE, an infiltrative process such as amyloidosis was added to the differential by CMR, Figs. 9 and 10. Patient 2 with wtATTR in the setting of MGUS also had extensive LGE and inability to null the myocardium on his CMR, Fig. 11. In addition to LGE of the ventricular myocardium, delayed enhancement of the atrial wall is a strong clue to the presence of CA [32]. Patient 1 had LGE enhancement of his left atria, which further helped delineate the diagnosis of CA versus HCM, Fig. 9. CMR patterns of LGE serve as a valuable adjunct to echo to clarify cardiomyopathy etiology, but cannot conclusively distinguish ATTR from AL amyloidosis.

Newer parametric CMR techniques are making it into the mainstream clinical arena, which further adds to the ability of CMR to differentiate tissue characteristics. Native T1

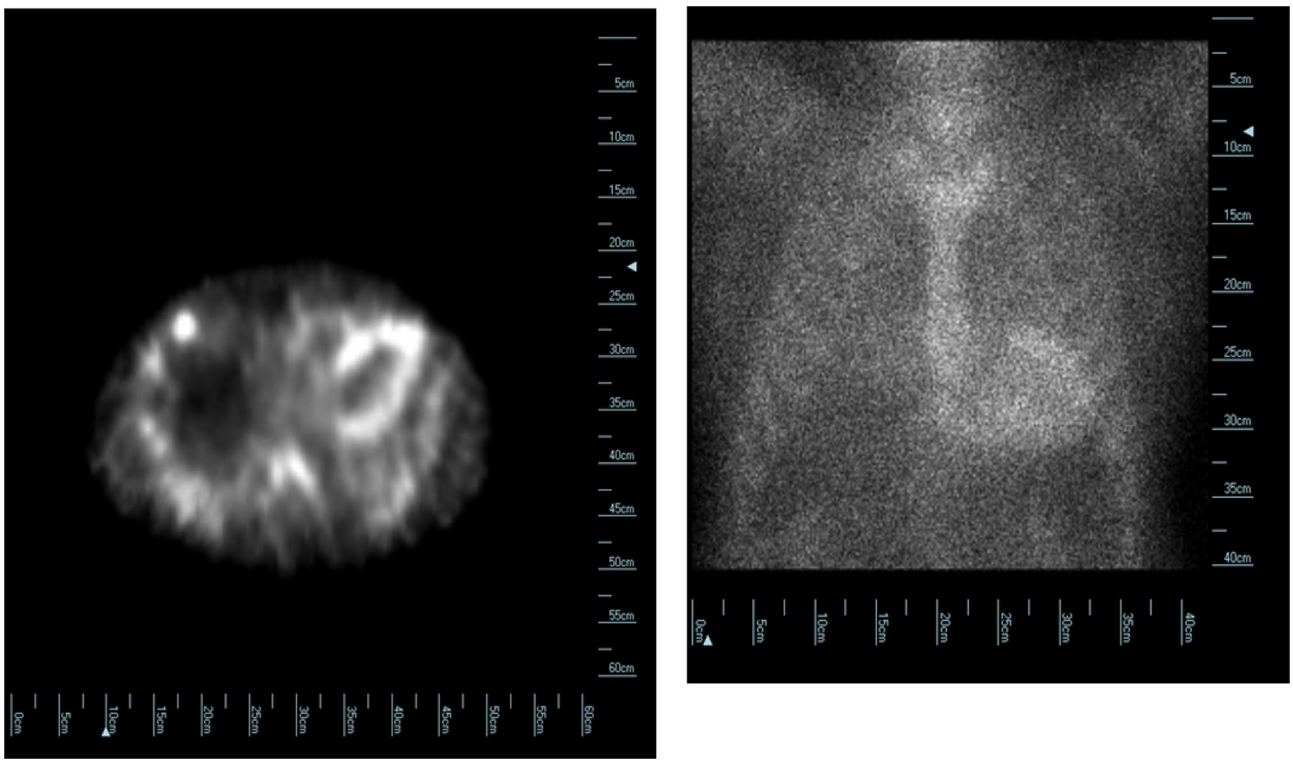

Fig. 14 **A** and **B** PYP-SPECT confirming diffuse radio-tracer uptake in the myocardium. Planar imaging at 3 h with H/CL ratio of 1.6 (> 1.3 abnormal)

