The Trojan Horse - A Case of Transthyretin Cardiac Amyloidosis Diagnosed Via Multi-Modality Imaging

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DISCLOSURE: None

Abstract

BACKGROUND: Observational studies have increasingly reported transthyretin amyloid cardiomyopathy (ATTR-CM) as an under-recognized cause of heart failure. We report the first ATTR-CM diagnosed via multi-modality imaging in the Philippines signifying an important milestone in recognition and management of this formerly believed rare disease, locally. Utilization of non-invasive imaging such as echocardiography, cardiac MRI and technetium-99m pyrophosphate scintigraphy (PYP) demonstrates the potential for accurate diagnosis as well as timely and appropriate treatment strategies.

DISCUSSION: An 81/M Filipino with a history of carpal tunnel surgery, post-percutaneous coronary intervention (PCI), had three months' history of refractory heart failure symptoms despite optimized medical treatment. His 2D-echo showed an ejection fraction (EF): 45%-50%, increased left ventricular (LV) posterior wall thickness with mild basal inferior wall hypokinesia and ECG: atrial fibrillation with low voltage. Speckle tracking imaging showed average global longitudinal strain: - 6.5% with cherry-on-top pattern on polar strain map. Cardiac MRI demonstrated diffuse late gadolinium enhancement from endocardial to transmural layers of biventricular and biatrial walls, highly suggestive of cardiac amyloidosis (CA). Light-chain amyloidosis was excluded by negative serum/urine protein electrophoresis/immunofixation. Tc-99m PYP scan revealed greater myocardial-than-bone uptake with a Perugini score 3 and calculated heart-to-contralateral ratio of 1.7. Congestion was controlled with intravenous loop diuretics and he was discharged stable with metoprolol succinate, dapagliflozin and apixaban. At the time of paper submission, he is currently being evaluated for tafamidis treatment.

CONCLUSION: The case highlighted the advantage of multi-modality imaging for noninvasive yet accurate identification of the disease. A tailored approach is required in slowing the disease progression and improving outcomes.

INTRODUCTION

Cardiac amyloidosis (CA), a rare condition marked by progressive extracellular accumulation of amyloid fibrils in the myocardium leading to restrictive cardiomyopathy, primarily affecting the elderly.[1,2] According to published literature, prevalence of CA is estimated to be fewer than 5 per 10,000 individuals, with data coming mostly from inpatient or outpatient claims and/or data registries.[1] Formerly thought to be rare, the clinical prevalence and associated prognostic implications in the general population remain poorly understood due to encountered diagnostic and treatment dilemmas.[1,2] Clinical presentation primarily revolves around diastolic dysfunction and heart failure with preserved ejection fraction; however, in advanced stages, systolic dysfunction and heart failure with reduced ejection fraction may ensue.[2] Amyloid deposits in the atrium and conduction system may result in the occurrence of atrial arrhythmias, conduction system abnormalities and consequently, syncope or presyncope.[2,3] Effort angina can occur due to small vessel disease despite angiographically normal epicardial coronary vessels.[3]

