

Transthyretin amyloid cardiomyopathy: The emerging role of cardiac amyloid imaging

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Transthyretin amyloidosis (or ATTR amyloidosis) is an under-recognised multisystemic disorder, arising from misfolding of transthyretin proteins into insoluble amyloid fibrils. As amyloid fibrils deposit into various tissues and organs, the process invariably leads to organ dysfunction. Deposition of amyloid fibrils into the heart results in cardiac amyloidosis (CA). Manifestations include restrictive cardiomyopathy, heart failure, conduction abnormalities and arrhythmias.¹ Early and accurate recognition of cardiac involvement is important, as it is a leading cause of morbidity and mortality in ATTR amyloidosis, and emerging therapies may delay disease progression.²

Definitive diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) has conventionally relied on endomyocardial biopsy.³ Over the last decade, however, advancements in imaging modalities, particularly radionuclide scintigraphy, have enabled non-invasive diagnosis of ATTR-CM.^{4,5} We present the case of a patient who was non-invasively diagnosed, and discuss the evidence, as well as the latest recommendations behind non-invasive diagnosis of ATTR-CM.

A 72-year-old Chinese man was admitted to the cardiology ward with a history of exertional dyspnoea and abnormal electrocardiogram (ECG) findings in routine outpatient primary care review. ECG showed sinus rhythm with poor R-wave progression and anteroseptal ST-segment elevations, without dynamic changes. There was no chest pain, dizziness or palpitations. He had a background of hypertension, hyperlipidaemia and diabetes, but no personal or family history of cardiac conditions. Vital signs and cardiorespiratory examination were unremarkable.

Further workup revealed elevated serum high-sensitivity troponin I levels (serial 36–38ng/mL; normal <14ng/mL). Transthoracic echocardiogram (TTE)

demonstrated left ventricular ejection fraction (LVEF) of 60% and concentric left ventricular hypertrophy (LVH), without regional wall motion abnormalities. Subsequent myocardial perfusion imaging revealed normal myocardial perfusion and dilated left ventricle, suggesting myopathic disease. Contrast-enhanced cardiovascular magnetic resonance (CMR) confirmed concentric LVH, dilated atria, LVEF of 58% and right ventricular ejection fraction of 57%. Left ventricular myocardial signal intensities were increased on T2-weighted fat suppressed turbo inversion recovery magnitude imaging. Diffuse subendocardial and mid-myocardial patterns of late gadolinium enhancement were present, together with gadolinium enhancement of atrial walls and atrial septum and rapid clearance of gadolinium from the blood pool, raising suspicion for CA (Fig. 1). Endomyocardial biopsy was then recommended to our patient for diagnosing CA. Given its invasive nature, he declined and subsequently failed to attend follow-up cardiology clinic appointments.

Over the next 2 years, the patient was readmitted twice for heart failure with volume overload, manifesting as worsening exertional dyspnoea and exercise intolerance, orthopnoea and lower limb swelling in the preceding few months. Notably, repeat TTE demonstrated a LVEF decline to 40%. The patient remained reluctant to undergo endomyocardial biopsy. In the latter admission, he underwent ^{99m}technetium-pyrophosphate (^{99m}Tc-PYP) scintigraphy, as a scintigraphy scan service for diagnosing ATTR-CM had become available since his last admission. The ^{99m}Tc-PYP scan performed with planar imaging at 1 hour showed a heart-to-contralateral lung ratio of 1.5 (Fig. 2). Combined with single-photon emission computed tomography (SPECT) imaging demonstrating increased myocardial radiotracer uptake equalling rib radiotracer uptake (grade 2), the findings suggested ATTR-CM. Light

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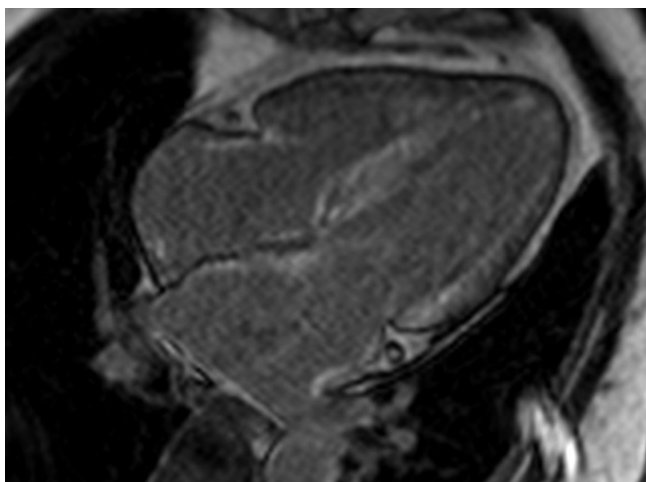


Fig. 1. Cardiac magnetic resonance imaging showing late gadolinium enhancement of the subendocardium and mid-myocardium of the left ventricle, atrial walls and atrial septum.

chain amyloid cardiomyopathy (AL-CM) remained an important differential diagnosis, which was excluded given the normal serum free light chain (sFLC) ratio (0.97; normal 0.26–1.65), and negative serum and urine immunofixation. In view of the patient's clinical history, strongly positive scintigraphy scan and negative monoclonal screen, he was therefore diagnosed with ATTR-CM, non-invasively.

