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CASE REPORT

Early and aggressive presentation of wild-type transthyretin amyloid cardiomyopathy: A case report

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Abstract

BACKGROUND

Wild-type transthyretin amyloidosis (ATTRwt) is the most common form of transthyretin amyloid cardiomyopathy, occurring mostly over age of 60 years (mean age of 80 years). Mean survival without treatment is 3.6 years, making early detection imperative. We report an unusual case of a 58-year-old patient with ATTRwt cardiomyopathy requiring heart transplantation.

CASE SUMMARY

A 58-year-old male presented with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. Approximately ten months before this clinical presentation, the patient had first received a diagnosis of heart failure with reduced ejection fraction (EF) of 15% to 20%. The patient was started on appropriate guideline-directed medical therapy with only mild improvement in his EF. Upon further investigation, echocardiogram, technetium pyrophosphate scan (Tc PYP), and cardiac magnetic resonance imaging (cMRI) suggested a diagnosis of amyloidosis, and ATTRwt was subsequently confirmed with native heart tissue biopsy, congo red staining, liquid chromatography-tandem mass spectrometry, and genetic testing. The patient was successfully treated with heart transplantation and is doing well post-transplant.

CONCLUSION

Wild-type ATTR amyloidosis should be kept on differentials in all patients (even less than 60 years old) with non-ischemic cardiomyopathy, especially in the setting of increased ventricular wall thickness and other classic echocardiogram,

cMRI, and Tc PYP findings. Early diagnosis and management can be consequential in improving patient outcomes.

Key Words: Wild-type; Transthyretin; Amyloidosis; Young; Heart failure; Heart transplant; Case report

Core Tip: Wild-type transthyretin amyloidosis (ATTRwt) continues to be an underdiagnosed condition. Although rare in patients under 60 years of age, physicians should include the condition in their differential as early diagnosis and early management can impact patient outcomes. Physicians should be aware of the findings on non-invasive testing that supports ATTRwt. Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, biatrial enlargement, apical sparing on longitudinal strain and signs of elevated filling pressures and restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities). Cardiac magnetic resonance imaging classically shows late gadolinium enhancement. A technetium pyrophosphate study shows an increased heart-to-contralateral ratio and increased Perugini visual grade.

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INTRODUCTION

Amyloid deposition is commonly found in aging populations. Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative, progressive, and potentially fatal cardiomyopathy that is caused by extracellular deposition of misfolded transthyretin-derived insoluble amyloid fibrils in the myocardium [1]. Wild-type transthyretin amyloidosis (ATTRwt) is the most common type of ATTR-CM[2]. ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old[2,3]. A retrospective review of 360 patients diagnosed with ATTRwt showed that 93% of the patients with an antemortem diagnosis were Caucasian males greater than 70 years old [4]. Another retrospective review showed only a handful of patients that were diagnosed with ATTRwt in their forties[2]. A recent case of ATTRwt was identified in a 34-year-old male in India[5]. Our case report highlights an unusual case of ATTRwt cardiomyopathy presenting in a relatively young, 58-year-old patient with end stage heart failure (HF) symptoms.

CASE PRESENTATION

Chief complaints

Progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea.

History of present illness

A 58-year-old Caucasian man presented to the heart failure clinic with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. On review of symptoms, the patient had no palpitations, carpal tunnel symptoms, neuropathy, or back pain.

History of past illness

Approximately ten months before this clinic presentation, the patient had first received a diagnosis of HF with reduced ejection fraction (EF) of 15% to 20%. At that time, he underwent left heart catheterization which showed no obstructive coronary artery disease. The patient was started on appropriate guideline-directed medical therapy (GDMT) with only mild improvement in his EF. The patient was followed in the heart failure clinic and had recurrences of acute on chronic heart failure episodes. Unfortunately, due to borderline hypotension, he was unable to reach maximum doses of GDMT which ultimately had to be stopped.

Personal and family history

His past medical history was significant for non-ischemic cardiomyopathy (EF 15%-20%), left ventricular hypertrophy, implantable cardioverter defibrillator in situ, atrial fibrillation, moderate to severe mitral regurgitation, prior left atrial thrombus, and prior tobacco use disorder. Other than atrial fibrillation, he had no significant history of other arrhythmias. He worked as a construction worker. His family history was notable only for his father who underwent a coronary artery bypass graft at age 59 years.