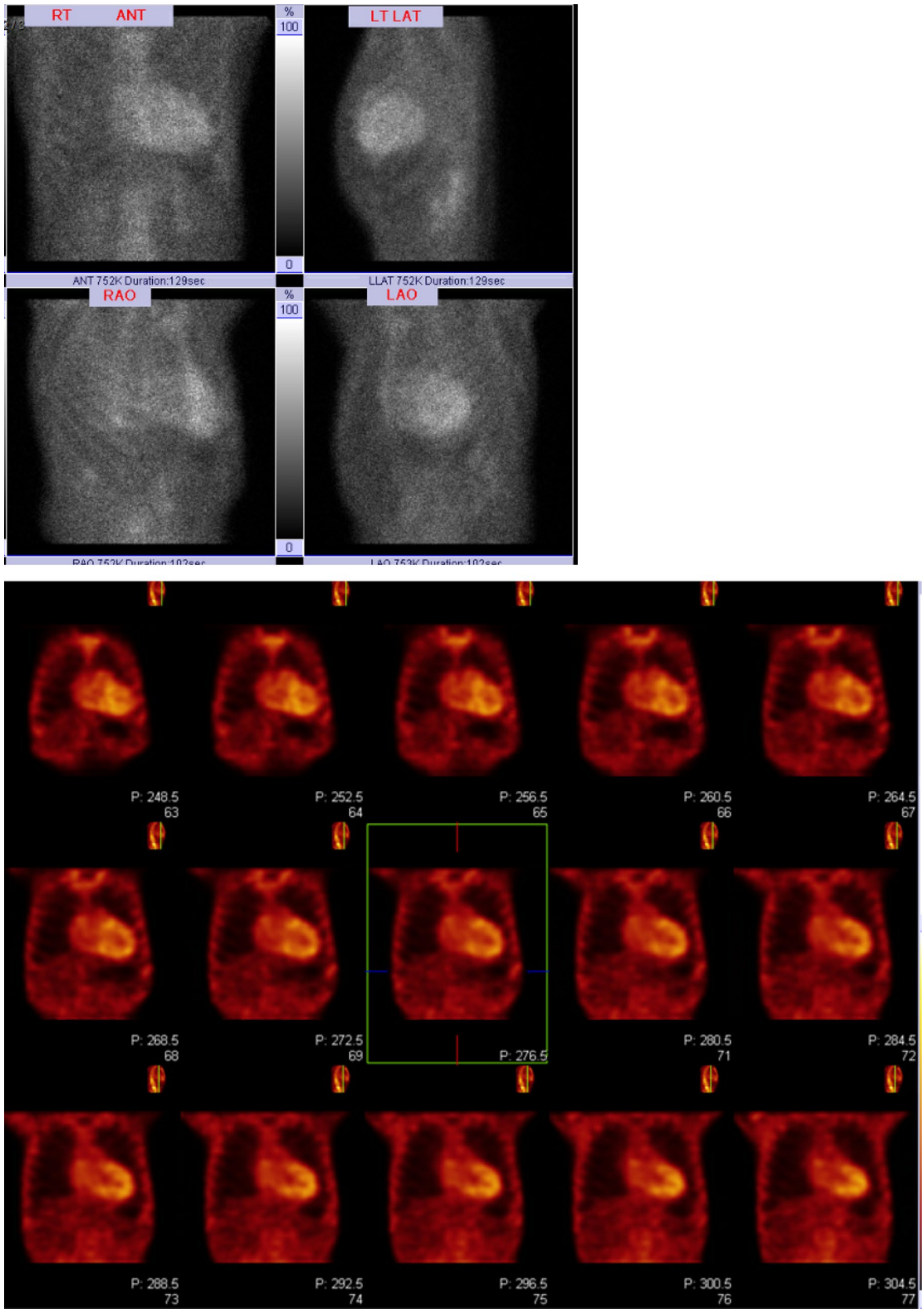

Fig. 15 **A** and **B** PYP planar chest views 1 h after injection with grade 3 uptake. 99mTc PYP myocardial uptake is greater than rib uptake with mild/absent rib uptake. SPECT images confirm diffuse increased cardiac uptake