In following up with the patient in our heart failure clinic, retrospective questioning revealed a 6-year history of bilateral carpal tunnel syndrome and lumbar spinal stenosis, both likely being associated with ATTR amyloidosis. Doxycycline/ursodeoxycholic acid, an off-label fibril-disruptor therapy for ATTR-CM was then commenced. Tafamidis, a transthyretin stabiliser and the only agent licensed for treating ATTR-CM was a less feasible option given its prohibitively high costs. The patient was counselled and offered transthyretin genetic (*TTR* gene) testing to differentiate hereditary ATTR amyloidosis (hATTR) from wild-type ATTR amyloidosis (wtATTR), for which he has requested for more time to discuss the test with his family. Patient remained otherwise well in follow-up clinics.

Cardiac involvement is the most important prognostic factor in amyloidosis, and is associated with poor life expectancy and quality of life.⁶ Amyloidosis can be classified based on misfolded precursor proteins, which form amyloid fibrils that deposit in the myocardium.² Over 30 proteins are known to form amyloid fibrils, including immunoglobulin light chain, transthyretin, amyloid A and β 2-microglobulin. However, immunoglobulin light chain (AL) amyloidosis and



Fig. 2. ^{99m}Technetium-pyrophosphate cardiac amyloid imaging scan showing grade 2 myocardial tracer uptake with heart-to-contralateral ratio of 1.5008.

ATTR amyloidosis are the most common types, accounting for more than 95% of cases.^{2,3} AL amyloidosis arises from the overproduction of misfolded immunoglobulin light chains by clonal plasma cells. In contrast, ATTR amyloidosis results from misfolding of transthyretin, a tetrameric transporter protein produced by the liver. Distinguishing between AL and ATTR amyloidosis is important, given their different manifestations, prognosis and management.⁷

ATTR amyloidosis can be further classified as hATTR, due to *TTR* gene mutations, or wtATTR associated with ageing and misfolded genetically normal transthyretin protein.² Previously, ATTR amyloidosis was thought to be rare and untreatable. However, autopsy studies have demonstrated wtATTR cardiomyopathy to be relatively prevalent in older adults, in around 25% of patients 80 years old and above.^{8,9} Recent advancements in diagnostic imaging modalities have also improved ATTR-CM detection, allowing it to become an increasingly recognised cause of heart failure with preserved ejection fraction (HFpEF). With new disease-modifying therapies available for ATTR-CM, timely diagnosis has becoming increasingly crucial.¹⁰

Diagnosis of ATTR-CM is challenging because of its heterogeneous presentation, perceived rarity, and limited awareness within the medical community.¹ Given the clinical overlaps with common disorders and frequent comorbidities, ATTR-CM is often misdiagnosed as hypertrophic cardiomyopathy, aortic stenosis, undifferentiated HFpEF or hypertensive heart disease.¹ Non-specific early symptoms and multisystemic manifestations (neurologic, orthopaedic,

gastrointestinal) further confound diagnosis.³ Carpal tunnel syndrome is prevalent in ATTR-CM (15–60% of cases), often preceding cardiac involvement by 5–9 years, as demonstrated in our patient. Hence, recognition of this association may promote earlier diagnosis of subclinical ATTR-CM.¹¹

Non-invasive diagnosis of ATTR-CM. Endomyocardial biopsy has been considered the gold standard for diagnosing ATTR-CM. However, it is invasive and carries a small but significant risk of complication. Consequently, many older patients are unwilling to undergo the procedure, potentially delaying diagnosis as seen in our patient. Furthermore, it is often limited to experienced specialised centres and not widely available. Following diagnosis, endomyocardial biopsy does not estimate cardiac amyloid burden and is impractical for monitoring disease progression.⁷ Conventional investigation modalities including ECG, TTE and CMR are useful adjuncts, as typical findings collectively raise suspicion for CA (Table 1). However, typical findings are not always present, and clinicians are unable to definitively diagnose nor distinguish between amyloid subtypes.¹²