Physical examination

Physical exam was notable for the patient appearing well-nourished; however, jugular venous distension, a holosystolic murmur consistent with known mitral regurgitation, abdominal distention, and bilateral lower extremity edema were present. Vital signs depicted borderline systolic blood pressure of 95/70 mmHg with a mean of 78 mmHg, normal heart rate, normal respiratory rate and saturation on room air, and normal temperature.

Laboratory examinations

The patient's presentation to the clinic with progressively worsening heart failure symptoms prompted admission to the hospital.

Imaging examinations

Electrocardiogram showed AV-paced complexes and low voltage in both limb and precordial leads. He underwent right heart catheterization which was consistent with cardiogenic shock with central venous pressure 18 mmHg, polymeraseacidicprotein 43/25 with mean of 32 mmHg, pulmonary capillary wedge pressure 23 mmHg, fick cardiac output of 4.6 L/min, and cardiac index of 2.1 L/min/m^2. Transthoracic echocardiogram demonstrated a reduced EF of 10%, concentric hypertrophy with interventricular septal thickness of 1.9 cm and posterior wall thickness of 1.4 cm, moderately reduced right ventricle (RV) function with a dilated RV, moderate mitral regurgitation, and trivial pericardial effusion (Figure 1A-C). Diastology additionally showed an E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time of 141 ms (Figure 1D). The increased myocardial wall thickness on echocardiogram as well as parameters consistent with restrictive pathology led to a detailed amyloidosis workup. A technetium pyrophosphate scan (Tc PYP) showed a heart/contralateral lung ratio of 1.77 and visual grade 3 as per the Perugini scale, highly suggestive of cardiac amyloidosis (Figure 2). Cardiac magnetic resonance imaging (cMRI) showed global myocardial delayed hyperenhancement and failure to null most likely due to cardiac amyloidosis (Figure 3). Amyloid light chain amyloidosis work-up including kappa and lambda light chains levels, serum protein electrophoresis, and urine protein electrophoresis was unremarkable. The native heart tissue pathology showed diffuse amyloid deposits between the myocardial fibrils, confirmed on Congo red staining (Figure 4). Liquid chromatography-tandem mass spectrometry was also performed on peptides extracted from the Congo red-positive areas of tissue and was consistent with ATTR-CM. The spectrometry did not detect an amino acid sequence abnormality in the transthyretin protein, suggesting ATTRwt as the diagnosis. Genetic testing was performed and was unremarkable, showing two variants of unknown significance, c.3262-3C>G in the LAMA4 gene and p.K963E in the RBM20 gene. Screening of the TTR gene was unremarkable ruling out hereditary TTR cardiomyopathy.

FINAL DIAGNOSIS

In conclusion, the history, exam, and workup, including genetic testing, confirmed ATTRwt as the final diagnosis.

TREATMENT

The patient was initially supported with inotropes; however, given the concern for end-stage cardiac amyloidosis and risk for progressive cardiogenic shock in the setting of biventricular failure, orthotopic heart transplant evaluation was initiated. He was deemed a suitable candidate for heart transplantation by our multidisciplinary transplant committee. The patient was maintained on milrinone and epinephrine for inotropic support until he underwent transplantation.