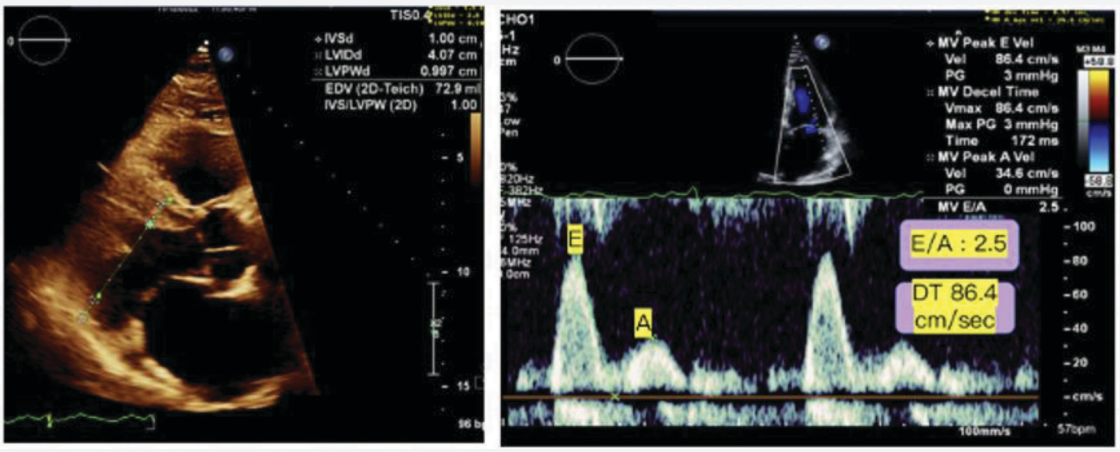

Figure 1. Two-dimensional echocardiogram demonstrating mild concentric left ventricular hypertrophy, thickened mitral and aortic valve leaflets (left image) and E/A ratio of 2.5 consistent with restrictive filling pattern (right image).

Recent studies have shed light on transthyretin amyloid cardiomyopathy (ATTR-CM) as a distinct and frequently overlooked subtype of heart failure that resists conventional heart failure treatments.[2,3] While endomyocardial biopsy is considered the definitive diagnostic modality, noninvasive imaging techniques have now opened doors to an accurate diagnosis of ATTR-CM precluding the need for invasive modalities.[2,4] In the Philippines, where access to advanced medical resources can be limited in some regions, diagnosing complex heart conditions like ATTR-CM using non-invasive modalities is a game-changer. Careful review of literature suggests that this is the first Philippine report of a noninvasive diagnosis of ATTR-CM using multi-modality imaging.

Case Presentation

The patient is an 81-year-old Filipino male, obese, pre-morbid with good functional capacity, hypertensive, stable coronary artery disease, post-percutaneous coronary intervention (PCI) x 1 stent (left anterior descending artery, 2016), post-cerebrovascular infarct with minimal left-sided residuals who came in for a three months' history of progressive exertional dyspnea. He had previous mild COVID-19 infection four months prior to consultation, recently diagnosed mild fatty liver detected on imaging with a provisional diagnosis of non-alcoholic fatty liver disease and history of carpal tunnel surgery more than 30 years ago. He denied known thyroidal illness, diabetes, asthma, or chronic obstructive pulmonary disease. Family history revealed pre-disposition to hypertension and diabetes. There was no history of early cardiac death or malignancy. He is a nonsmoker, an occasional alcoholic beverage drinker and a retired army general.

Three months prior to initial consultation, he noted onset of shortness of breath and easy fatigability during his regular daily morning walk of two street blocks, subsequently progressing to less than 300 meters after two weeks. This was accompanied by palpitations described as irregular heartbeat, rotatory dizziness and lightheadedness during positional changes or when alighting from the car. At this time, he denied symptoms of chest pain, orthopnea, paroxysmal nocturnal dyspnea or leg swelling. Due to persistent palpitations and heart rate of 120 beats/minute measured using a home pulse oximeter, he sought consultation at a primary outpatient clinic where atrial fibrillation was noted on a 12-lead electrocardiogram prompting the initiation of oral amiodarone at 200 mg/tab three times daily by the primary care physician. He was advised cardiology consult for further work-up, hence a referral to our institution.

During physical examination, he preferred a left lateral decubitus position and showed mild shortness of breath during conversation. Vital signs were within normal limits. There were no crackles but there were occasional expiratory wheezes on dry forceful coughing. Precordium was adynamic with no heaves/thrills and the point of maximal impulse was at the fifth intercostal space lateral to the mid clavicular line. Heart sounds showed distinct S1 heart sounds, no S3/S4, no murmurs and an irregularly irregular rhythm. Prominent features of right-sided heart failure were noted: jugular vein distention, globular and tympanitic abdomen with dullness on flanks and bilateral lower extremity edema. Pulses were full and equal.