In recent years, technetium-labelled cardiac amyloid imaging has emerged as a reliable method for non-invasive diagnosis of ATTR-CM. The advantages include its ease of access, relatively lower costs, repeatability for assessing treatment response, and being non-invasive. It can be used in centres without endomyocardial biopsy access, or in patients who refuse, or are poor candidates for biopsy.¹² The main technetium-labelled radiotracers are ^{99m}Tc-PYP, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP). These tracers preferentially bind to myocardial transthyretin amyloid fibrils, and are visualised using planar and SPECT imaging at 1 or 3 hours.⁵ With planar imaging, myocardial uptake can be graded using 2 scoring systems: semi-quantitatively by visual grading of myocardial uptake relative to rib bone uptake (grade 0: no myocardial uptake; grade 1: myocardial uptake less than rib bone uptake; grade 2: equal uptake; grade 3: myocardial uptake greater than rib bone uptake), and quantitatively using heart-to-contralateral lung (H/CL) ratio. SPECT imaging is necessary to confirm myocardial uptake, as the left ventricle blood pool can cause false-positive results on planar imaging alone.⁷

Technetium-labelled cardiac amyloid imaging has shown high diagnostic accuracy for ATTR-CM.¹⁰ In a large multicentre study by Gillmore et al., radiotracer uptake was >99% sensitive and 86% specific for

biopsy-proven ATTR-CM, with false positives largely attributed to radiotracer uptake in AL-CM. Notably, when grades ≥ 2 radiotracer uptake was combined with negative monoclonal protein testing, ^{99m}Tc-PYP scintigraphy had 100% specificity and positive predictive value for ATTR-CM.⁴ In another smaller study, Perugini et al. similarly demonstrated high sensitivity and accuracy of scintigraphy for differentiating ATTR-CM from AL-CM.¹³ Subsequently, Bokhari et al. showed that $H/CL > 1.5$ had 97% sensitivity and 100% specificity for detecting ATTR-CM.⁵ These findings were later confirmed by another multicentre study, which additionally found $H/CL \geq 1.6$ to be associated with poorer survival in ATTR-CM.¹⁴

Current recommendations for the diagnosis of ATTR-CM. Multisocietal guidelines support technetium-labelled cardiac amyloid imaging for diagnosing ATTR-CM.^{7,15} In the diagnostic algorithm, patients with suspected CA, either clinically or through typical ECG, TTE and/or CMR findings, should undergo monoclonal protein testing (sFLC and serum/urine immunofixation) and technetium-labelled cardiac amyloid imaging (Fig. 3).⁷ Endomyocardial biopsy has become reserved for cases with equivocal or conflicting clinical and imaging findings, or unavailable scintigraphy.¹² Definitive diagnosis of ATTR-CM can be made non-invasively, provided that clinical (eg. unexplained heart failure or clinical red flags with TTE and/or CMR findings suggestive of CA), laboratory (absent monoclonal proteins) and imaging criteria (positive scintigraphy with SPECT imaging; grades ≥ 2 myocardial uptake) are fulfilled.¹⁵ Following diagnosis of ATTR-CM, genetic counselling and testing should be offered to patients and families to differentiate hATTR from wtATTR.²

Importantly, AL-CM is a differential diagnosis that must be excluded. Positive scintigraphy cannot exclude AL-CM, as radiotracer uptake (grades ≥ 2) is seen in approximately 22% of biopsy-proven AL-CM.^{4,15} Consequently, monoclonal protein testing should always accompany scintigraphy.⁷ In the absence of monoclonal proteins, positive scintigraphy is diagnostic of ATTR-CM. When monoclonal proteins are present, positive scintigraphy cannot diagnose ATTR-CM. Endomyocardial biopsy with amyloid typing is hence required to assess for AL-CM.¹⁵ Finally, positive monoclonal proteins may not necessarily indicate AL-CM, as monoclonal gammopathy of undetermined significance is relatively common and can coexist with ATTR-CM, especially in older patients with wtATTR.¹³

Table 1. Typical findings of conventional cardiac investigation modalities in cardiac amyloidosis^a