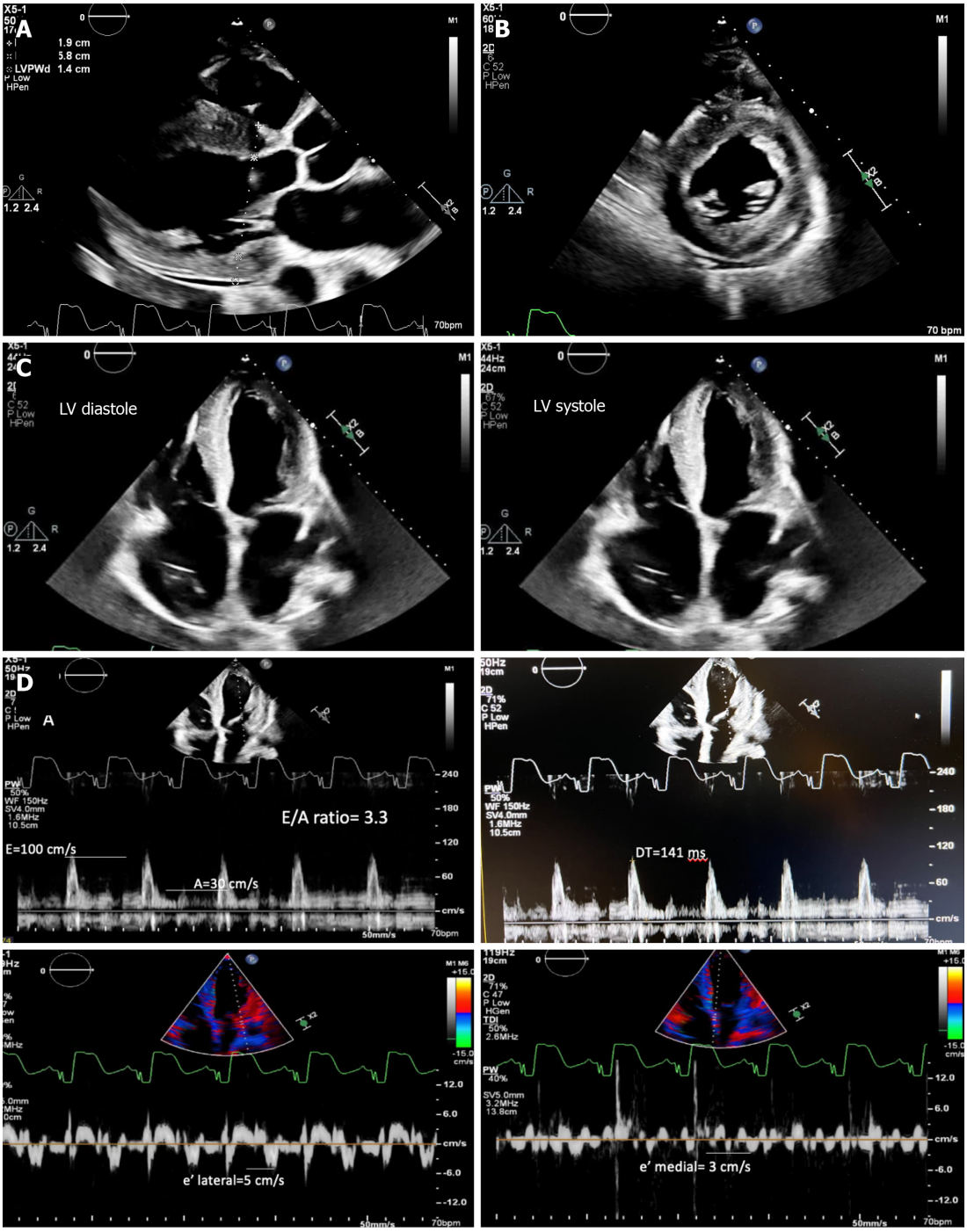

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Figure 1 Transthoracic echocardiography. A: Parasternal long axis of left ventricle shows concentric hypertrophy with an increased interventricular septum and posterior wall thickness and a trivial pericardial effusion; B: Parasternal short axis showing thickened walls of the left ventricular myocardium; C: Four-chamber view showing lehigh valley diastole and systole; D: E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time time of 141 ms, consistent with restrictive pathology. LV: Lehigh valley.

OUTCOME AND FOLLOW-UP

Unfortunately, a few days following the transplant, the patient had pericardial bleeding with tamponade followed by successful evacuation of blood. He had no other postoperative complications and was discharged home on postoperative day eight. The patient has followed closely in the heart failure clinic and is doing very well post-transplant.