Initial workup showed normal complete blood count, renal and liver enzyme panels, elevated NT-proBNP of 1695.8 pg/mL (Ref: 0-450 pg/mL), high sensitivity troponin I of 24 ng/mL (N: <25 ng/mL) and atrial fibrillation with low-voltage QRS complexes, on 12-lead ECG. Transthoracic echocardiogram demonstrated an estimated ejection fraction of 45%-50%, mild hypokinesia of basal and mid segments, mild concentric left ventricular hypertrophy, bi-atrial dilatation, thickened mitral and aortic valve leaflets, mildly elevated pulmonary pressures and E/A ratio of 2.5 (Figure 1). An initial working impression of decompensated heart failure with mildly reduced ejection fraction (HFmrEF, 47%) probably secondary to cardiac dysrhythmia (atrial fibrillation) and a possibility of COVID-19 myocarditis given the history of previous mild infection were considered at that time.

Heart failure regimen was started with sacubitril-valsartan, spironolactone, dapagliflozin, furosemide, apixaban and tapering doses of oral amiodarone. On an initial follow-up after a week, there was noted improvement of exertional dyspnea, bipedal edema and non-recurrence of palpitations

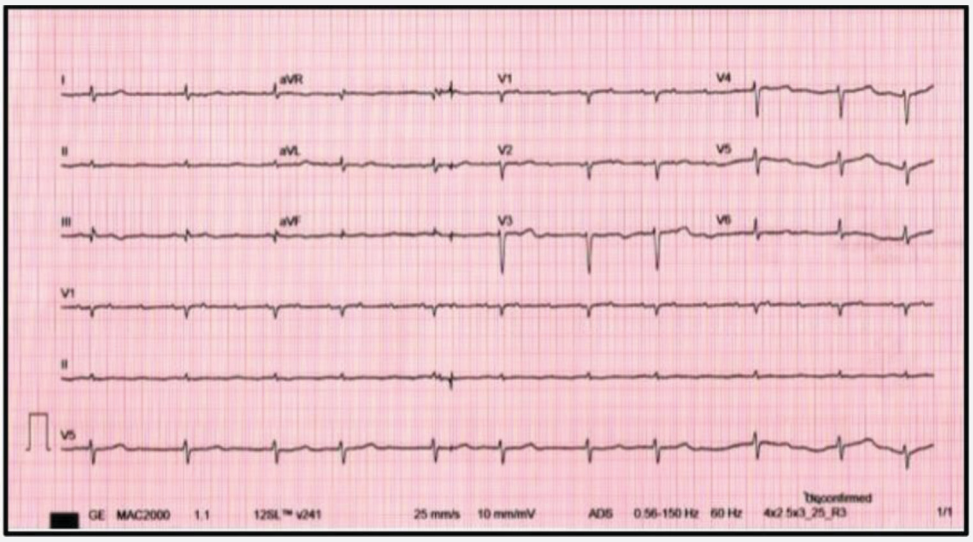

Figure 2. Twelve-lead electrocardiogram showing atrial fibrillation with low voltage QRS complexes.

with recorded average heart rate of 80 beats/minute at home. Spironolactone and furosemide were eventually discontinued due to recorded low average blood pressure of 90/60 mmHg from a previous baseline usual of systolic blood pressure (SBP) 110-120 mmHg.

After a month, he was re-admitted due to recurrence of previously mentioned congestive symptoms (exertional dyspnea and bipedal edema) and concomitant community-acquired pneumonia treated with antibiotics and nebulization. Furosemide was re-introduced and metoprolol added to medical therapy, which led to clinical improvement and subsequent hospital discharge after five days. After two weeks, there was recurrence of exertional dyspnea now accompanied by two-pillow orthopnea, bloatedness, abdominal enlargement, bipedal edema and a trend of decreasing urine output to less than one liter per day leading to a most recent admission.