Modality	Findings	Strengths	Limitations
ECG	Pseudo-infarct pattern ¹⁷	Widely available investigation ¹	Low voltage has poor sensitivity with various causes (eg. pericardial or pleural effusions, obesity, chronic obstructive lung disease) ¹⁸
	Low QRS complex voltage (limb leads $\leq 0.5\text{mV}$ and praecordial leads $\leq 1\text{mV}$; or Sokolow-Lyon index: S in $V1 + R$ in $V5/V6 \leq 1.5\text{mV}$) ¹⁸	Pseudo-infarct pattern is relatively common, seen in 47–74% cases ¹⁷	Low voltage is often a relatively late finding, hence not useful for early identification of CA ¹⁸
	Conduction abnormalities		
	Arrhythmia (eg. atrial fibrillation, atrial flutter, ventricular tachycardia) ¹⁷		
TTE	Two-dimensional imaging ⁷ - Increased LV wall thickness ($>1.2\text{cm}$) - Biatrial enlargement - Impaired diastolic and systolic function in early and advanced stages, respectively - Small pericardial effusion	Widely available, cost-effective and quick to perform by bedside ¹	Lacks specificity for CA, especially in early stages ¹²
	Strain imaging ¹² - Relative apical-sparing pattern of global LS (apical LS/average of combined mid and basal LS >1.0)	Relative apical sparing of LS has good sensitivity (82%) and specificity (93%) for CA ¹⁹	Typical features only most prominent in advanced disease ¹²
		Longitudinal LV strain imaging can distinguish CA from other causes of LVH (eg. hypertension, HCM) ¹⁰	Cannot definitively diagnose, nor distinguish between CA subtypes ¹²
CMR	Increased LV wall thickness ⁷	High-resolution structural and functional assessment ⁷	CMR cannot definitively diagnose, nor distinguish between CA subtypes ¹²
	LGE - Diffuse subendocardial or transmural LGE pattern ⁷	Can differentiate CA from other causes of LVH ⁷	LGE - Not easily quantifiable and unreliable for tracking disease progression ¹²
	Parametric mapping ^{7,12} - Native T1 mapping (pre-contrast): increased values - ECV mapping: increased values, with $\text{ECV} > 0.40$ highly suggestive - T2 mapping: increased values	LGE - Enables tissue characterisation through LGE, which has high sensitivity (80%) and specificity (94%) for CA ^{7,20} - LGE is a significant predictor of prognosis and mortality in CA ^{7,12}	Limitations regarding gadolinium contrast use in severe renal impairment ⁷
		Native T1 mapping ^{7,12} - High diagnostic accuracy, with 92% sensitivity and 91% specificity for CA - Quantitative measure and indicator of amyloid infiltration, which correlates with markers of systolic and diastolic dysfunction - Useful when contrast administration is contraindicated	Parametric mapping ^{7,12} - Lack of reproducibility when different scanners or magnetic field strengths used - Heterogeneity in reported reference ranges - T2 more variable than native T1 measures, and less extensively studied in CA compared to native T1 and ECV
		ECV mapping ¹² - Surrogate marker of amyloid infiltration, and strong predictor of outcomes - Can potentially detect early disease (before LGE findings present), and track disease progression and treatment response	
		T2 mapping - Specific marker for myocardial oedema, which is present in CA ¹²	

CA: cardiac amyloidosis; CMR: cardiac magnetic resonance; ECG: electrocardiogram; ECV: extracellular volume; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LS: longitudinal strain; LV: left ventricle; LVH: left ventricular hypertrophy; TTE: transthoracic echocardiogram.