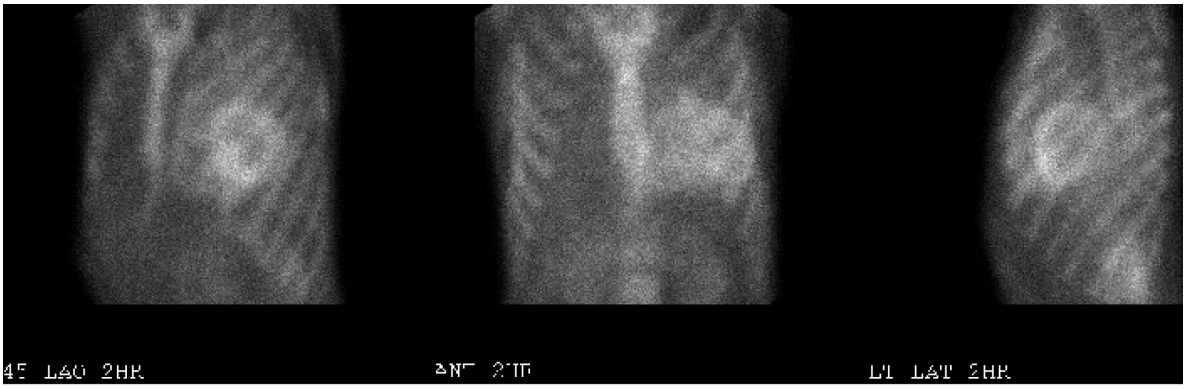

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Figure 2 Technetium pyrophosphate scan showing increased myocardial uptake of tracer (visual grade 3) suggestive of transthyretin-mediated cardiac amyloidosis.

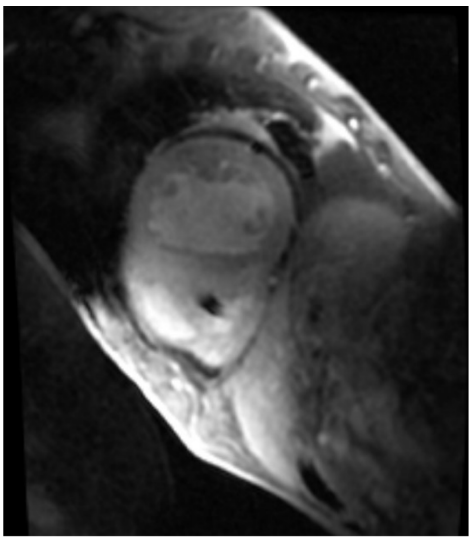

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Figure 3 Cardiac magnetic resonance imaging showing delayed global hyperenhancement and failure to null likely due to cardiac amyloidosis.

DISCUSSION

ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old. Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential. Our patient not only developed ATTRwt below the age of 60, but also within 1 year of the patient's HF diagnosis that rapidly progressed to end-stage cardiomyopathy. After review of the literature, it remains uncertain why some individuals may be predisposed to developing ATTRwt at an earlier age. However, early diagnosis can lead to improved management and outcomes as ATTRwt continues to be an underdiagnosed condition.

Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, valve thickening, atrial enlargement, apical sparing on strain and signs of elevated filling pressures, restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities)[6]. In patients with ATTR-CM amyloidosis, late gadolinium enhancement (LGE) is almost always present on cMRI. Studies have shown with LGE cMRI, an inability to suppress or "null" the myocardial signal or the presence of diffuse subendocardial or transmural enhancement patterns, which suggests amyloidosis with a sensitivity and specificity that approach 85%-90%[7,8]. cMRI also shows elevated native T1 values and increased extracellular volume[7]. Bone scans using Tc PYP scan show increased ^{99m}Tc-PYP uptake in the heart of patients with amyloid infiltration leading to increased heart-to-contralateral ratio and visual grading[3]. The non-biopsy diagnosis of ATTR-CM with TcPYP scan (first described by Gillmore *et al*[9]) is now widely accepted and has replaced the historical endocardial biopsy provided AL amyloidosis is ruled out.