Complete blood count and blood urea nitrogen trends remained normal, but creatinine level was observed to have been gradually increasing over the past month from 1.1 to 1.7 mg/dL. ECG remained in atrial fibrillation with low voltage QRS complexes (Figure 2). NT-proBNP levels remained persistently high at 3386 pg/mL while Troponin I level was borderline high at 60.1 ng/mL (N: <25 ng/mL). Liver function tests revealed nonspecific and mildly elevated bilirubin levels (total bilirubin 1.4 mg/dL, conjugated bilirubin 0.5 mg/dL, unconjugated bilirubin 0.9 mg/dL), normal albumin (4.2 mg/dL) and transaminases (SGPT 20 mg/dL and SGPT 26 mg/dL). Whole abdominal ultrasound revealed mild fatty liver, slightly enlarged prostate and a benign cyst with physiological findings for the rest of the abdominal organs.

Holter monitoring showed a basic rhythm in atrial tachycardia, low-frequency monomorphic ventricular ectopic beats and symptoms of shortness of breath coinciding with runs of atrial tachycardia. Chest x-ray displayed resolution of previous bilateral pneumonia with evidence of cardiomegaly and mild

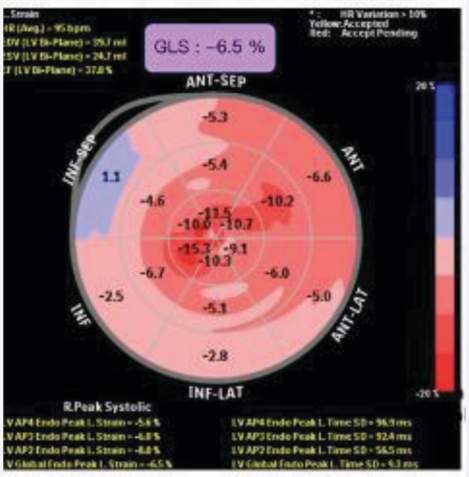

Figure 3. Speckle-tracking echocardiography shows markedly reduced global longitudinal strain (GLS) of -6.5%, indicating subclinical LV systolic dysfunction. The polar strain map demonstrates apical sparing with a characteristic "cherry-on-top" pattern.

venous congestive changes. A repeat 2D echocardiogram did not show significant interval change from baseline. Speckle tracking imaging revealed evidence of severely reduced (subclinical) left ventricular systolic dysfunction with an average global longitudinal strain (GLS) of -6.5% and a cherry on top pattern evident in the polar strain map, suggestive of apical sparing (Figure 3).

With clinical signs, symptoms and diagnostic results raising red flags for the possibility of cardiac amyloidosis, a cardiac magnetic resonance imaging (Figure 4) was done which revealed global hypokinesia, diffuse/global endocardial to transmural late gadolinium enhancement of the biventricular and bi-atrial myocardial segments with elevated native T1 map values of 1139 +/- 34 ms and increased extracellular volume of