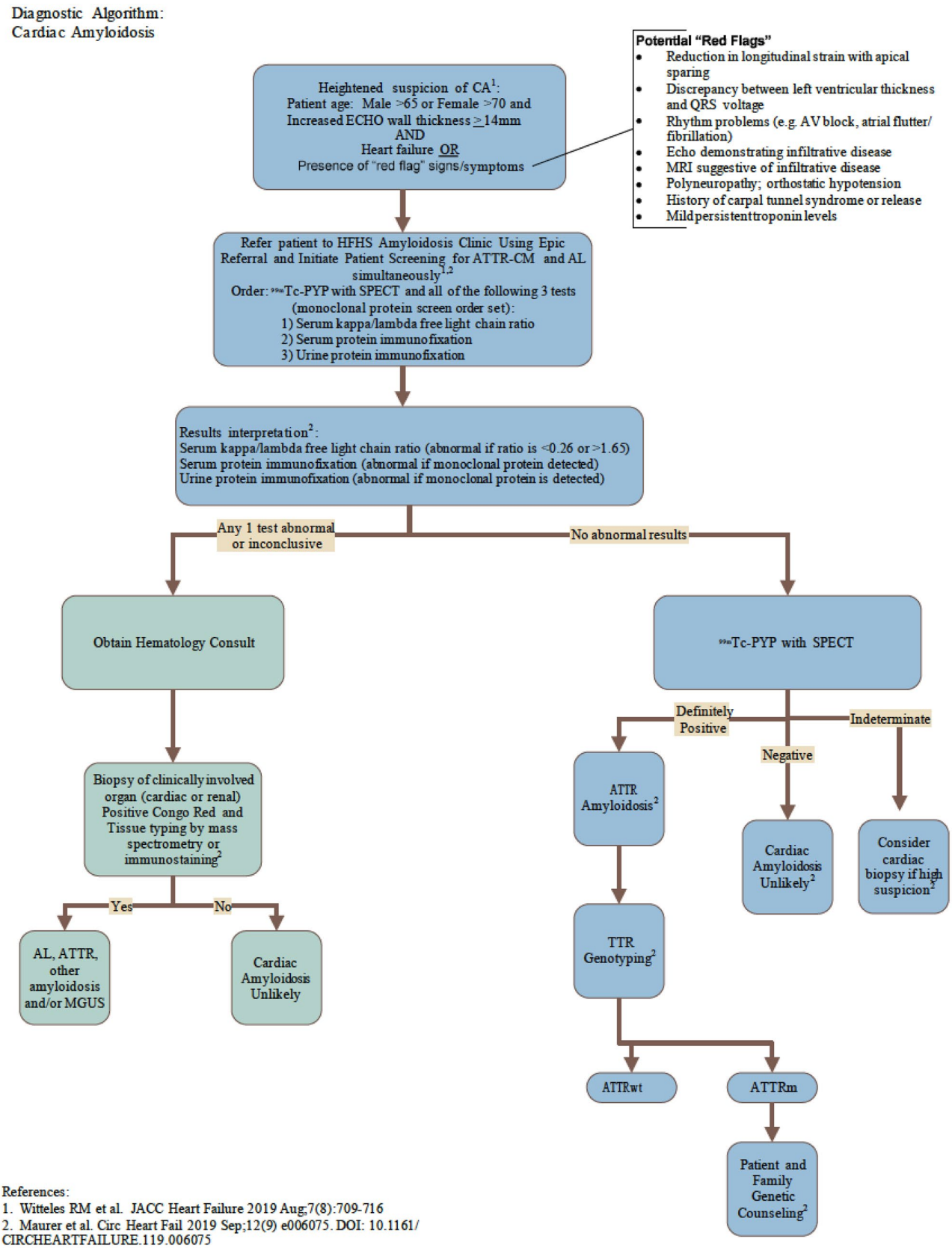

Fig. 16 Henry Ford Cardiac Amyloidosis Clinic Algorithm. Adapted and modified from references in figure. Note: Patients get monoclonal screen completed prior to PYP-SPECT being done