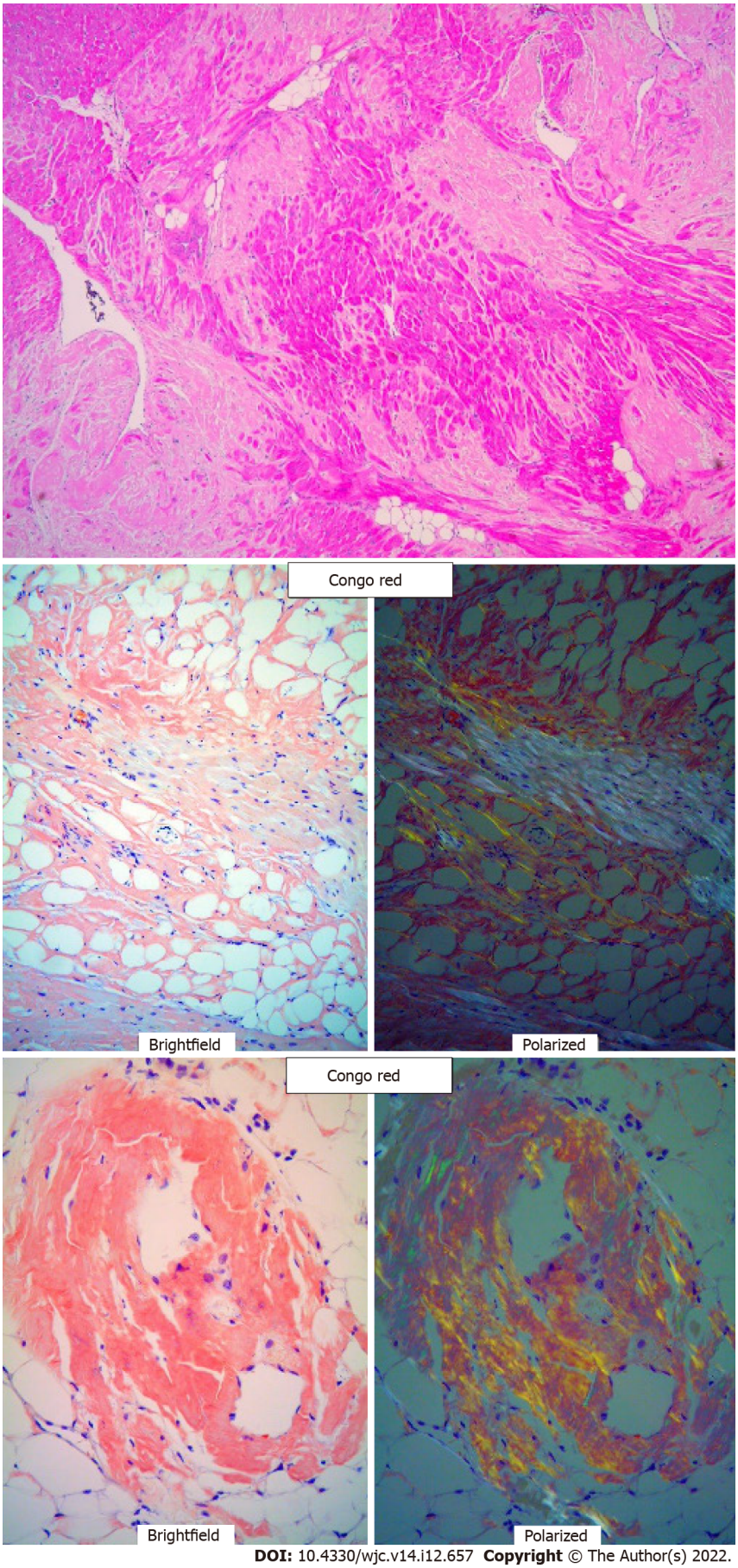

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Figure 4 Native heart tissue pathology on H and E staining showing extracellular amyloid deposits, followed beneath by Congo red

staining showing apple green refringence of amyloid deposits (100× magnification).

In ATTR-CM, several new pharmaceutical therapies that target the disease at various levels have emerged, including TTR stabilizers (example: Tafamidis), and antisense oligonucleotides, RNA interference (example: Patisiran, Vutrisiran and Inotersen). Tafamidis is the only drug approved for ATTR cardiomyopathy so far, although trials with patisiran, vutrisiran, inotersen and eplontersen are underway. All of these are most effective when administered prior to significant cardiac dysfunction[3, 10]. There are rare and isolated case reports of amyloid cardiac deposition recurrence post-transplant [11]. Since there are very few cases of heart transplantation for ATTR-CM reported in the literature given that most patients have a median age of 80, it is unknown how to best prevent the deposition of amyloid again in the transplanted heart. Our patient remains on Tafamidis post-transplant with the hope of stabilizing TTR protein tetramer and preventing amyloid fibrils from depositing in the myocardium.

Hence, it is imperative to diagnose ATTR-CM at earlier stages with available non-invasive testing and FDA approved treatments. Heart transplantation can be considered in select patients with Stage D HF [12]. The current allocation system provides priority as Status 4 to these stage D ATTR-CM patients due to a lack of durable mechanical support options[10].

CONCLUSION

Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential, especially in non-ischemic cardiomyopathy patients with thickened interventricular septum, posterior wall thickness, and arrhythmias especially atrial fibrillation. Early diagnosis of ATTRwt combined with newer therapies can be consequential in increasing patients' quality of life and survival [3].

FOOTNOTES

Author contributions: Boda I contributed to manuscript writing, editing, and data collection; Farhoud H assisted with writing and edits; Dalia T and Goyal A assisted with edits; Shah Z and Vidic A have contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

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