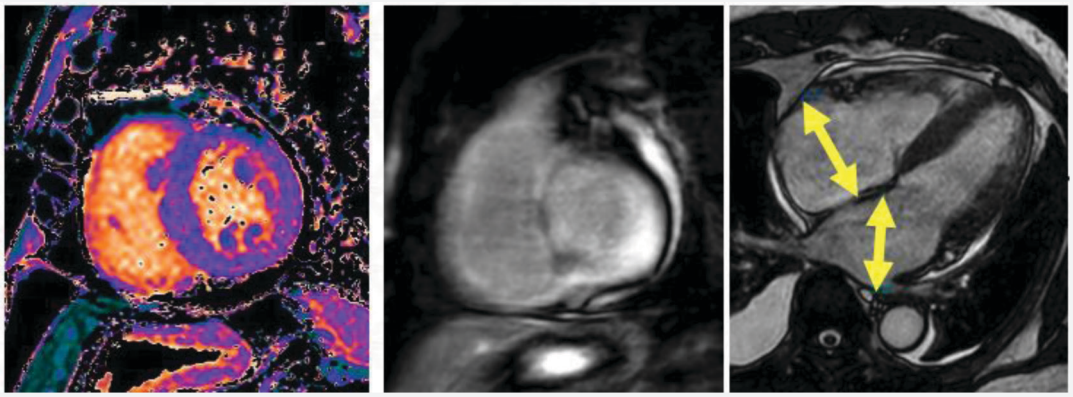

Figure 4. Left image shows diffuse elevation of native T1 map values and markedly elevated calculated extra-cellular volume (ECV); middle image showing global endocardial to transmural late gadolinium enhancement of the left ventricular walls, right ventricular and both atrial walls; and right image showing dilated left and right atria.

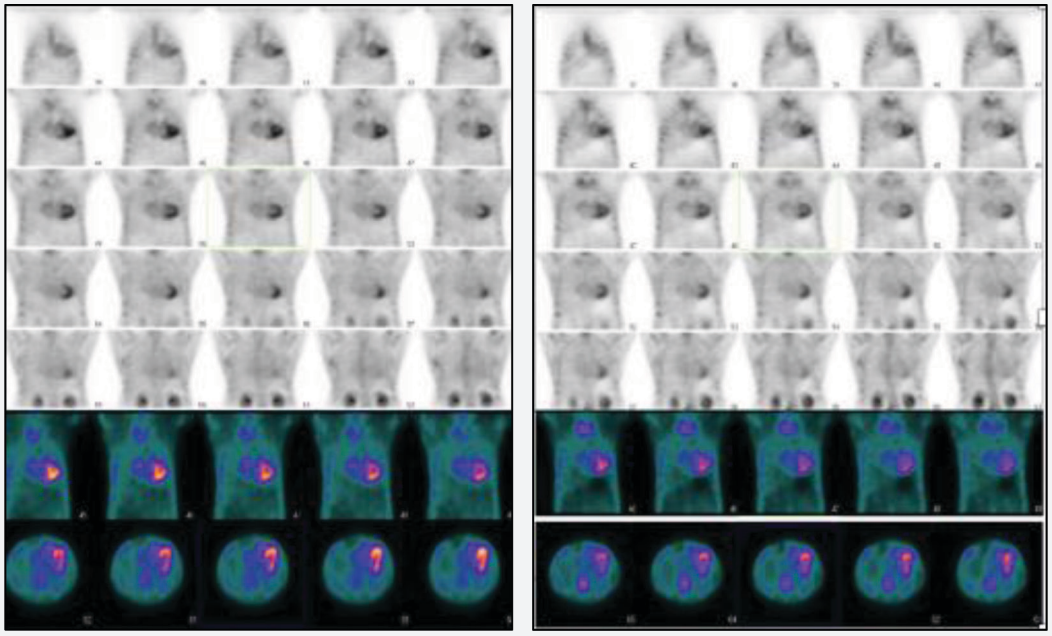

Figure 5. Overview tomographic acquisition done with the planar and SPECT views, taken 1 hour (left image) and 3 hours (right image) after injecting 15.92 mCi of TC-99m PYP showing a greater myocardial uptake with mild to absent rib uptake and PERUGINI score of 3.

42%-50%. Both atria and major pulmonary arteries were dilated. The left ventricle was normal in size with adequate wall thickness and mildly reduced systolic function, while the right ventricle displayed mildly thickened walls with normal systolic function.

Serum and urine electrophoresis with immunofixation were negative, hence ^{99m}Technetium pyrophosphate scintigraphy was performed using planar and single-photon emission computed tomography (SPECT) views at 1 and 3 hours post-injection (Figure 5) at 15.92 mCi showing a greater myocardial uptake with a Perugini score of 3 and calculated heart-to-contralateral ratio of 1.7 on both scans (Figure 6), strongly suggesting transthyretin cardiac amyloidosis. Extra-cardiac findings included unremarkable kidneys and degenerative changes in sternoclavicular joints.