^a Superscript numbers: Refer to reference numbers in REFERENCES

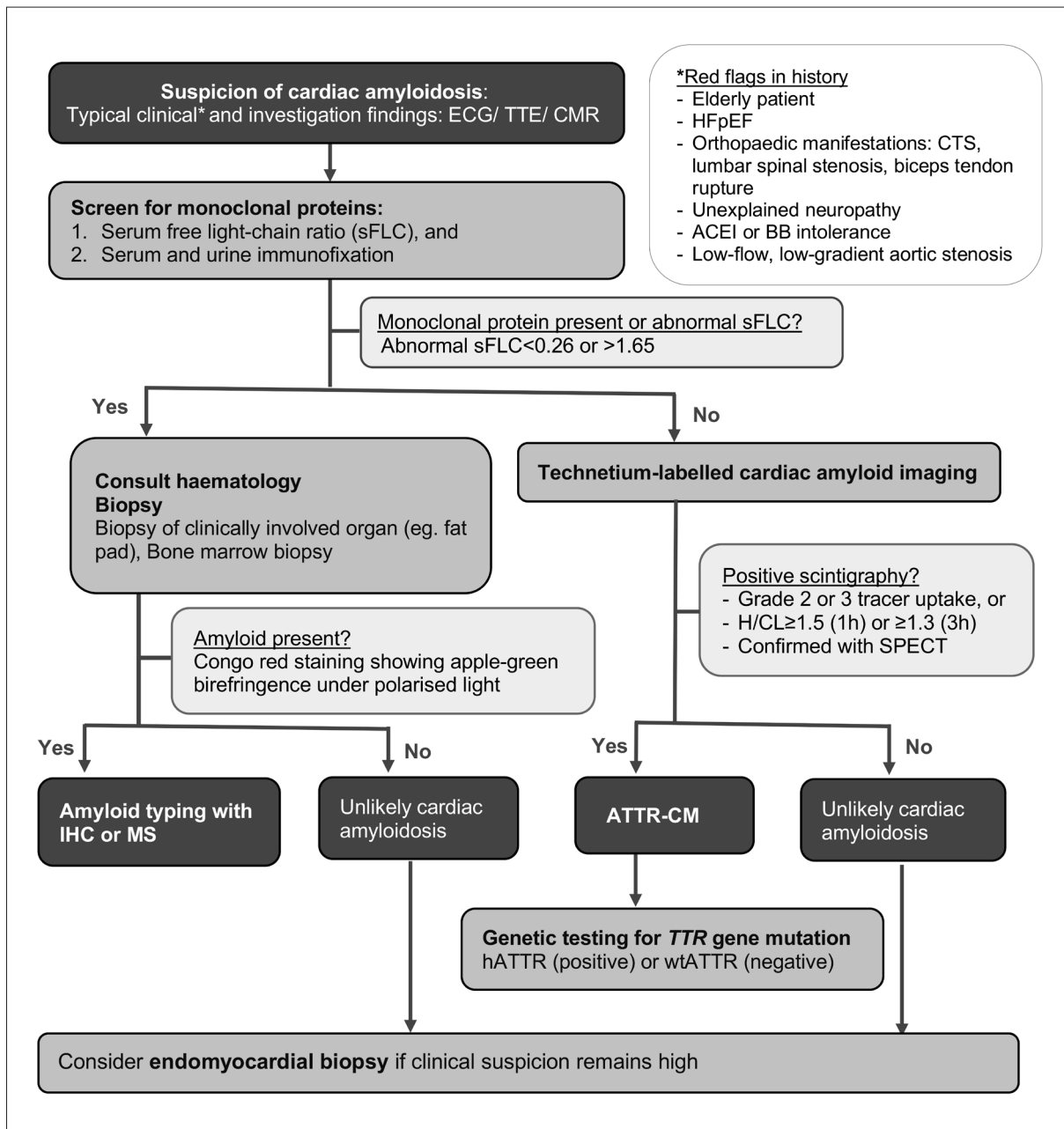


Fig. 3. Diagnostic algorithm for cardiac amyloidosis based on recent multisocietal guidelines. Definitive diagnosis of ATTR-CM can be established with a combination of positive ^{99m}Tc-PYP scintigraphy scan and negative monoclonal protein testing (adapted from Maurer et al.,¹ Hanna et al.,¹⁵ Dorbala et al.⁷).

ACEI: angiotensin-converting enzyme inhibitor; ATTR-CM: transthyretin amyloid cardiomyopathy; BB: beta blocker; CMR: cardiac magnetic resonance; CTS: carpal tunnel syndrome; ECG: electrocardiogram; hATTR: hereditary transthyretin amyloidosis; H/CL: heart-to-contralateral lung ratio; HFpEF: heart failure with preserved ejection fraction; IHC: immunohistochemistry; MS: mass spectrometry; sFLC: serum free light chain ratio; SPECT: single-photon emission computed tomography; TTE: transthoracic echocardiogram; TTR: transthyretin; wtATTR: wild-type transthyretin amyloidosis.

Future directions. The ^{99m}Tc-PYP scintigraphy service in Singapore for diagnosing ATTR-CM has shown potential for diagnosing ATTR-CM in patients with TTE and/or CMR findings suggesting CA. Scintigraphy and diagnostic recommendations have allowed our patient to be diagnosed with ATTR-CM

non-invasively. With the recent establishment of a ATTR amyloidosis registry in Singapore to characterise epidemiology and disease course; response to treatment approaches; and factors contributing to delayed diagnoses, clinicians will gain a better understanding of ATTR amyloidosis to optimise diagnostic and

therapeutic strategies in ATTR-CM.¹⁶ Positive scintigraphy can definitively diagnose ATTR-CM, following AL-CM exclusion. Diagnosing CA requires a high index of clinical suspicion and combined multimodality imaging and multidisciplinary approach, involving cardiologists, neurologists, haematologists, nuclear radiologists, pathologists and geneticists. With clearer diagnostic guidelines and non-invasive diagnostic modalities now available, early detection of ATTR-CM has become increasingly possible and may translate into improved patient outcomes.

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