mapping performed pre-gad and post-gad T1 maps allow a quantitative measure of ECV, which is significantly elevated in CA. Furthermore, ECV is elevated even when conventional testing and gadolinium-enhanced imaging techniques suggest no cardiac involvement. Therefore, ECV measurements may be helpful in early disease as well as to track progression and even treatment as ECV parallels amyloid burden [33, 34]. Significantly, prolonged T1 time is a characteristic of CA [35] and post-contrast shortening of T1 time is also seen with CA [34, 36]. Furthermore, T1 is elevated in ATTR patients compared with HCM and normal subjects [36]. T1 pre- and post-contrast maps and calculations of ECV are included for patient 2, Fig. 12. An advantage of native T1 mapping is that it does not require gadolinium. Therefore, if certain CMR morphologic features suggest CA, pre-contrast T1 time may further support that diagnosis in patients where gadolinium administration may not be suitable such as those with advanced chronic kidney disease.

Technetium-99 m pyrophosphate nuclear cardiac scintigraphy

There is a unique myocardial uptake pattern in CA with nuclear scintigraphy using 99mTechnetium (Tc)-bisphosphonate derivatives such as 99mTc-pyrophosphate (PYP) available in USA), as well as 99mTc-3,3-diphosphono-1,2-propanodicarboxylicacid (99mTc-DPD) and 99mTc hydroxymethylenediphosphonate (99mTc-HMDP) which are both used in other parts of the world and not available in USA. The mechanism underlying the myocardial retention of these tracers is unknown but has been attributed to the presence of microcalcifications that are more common in ATTR than AL cardiac tissue [37]. Therefore, radionuclide imaging provides critical information on amyloid type that is not available by echo or CMR. PYP imaging has brought the reality "non-biopsy diagnosis" of CA to fruition. A seminal study involving a large cohort of endomyocardial biopsy-proven cases of ATTR-CM concluded that these bone avid tracers conferred 100% specificity for ATTR-CM when grade 2 or 3 uptake of PYP was seen in the absence of a monoclonal protein by serum and urine testing in patients with HF and typical echocardiographic or CMR findings of amyloidosis [38]. PYP scanning is also capable of identifying the presence of cardiac amyloidosis prior to LGE on CMR.

The diagnostic parameters of PYP scan have traditionally included the ratio heart-to-contralateral (H/CL) lung uptake (semiquantitative scoring), the Perugini grading system of heart-to-bone uptake (visual grade) based on uptake in the heart on planar at both 1 and 3 h. However, increasingly false positive cases and overdiagnosis of CA based on planar imaging due to blood pool accumulation of isotope have brought to light the importance of SPECT-CT in the confirmation of diffuse myocardial uptake, now considered an integral finding to confirm ATTR-CA to avoid misdiagnosis [18]. Single-photon emission computed tomography (SPECT) should be assessed in all positive scans to confirm that uptake actually represents myocardial retention of the tracer, not simply blood pool signal [39]. The visual assessment of SPECT-CT uptake is now the preferred approach to PYP to confirm CA.

Patient 1 demonstrated heart/contralateral lung ratio of 2.4 as well as visual grade 3 myocardial uptake on PYP as well as diffuse uptake of PYP on SPECT, Fig. 13. Patient 2 had a 3-h PYP study. The H/CL for patient 2 was 1.6 at 3 h, Fig. 14. The SPECT-CT images also indicated grade 3 uptake with activity significantly over adjacent rib bony uptake confirming ATTR-CA, Fig. 14. The planar and SPECT images for patient 3 show grade 3 Perugini grading as well as diffuse myocardial uptake and not pooling of the radionuclide tracer within the blood pool, Fig. 15.

Summary

The 3 cases above and accompanying discussion on multimodality imaging illustrate the complementary roles of multimodality imaging in CA. As discussed, a systematic approach with suspicion for the clinical clues, EKG and echo features, and use of advanced cardiac imaging with CMR and PYP imaging along with genetic analysis helps to solidify a non-biopsy diagnosis of CA. However, despite use of imaging, there may be some cases which fall in the "grey zone" and these require conclusive evaluation with EMB which is the preferred tissue approach for diagnosis. We present an algorithm of our systematic approach adapted and modified from existing data that we use in practice to integrate all tools to arrive at the diagnosis of cardiac amyloidosis, Fig. 16.

Declarations

Conflict of interest The authors declare no competing interests.

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