The patient was referred to heart failure service and congestion was controlled with intravenous loop diuretic (furosemide) while closely monitoring renal parameters. Urine output was adequate throughout the hospital stay. He was eventually discharged stable with oral furosemide, metoprolol succinate, dapagliflozin, apixaban and tapering doses of amiodarone. He was enrolled to cardiac rehabilitation and tolerated prescribed exercises well.

Following the optimization of loop diuretics and cardiac rehabilitation, there were no noted recurrences of palpitations

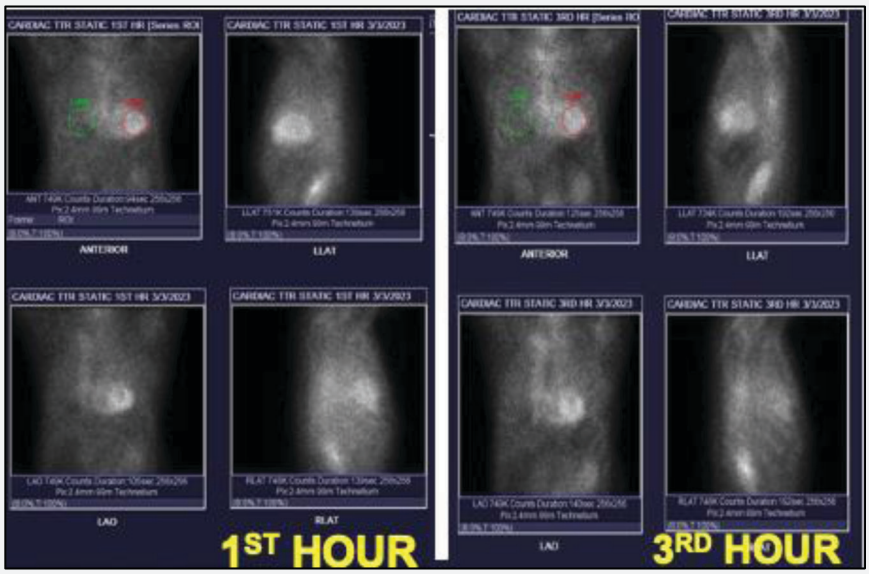

Figure 6. SPECT images showing diffuse myocardial tracer uptake. The calculated heart/contralateral chest ratio (HCR) was 1.7 on both the 1st and 3rd hour scan which strongly suggest TTR cardiac amyloidosis

and congestive episodes. He is currently tolerating a once daily 200 mg of oral amiodarone and twice daily apixaban with no bleeding episodes. Beta-blocker (metoprolol) was eventually withheld due to noted borderline average systolic blood pressure level of 85-90 mmHg at home from a previous baseline average blood pressure of 110/70 mmHg. Close monitoring of creatinine, blood urea nitrogen and NTpro-BNP levels are also being implemented on an outpatient basis.

Repeat 24-hour Holter monitoring still showed atrial fibrillation with low voltage QRS complexes but with absence of bradycardia or any form of ventricular arrhythmias. Continued participation in cardiac rehabilitation exercises were reinforced and the patient is currently on his Phase III rehabilitation. On three months' follow-up, he remains functional Class II and is currently being evaluated for the use of tafamidis. The patient and his family members were also referred for genetic screening and counseling at the time of this case submission.

CASE DISCUSSION

We report an 81-year-old elderly male who initially presented with atrial arrhythmia and subsequent recurrent admissions for persistent and progressive heart failure symptoms refractory to standard guideline-directed medical therapy (GDMT) optimization. He manifested red flags of a possible cardiac amyloidosis on history, physical exam, electrocardiogram and serum biomarkers. By employing a combination of imaging techniques: echocardiography, cardiac magnetic resonance imaging (CMR) and nuclear scintigraphy the patient received a clear diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) signifying how multi-modality imaging is indispensable in expediting a non-invasive diagnostic process with more precision and accuracy, even in a resource-limited area like the Philippines. This achievement carries the potential to provide timely intervention and improved outcomes for patients with this phenotype of cardiac disease.

Initially, a transthoracic two-dimensional echocardiogram was utilized as the first-line imaging tool to identify the presence of ventricular wall hypertrophy, systolic dysfunction, bi-atrial dilatation and restrictive pattern on Doppler studies.[3,5] Strain imaging helped provide diagnostic clues through findings of an abnormal left ventricular global longitudinal strain and apical sparing with a 'cherry on top' appearance, which is considered to be the most sensitive and specific finding for cardiac amyloidosis.[6] Cardiac magnetic resonance imaging through its high quality resolution allows for tissue characterization of increased extracellular T1 mapping volumes and late gadolinium enhancement in both early diffuse subendocardial or late transmural myocardial involvement.[7] Although a combination of these three modalities raise the imaging red flags for cardiac amyloidosis, the specific type can only be detected through a more disease-specific modality tool in the form of Technetium-99m pyrophosphate (99mTc-PYP) scintigraphy, which when positive (Positive: grade 2—myocardial uptake equal to rib uptake or grade 3—myocardial uptake greater than rib uptake with mild/absent rib uptake) plus an uptake ratio between the heart-to-contralateral lung area of ≥1.5 at one hour, in the context of a negative monoclonal light chain screen, provides additional sensitivity and specificity. This further confirms the diagnosis of ATTR-CM similar to the case of our patient.[8-9]

ATTR-CM is a complex and underdiagnosed cause of heart failure associated with significant morbidity and mortality owing to its ability to mimic other cardiac conditions. It remains a diagnostic and treatment challenge requiring increased disease awareness and heightened index of suspicion among patients who remain resistant to conventional heart failure treatment.[2,3,9] Early recognition and timely interventions are pivotal in improving symptoms and increasing survival. It does not

typically respond well to conventional heart failure pillars despite attempts for optimization as has been seen in our patient's case because the underlying pathophysiology differs from other forms of heart failure.[2] Hence a tailored approach is required in slowing disease progression and improving clinical outcomes. Loop diuretics and guideline-directed medical therapy remain the cornerstones of treatment together with a disease-modifying targeted agent tafamidis, a transthyretin stabilizer, which is the only medication to have demonstrated its efficacy in reducing all-cause mortality and cardiovascular-related hospitalizations in patients with ATTR cardiomyopathy.[2,3,10] Other medications are still undergoing trial investigations for treatment efficacy as of this time of writing.[10]

CONCLUSION

Our report highlighted the advantage of multi-modality imaging for noninvasive yet accurate identification of ATTR-CM in an elderly Filipino male with recurrent admissions for persisting and progressive heart failure symptoms resistant to GDMT optimization who manifested early clinical and diagnostic red flags of the said disease.

The remarkable advancement in noninvasive diagnostic tools has ushered in a new era in the diagnosis of ATTR-CM as an emerging phenotype of heart failure, which in turn can guide timely therapeutic interventions. We consider this as a pioneering milestone in the Philippines that underscores several key elements critical to the advancement of diagnosing and treating this complex condition.

In summary, cardiac amyloidosis is a complex and often underdiagnosed cause of heart failure associated with significant morbidity and mortality. Differentiating between its various forms is critical for both prognosis and management, and noninvasive multi-modality imaging diagnostic techniques, especially 99mTc-PYP scintigraphy, have revolutionized the approach to diagnosis. With effective and timely treatments emerging in recent decades, there is a pressing need to increase awareness of this condition to improve early recognition of disease, patient outcomes and survival.

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